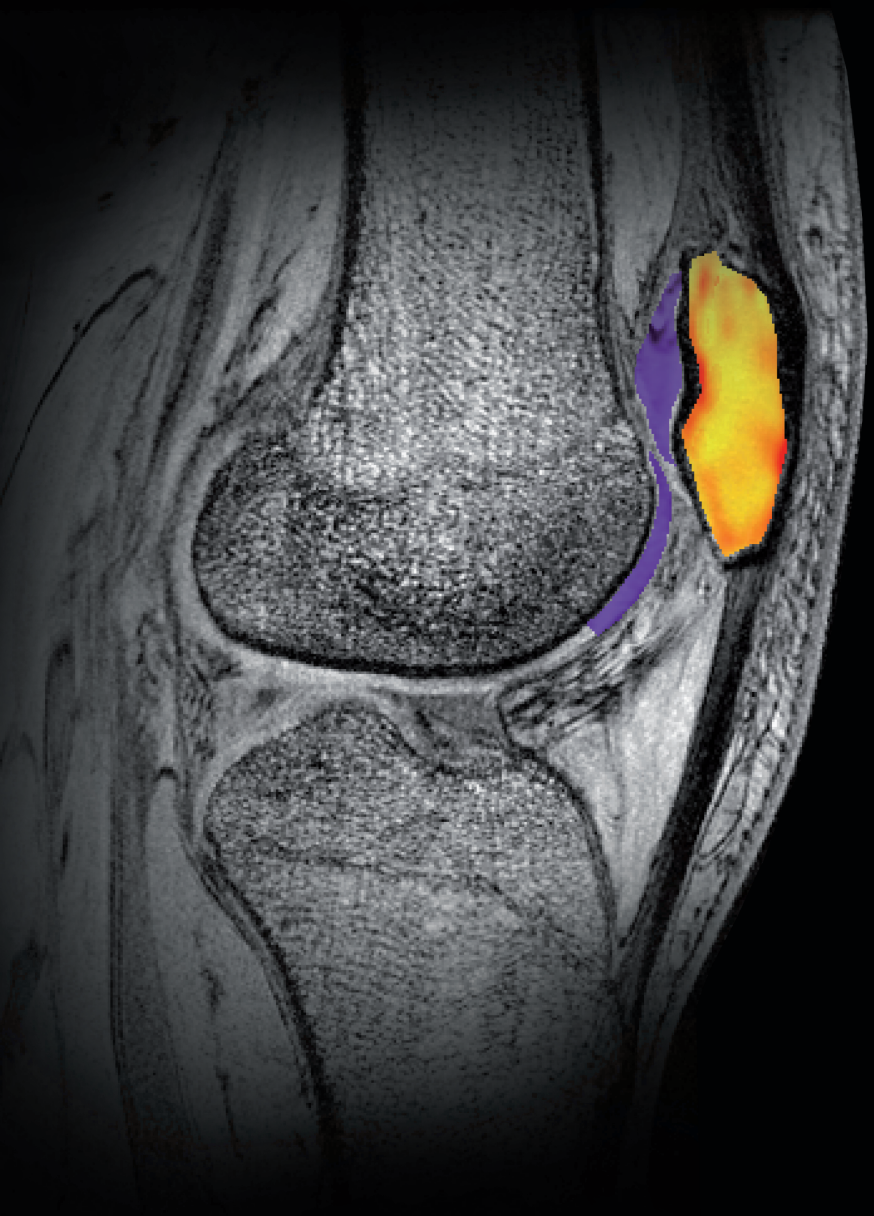

Rianne A. van der Heijden

# Patellofemoral Pain

## *Where does the pain come from?*

# Patellofemoral Pain

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Rianne A. van der Heijden

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**Patellofemoral Pain**
*Where does the pain come from?*

Patellofemorale pijn
*Waar komt de pijn vandaan?*

**Proefschrift**

ter verkrijging van de graad van doctor aan de
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| **Copromotoren:** | Dr. M. van Middelkoop<br>Dr. E.H.G. Oei |

**CONTENTS**

# Chapter 1

## General introduction

## INTRODUCTION

Patellofemoral pain (PFP) is a common knee complaint, also referred to as 'anterior knee pain', 'patellar dysfunction', 'chondromalacia patellae', or 'retropatellar chondropathy'. PFP is particularly prevalent among physically active young individuals.[1] PFP is characterized by retropatellar pain (behind the kneecap) or peripatellar pain (around the kneecap) (Figure 1), specifically during knee loading activities, like running, cycling, squatting, stair climbing, and/or during prolonged sitting with the knees flexed in 90 degrees. Other symptoms can be crepitus and a feeling of giving way.[2-4] On average, a general practitioner diagnoses five to six new cases per 1000 registered patients yearly, whereas the incidence reaches up to 22 new cases per 1000 patients per year in highly active populations.[5-8] In fact, of all patients with a new running injury in sports medicine practices 17% is diagnosed with PFP and the annual prevalence in elite cyclists is 36%.[9,10] The diagnosis PFP is made per exclusionem of other specific knee pathologies, such as Hoffa syndrome, Osgood Schlatter syndrome, patellar tendinitis, intra-articular pathology (including osteoarthritis), plica syndromes, and traumatic injuries (such as injured ligaments, meniscal tears, and patellar luxation). Sensitivity and specificity of physical tests, such as the Clarke compression test, are disputable.[11,12]

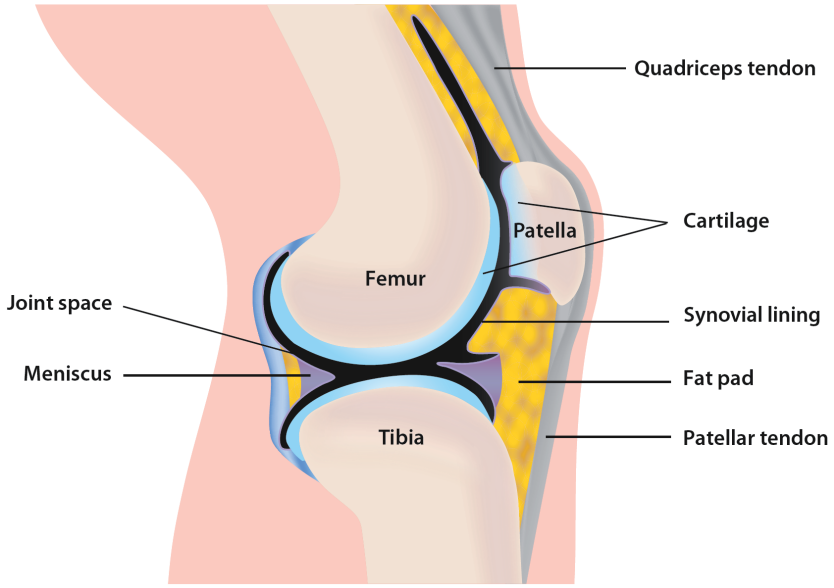


**Figure 1.** Knee joint anatomy

## Exercise therapy

The majority of people with PFP are treated conservatively with knee orthoses[13], foot orthoses[14], patellar taping[15], exercise therapy[16], or a combination of these. In the past, exercise therapy focused solely on quadriceps muscle strengthening, since less knee extension strength was found to be associated with PFP[17] and lower knee extension peak torque was identified as a possible risk factor for PFP.[18] More recently, focus has shifted to the whole chain of movement and hip muscle dysfunction was identified as a possible contributor to PFP.[19-21] This thesis comprises a Cochrane review (Chapter II) assessing the effects of exercise therapy in PFP including multiple comparisons, such as quadriceps focused exercise therapy versus a control strategy (no treatment, placebo or waiting list controls), hip exercise versus quadriceps exercises alone, or a combination of quadriceps and hip exercises.

## Pathogenesis

Despite the application of a variety of treatment modalities, a substantial group of patients has persistent complaints.[13,15,22-25] PFP is no self-limiting disorder as was thought in the past, but can have a debilitating effect, due to the common recurrence of symptoms, tendency to chronicity, and its impact on physical activity levels.[26-30] Previously, research emphasis was primarily placed on mechanical and neuromuscular deficits. However, it is still unknown where the pain originates. The pathogenesis, which is the biological mechanism that leads to the diseased state, of PFP is considered to be multifactorial, but still largely unknown.

In the beginning of this century, Dye introduced quite a new view on the pathogenesis of PFP by focusing on tissue homeostasis, which is the internal steady state within a defined tissue of an organism.[31] Dye proposed that certain high loading conditions of the patellofemoral joint can induce a symptomatic loss of tissue homeostasis, which, once initiated, may persist indefinitely.[31] Some of the proposed pathophysiologic mechanisms for knee pain in literature are structural joint tissue abnormalities, inflammation, increased intraosseous hydrostatic pressure, and patellar bone ischemia.[7,32-49] Nowadays, it is possible to study these mechanisms in depth with innovative MRI techniques. Two of these mechanisms will be discussed in more detail in the following paragraphs.

### *Structural joint tissue abnormalities*

Around 1960 it was believed that PFP was caused by chondromalacia and subsequently patients underwent arthroscopy with shaving of the patellar cartilage. Between 1970 and 1990, arthroscopic studies clarified that PFP is not necessarily related to cartilage defects, which was confirmed in 1999 by the study of Kannus et al. with the use of magnetic resonance imaging (MRI)[7,27,50,51] To date evidence on the association between PFP and retropatellar cartilage damage is not conclusive and 'retropatellar chondropathy'

is still widely used as synonym for PFP. With current-day MRI with high spatial resolution it is nowadays possible to detect even minor cartilage defects, such as signal abnormalities, fraying or fissuring, and hypertrophy, which could potentially have been undetected with prior imaging techniques. Furthermore, other abnormalities, such as patellar retinaculum, synovial plicae, Hoffa's fat pad and subchondral bone marrow, have long been mentioned in literature as possible sources of pain, but have not yet been systematically investigated in a PFP population with MRI.[7,32-34,52] Therefore, chapter III focuses on the association between PFP and structural joint tissue abnormalities of the patellofemoral joint on MRI.

Chapter IV takes it one step further by focusing on the association between PFP and patellofemoral cartilage composition. PFP has been suggested as a precursor of patellofemoral osteoarthritis (OA)[53,54] and changes in cartilage composition are known to precede changes in cartilage morphology in OA.[55] So, if cartilage changes are expected in PFP, which typically involves a young patient population without morphologic cartilage defects, this would be changes in cartilage composition. Structural components of cartilage are essential for cartilage structure and its mechanical behavior. The latter depends on the interaction of these structural components and water.[56] Hypothetically, in case of an altered cartilage composition, pain receptors of the subchondral endplate may be exposed to stress that normally would be absorbed by healthy cartilage.[57] Nowadays, cartilage composition can be measured with quantitative MRI techniques such as delayed gadolinium enhanced MRI of cartilage (dGEMRIC), $T1_\rho$ and T2 mapping. These techniques estimate the amount and network integrity of structural components of cartilage, like collagen and glycosaminoglycans.[58]

***Patellar bone ischemia***

An increasing body of research suggests that vascular problems leading to an increased intraosseous pressure or bone ischemia might play a role in PFP.[35-39] This might be especially important in patients with PFP during prolonged sitting, since Naslund et al. measured a reduced pulsatile blood flow in the patella during knee flexion.[59] Quantitative analysis of blood perfusion is nowadays possible with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). DCE-MRI measures the amount of contrast taken up in a preselected volume over a time period, as a measure of blood perfusion.[60] Due to the relatively poor vascularization of bone compared to other tissues, DCE-MRI of bone poses important challenges, and only a few studies used a quantitative approach.[61-65] To our knowledge, DCE-MRI has neither been applied in the patellar bone nor in patients with PFP previously. Therefore, chapter V describes the development of a method to apply DCE-MRI in patellar bone. Subsequently, chapter VI describes the association between blood perfusion of the patellar bone and PFP.

***Altered pain perception***

Next to this structural approach, an altered pain perception has also been proposed as possible mechanism contributing to PFP. Pain is normally present when a nociceptor, a pain receptor, is stimulated. If an altered pain perception exists, there is no longer a nociceptive stimulus present or only a small stimulus, which cannot account for the amount of pain felt. Previous studies by Jensen et al. indicated that aberrations of the nervous system leading to an altered pain perception might play a role in chronic patellar PFP.[66,67] More recently, two studies demonstrated the presence of pressure hyperalgesia, an increased response to a pain provoking mechanical stimulus, in a population of adult females with PFP.[68,69] Pressure hyperalgesia can be assessed with the pressure pain threshold (PPT); this is the amount of mechanical pressure needed to induce pain. The PPT can be tested with a handheld dynamometer with algometry tip. Chapter VII focuses on the inter-rater reliability of handheld dynamometry testing of the pressure pain threshold, while chapter VIII describes the association between PFP and pain perception.

**In summary**

The aims of this thesis are to assess the effects of exercise therapy in patients with PFP and to contribute to a better understanding of the pathogenesis of PFP. Figure 2 summarizes the hypothetic pathophysiologic mechanisms of patellofemoral pain. The white boxes depict the mechanisms, which will be discussed in this thesis.

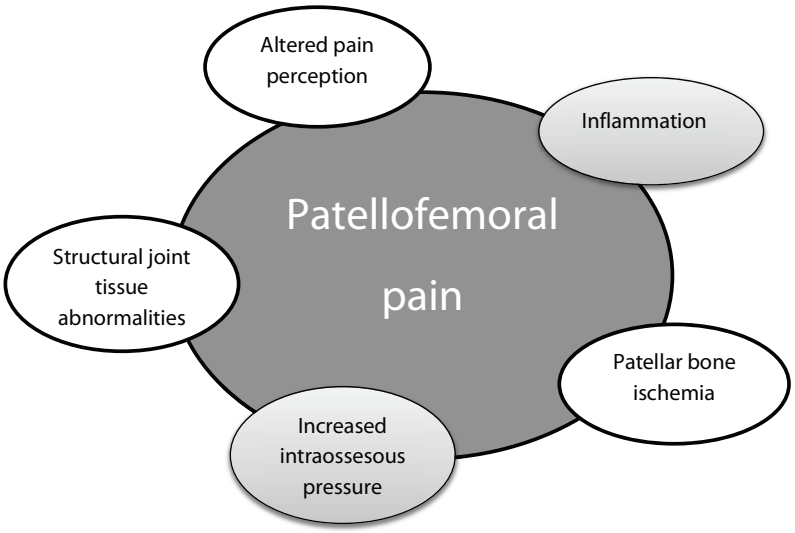


**Figure 2.** Hypothetic pathophysiologic mechanisms of patellofemoral pain

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# Chapter 2

## Exercise for treating patellofemoral pain syndrome (Review)

**VAN DER HEIJDEN RA, LANKHORST NE, VAN LINSCHOTEN R, BIERMA-ZEINSTRA SMA, VAN MIDDELKOOP M**

*COCHRANE DATABASE SYST REV. 2015 JAN 20;1: CD010387. DOI: 10.1002/14651858. CD010387.PUB2. PMID: 25603546*

## ABSTRACT

### Background

Patellofemoral pain syndrome (PFPS) is a common knee problem, which particularly affects adolescents and young adults. PFPS, which is characterised by retropatellar (behind the kneecap) or peripatellar (around the kneecap) pain, is often referred to as anterior knee pain. The pain mostly occurs when load is put on the knee extensor mechanism when climbing stairs, squatting, running, cycling or sitting with flexed knees. Exercise therapy is often prescribed for this condition.

### Objectives

To assess the effects (benefits and harms) of exercise therapy aimed at reducing knee pain and improving knee function for people with patellofemoral pain syndrome.

### Search methods

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (May 2014), the Cochrane Central Register of Controlled Trials (2014, Issue 4), MEDLINE (1946 to May 2014), EMBASE (1980 to 2014 Week 20), PEDro (to June 2014), CINAHL (1982 to May 2014) and AMED (1985 to May 2014), trial registers (to June 2014) and conference abstracts.

### Selection criteria

Randomised and quasi-randomised trials evaluating the effect of exercise therapy on pain, function and recovery in adolescents and adults with patellofemoral pain syndrome. We included comparisons of exercise therapy versus control (e.g. no treatment) or versus another non-surgical therapy; or of different exercises or exercise programmes.

### Data collection and analysis

Two review authors independently selected trials based on pre-defined inclusion criteria, extracted data and assessed risk of bias. Where appropriate, we pooled data using either fixed-effect or random-effects methods. We selected the following seven outcomes for summarising the available evidence: pain during activity (short-term: ≤ 3 months); usual pain (short-term); pain during activity (long-term: > 3 months); usual pain (long-term); functional ability (short-term); functional ability (long-term); and recovery (long-term).

### Main results

In total, 31 heterogeneous trials including 1690 participants with patellofemoral pain are included in this review. There was considerable between-study variation in patient characteristics (e.g. activity level) and diagnostic criteria for study inclusion (e.g.

minimum duration of symptoms) and exercise therapy. Eight trials, six of which were quasi-randomised, were at high risk of selection bias. We assessed most trials as being at high risk of performance bias and detection bias, which resulted from lack of blinding. The included studies, some of which contributed to more than one comparison, provided evidence for the following comparisons: exercise therapy versus control (10 trials); exercise therapy versus other conservative interventions (e.g. taping; eight trials evaluating different interventions); and different exercises or exercise programmes. The latter group comprised: supervised versus home exercises (two trials); closed kinetic chain (KC) versus open KC exercises (four trials); variants of closed KC exercises (two trials making different comparisons); other comparisons of other types of KC or miscellaneous exercises (five trials evaluating different interventions); hip and knee versus knee exercises (seven trials); hip versus knee exercises (two studies); and high- versus low-intensity exercises (one study). There were no trials testing exercise medium (land versus water) or duration of exercises. Where available, the evidence for each of seven main outcomes for all comparisons was of very low quality, generally due to serious flaws in design and small numbers of participants. This means that we are very unsure about the estimates. The evidence for the two largest comparisons is summarised here.

Exercise versus control. Pooled data from five studies (375 participants) for pain during activity (short-term) favoured exercise therapy: mean difference (MD) -1.46, 95%confidence interval (CI) -2.39 to -0.54. The CI included the minimal clinically important difference (MCID) of 1.3 (scale 0 to 10), indicating the possibility of a clinically important reduction in pain. The same finding applied for usual pain (short-term; two studies, 41 participants), pain during activity (long-term; two studies, 180 participants) and usual pain (long-term; one study, 94 participants). Pooled data from seven studies (483 participants) for functional ability (short-term) also favoured exercise therapy; standardised mean difference (SMD) 1.10, 95% CI 0.58 to 1.63. Re-expressed in terms of the Anterior Knee Pain Score (AKPS; 0 to 100), this result (estimated MD 12.21 higher, 95% CI 6.44 to 18.09 higher) included the MCID of 10.0, indicating the possibility of a clinically important improvement in function. The same finding applied for functional ability (long-term; three studies, 274 participants). Pooled data (two studies, 166 participants) indicated that, based on the 'recovery' of 250 per 1000 in the control group, 88 more (95% CI 2 fewer to 210 more) participants per 1000 recovered in the long term (12 months) as a result of exercise therapy.

Hip plus knee versus knee exercises. Pooled data from three studies (104 participants) for pain during activity (short-term) favoured hip and knee exercise: MD -2.20, 95% CI -3.80 to -0.60; the CI included a clinically important effect. The same applied for usual pain (short-term; two studies, 46 participants). One study (49 participants) found a clinically important reduction in pain during activity (long-term) for hip and knee exercise. Although tending to favour hip and knee exercises, the evidence for functional ability

(short-term; four studies, 174 participants; and long-term; two studies, 78 participants) and recovery (one study, 29 participants) did not show that either approach was superior.

### Authors' conclusions

This review has found very low quality but consistent evidence that exercise therapy for PFPS may result in clinically important reduction in pain and improvement in functional ability, as well as enhancing long-term recovery. However, there is insufficient evidence to determine the best form of exercise therapy and it is unknown whether this result would apply to all people with PFPS. There is some very low quality evidence that hip plus knee exercises may be more effective in reducing pain than knee exercise alone. Further randomised trials are warranted but in order to optimise research effort and engender the large multicentre randomised trials that are required to inform practice, these should be preceded by research that aims to identify priority questions and attain agreement and, where practical, standardisation regarding diagnostic criteria and measurement of outcome.

## BACKGROUND

### Description of the condition

Patellofemoral pain syndrome (PFPS) is a common knee problem, which particularly affects adolescents and young adults.[1] Synonyms for patellofemoral pain syndrome are 'anterior knee pain syndrome', 'patellar dysfunction', 'chondromalacia patellae' or 'chondropathy'. Its incidence varies from 22 new cases per 1000 persons/year in highly active populations to five to six new cases per 1000 in general practice.[2 3] PFPS is characterised by retropatellar pain (behind the kneecap) or peripatellar pain (around the kneecap), mostly occurring when load is put on the knee extensor mechanism such as when climbing stairs, squatting, running, cycling or sitting with flexed knees.[4 5] The diagnosis is based on these symptoms after excluding other distinct knee pathologies, which potentially cause anterior knee pain, such as Hoffa's syndrome, Osgood Schlatter syndrome, Sinding-Larsen-Johansson syndrome, iliotibial band friction syndrome, tendinitis, neuromas, intra-articular pathology including osteoarthritis, rheumatoid arthritis, traumatic injuries (such as injured ligaments, meniscal tears, patellar fractures and patellar luxation), plica syndromes and more rarely occurring pathologies. Physical tests, for example the Clarke's compression test, are used to diagnose PFPS, but the sensitivity and specificity of these tests are debated.[6 7] Several factors have been implicated in the aetiology of PFPS. These include local factors (contribution of patellofemoral joint mechanics and surrounding tissues to patellofemoral pain), distal factors (contribution of foot and ankle mechanics) and proximal factors (contribution of hip, pelvis and trunk

mechanics).[4] However, the aetiology of the condition is still unclear, as is the origin of the pain. Other factors that have recently been described as factors associated with PFPS are a lower knee extension strength, a lower hip extension strength and decreased flexibility of the lower extremity muscles.[5]

## Description of the intervention

The majority of people with PFPS are treated conservatively (non-surgically). Physically-based conservative interventions include knee orthoses, foot orthoses[8], patellar taping[9] and exercise therapy. Most exercise therapy programmes for PFPS have focused on strengthening the quadriceps muscles, which was seen as the most promising conservative treatment method for patellofemoral pain syndrome.[10-12] More recently, studies have focused on hip muscle dysfunction as a possible contributor to patellofemoral pain.[13-15] Exercise therapy comprises a broad range of possible variations and accompanying terms. Activity of the quadriceps muscles – and other muscles involved in knee function - can either be concentric, eccentric or isometric. During concentric activities the muscles shorten, whereas during eccentric activities the muscles lengthen in an actively controlled manner. During isometric activity the muscle length remains the same. Exercises can either be static or dynamic. Exercises are referred to as static if the position of the knee does not change. If the position of the knee does change, the exercise is called dynamic. In cases where the lower leg moves at a predetermined, constant speed, which requires an isokinetic dynamometer to control the velocity, the dynamic exercise is also called isokinetic. Exercises where the foot is in contact with a fixed surface are referred to 'closed kinetic chain exercises', as opposed to 'open kinetic chain' exercises where the foot is not in contact with a fixed surface. Thus, exercises can be arranged in three ways: the type of muscle activity (concentric, eccentric, isotonic), joint movement (dynamic versus static) and the presence of reaction forces caused by contact of the foot with a fixed surface (closed versus open kinetic chain).[16 17] Combinations of the above apply to every type of exercise, and the terminology used for exercise programmes reflects the emphasis intended by the therapist or researcher. Emphasis during exercise therapy may be put on the co-ordinated contraction of the medial and lateral parts of the quadriceps muscle, and also on the co-ordinated contraction of hip adductor, hip abductor and gluteal muscles.[18] In addition, there are other differences such as in the delivery of exercise, for example, supervised exercise versus home exercise; or in the duration or intensity of exercise.

## How the intervention might work

A recent published review on factors associated with PFPS concluded that people with PFPS have lower knee extension strength, lower hip extension strength and decreased flexibility of the lower extremity muscles compared with people without PFPS.[5] Exercise

programmes that comprise static and dynamic muscular exercises for both quadriceps and hip muscles aim to improve the strength of these muscles and consequently reduce pain by decreasing the load on the patellofemoral joint and improve function by normalising the kinematics.

### Why it is important to do this review

Patellofemoral pain syndrome (PFPS) is a common knee problem, particularly affecting adolescents and young adults and exercise therapy to strengthen the quadriceps is often prescribed. However, the aetiology of the condition, including the structures causing the pain, and treatment methods are all debated and consensus has not been reached so far. This review updates and supercedes a former Cochrane review.[10]

## OBJECTIVES

To assess the effects (benefits and harms) of exercise therapy aimed at reducing knee pain and improving knee function for people with patellofemoral pain syndrome.

## METHODS

### Criteria for considering studies for this review

#### *Types of studies*

Randomised and quasi-randomised (using a method of allocating participants to a treatment or control condition by a method that is not strictly random, e.g. by hospital number) controlled clinical trials that evaluate exercise therapy for patellofemoral pain syndrome.

#### *Types of participants*

Adolescents and adults with patellofemoral pain (or a synonym of this) as defined by trial authors. We excluded studies focusing on other named knee pathologies such as Hoffa's syndrome, Osgood Schlatter syndrome, Sinding-Larsen-Johansson syndrome, iliotibial band friction syndrome, tendinitis, neuromas, intra-articular pathology including osteoarthritis, rheumatoid arthritis, traumatic injuries (such as injured ligaments, meniscal tears, patellar fractures and patellar luxation), plica syndromes and more rarely occurring pathologies.[12 19]

***Types of interventions***

We included studies evaluating exercise therapy for patellofemoral pain syndrome. Exercises could be applied on their own or in combination with other non-surgical interventions, provided the same other intervention was applied to the whole population in the comparison. Exercises could be performed at home or under supervision of a therapist.

***Comparisons***

1. Exercise therapy versus control (no treatment, placebo or waiting list controls). This also includes 'exercise therapy + another intervention (e.g. taping) versus the other intervention alone (e.g. taping)'
2. Exercise therapy versus different conservative interventions (e.g. taping)
    i) Exercise therapy versus unimodal conservative interventions
    ii) Exercise therapy versus multimodal conservative interventions
3. Comparisons of different exercises or exercise therapy programmes:
    i) Delivery of exercises or exercise programmes (e.g. supervised versus home exercise; group versus individual supervision)
    ii) Medium of exercises or exercise programmes (water versus land-based exercise)
    iii) Types of exercises or exercise programmes (e.g. closed versus open kinetic chain exercises; dynamic versus static)
    iv) Target of exercises or exercise programmes (strengthening of hip or abdominal muscles versus quadriceps muscles)
    v) Duration of exercises or exercise programmes (e.g. long duration (more than three months) versus shorter duration (three months or less))
    vi) Intensity of exercises or exercise programmes (e.g. high-intensity (several times per week) versus low-intensity (once weekly))

We defined the intervention group for comparisons of different exercises as the most novel, intensive or resource-dependent intervention. For instance, the intervention was supervised exercise and the control was home exercise in the first comparison (3a). We also gave consideration to consistency in the choice of control groups. For comparison 3c, types of exercises, we implemented a secondary categorisation based on the type of kinetic chain involved. These were closed versus open kinetic chain exercises; variants of closed kinetic chain exercise; and open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action (isometric, isotonic (concentric or eccentric) or isokinetic). We presented separately any exceptions that did not fit in. In terms of the 'exercise therapy' group, combined interventions or treatment packages including exercise were not tested in this review, with the exception of exercises provided with instructions or advice, where exercise was the predominant intervention.

***Types of outcome measures***

***Primary outcomes***

1. Knee pain measured by validated self reporting methods (visual analogue scale (VAS), numerical rating scale (NRS) or McGill Pain questionnaire).[20] If multiple pain scales were reported in one study, we only included pain in daily life (usual pain, worst pain and pain at activities (e.g. sports, pain during descending stairs)[21] in the analyses. We selected pain at descending for pooling on 'pain at activities' as this outcome measure was present in most studies eligible for pooling of pain at activity.

***Secondary outcomes***

1. Functional ability (i.e. knee function in activities of daily living) measured by questionnaires focusing on knee function (such as Functional Index Questionnaire (FIQ)[22], Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[23], Kujala Patellofemoral Function Scale or Anterior Knee Pain Score (AKPS)[24] and Lysholm scale[25]). If multiple scales for functional ability were measured including the AKPS, we used the latter for pooling.
2. Functional performance tests, including squatting and hopping on one leg.[26]
3. Subjective perception of recovery. Recovery from patellofemoral pain syndrome is an outcome measure inconsistently reported in studies and different methods are used to describe recovery. In this review, we gave preference to 'number of patients no longer troubled by symptoms' or 'perceived recovery' measured on a Likert scale.[27]
4. Adverse events: we considered knee swelling or substantially increasing pain levels as a direct effect of treatment.

Based on Crossely et al.[21], we chose the following minimal clinically important differences for pain and function: 1.3 points on a VAS (0 to 10) for pain during activity; 2.0 points on a VAS (0 to 10) for usual and worst pain; 10 points for the AKPS (0 to 100) and 2 points for the FIQ (0 to 16).

Changes in knee function measured on impairment level only (e.g. range of motion, muscle strength) do not directly represent changes in the symptoms of patellofemoral pain or the resulting disability, and we therefore did not consider them clinically relevant outcome measures in this review.[28 29]

***Timing of outcome measurement***

We considered outcomes measured within three months after the baseline measurement short-term outcomes of exercise therapy, and we considered measurements more than three months after the baseline measurement long-term outcomes. If multiple

short-term outcomes were measured in one trial, we used the time point closest to three months for pooling.

## Search methods for identification of studies

### *Electronic searches*

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (23 May 2014), the Cochrane Central Register of Controlled Trials (2014, Issue 4), MEDLINE (1946 to May Week 2 2014), MEDLINE In-Process & Other Non-Indexed Citations (22 May 2014), EMBASE (1980 to 2014 Week 20), PEDro - The Physiotherapy Evidence Database (to 26 June 2014), CINAHL (1982 to 23 May 2014) and AMED (1985 to May 2014). We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform and Current Controlled Trials for ongoing and recently completed trials (30 June 2014). In MEDLINE (Ovid Online), we combined a subject-specific strategy with the sensitivity-maximising version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials.[30] Search strategies for MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, CINAHL and AMED are shown in Appendix 1. We did not apply any language restrictions.

### *Searching other resources*

We checked reference lists of included studies and other relevant articles, including a previous Cochrane review[10], for additional trials. We contacted institutions and experts in the field in order to identify unpublished studies. We searched conference abstracts from the International Patellofemoral Pain Research Retreat.[4]

### *Data collection and analysis*

The intended methodology for data collection and analysis was described in our published protocol[31], which was based on the *Cochrane Handbook for Systematic Reviews of Interventions*.[32]

### *Selection of studies*

Two review authors (RAH and NEL) selected potentially eligible articles by reviewing the title and abstract of each citation. After obtaining full articles, both authors independently performed study selection. In cases of disagreement, we reached a consensus through discussion.

### *Data extraction and management*

Two review authors (RAH and NEL) independently extracted the data within included trials using a piloted data collection form. We resolved any disagreements by consensus.

Where data were missing or incompletely reported, we contacted authors of trials. Where pooling was possible, and if necessary, we converted pain scores (VAS, NRS) to a 0 to 10 scale and function scores to a 0 to 100 scale.

***Assessment of risk of bias in included studies***

Two review authors (RAH and NEL) independently assessed the risk of bias of the included trials using The Cochrane Collaboration's 'Risk of bias' tool.[32] We assessed the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Other sources of bias included bias from major imbalance in baseline characteristics and performance bias such as from lack of comparability in clinicians' experience with the interventions under test, differences in care other than the interventions under test or compliance with the intervention. We explicitly judged each of these criteria using: low risk of bias; high risk of bias; and unclear risk of bias (where 'unclear' relates to a lack of information or uncertainty over the potential for bias). Disagreements between review authors regarding the risk of bias for domains were resolved by consensus.

***Measures of treatment effect***

We calculated risk ratios with 95% confidence intervals for dichotomous outcomes. We calculated mean differences with 95% confidence intervals for continuous outcomes as appropriate. When two or more studies presented their data derived from the same instrument of evaluation (with the same units of measurement), we pooled data as a mean difference (MD). Conversely, we used the standardised mean difference (SMD) when primary studies express the same variables through clearly different instruments (and different units of measurement). In case of pooling of different units of measurements, we scaled values to 0 to 10 (lower is better) for pain and 0 to 100 (higher is better) for functional ability. In order to re-express SMDs in VAS (0 to 10) and AKPS (0 to 100), we multiplied SMDs and 95% CIs by an estimate (the median of all control and intervention standard deviations (SDs)) of the SD of VAS or AKPS respectively.

***Unit of analysis issues***

The unit of randomisation in the studies likely to be included in this review is usually the individual participant. Exceptionally, as in the case of trials including people with bilateral complaints, data for trials could be evaluated for knees, instead of individual patients. Where such unit of analysis issues arose and appropriate corrections had not been made, we proposed to present data for such trials only where the disparity between the units of analysis and randomisation was small. Where data were pooled, we aimed to perform a sensitivity analysis to examine the effects of pooling these incor-

rectly analysed trials with the other correctly analysed trials. However, all the outcome measures, except functional performance, presented their outcome data based on the individual participant. For functional performance, studies including participants with bilateral complaints used the most painful side for analysis. So, no unit of analysis issues occurred. For multi-comparison studies, we attempted to combine data where two or more of the groups tested interventions in the same category. When combining was not appropriate but the data presented for the difference comparisons were presented in the same analysis, we divided the number of participants in the shared comparison (e.g. halved where this intervention appears twice) in order to avoid the 'double-counting' of participants for the 'shared comparison' in the meta-analyses. For cross-over trials, we proposed to present data collected prior to the cross-over of the intervention, but there were no cross-over trials included.

***Dealing with missing data***

We contacted trial authors where further details of methodology or data were required for trial inclusion. Where possible we performed intention-to-treat analyses to include all people randomised. However, where dropouts were identified, we used the actual numbers of participants contributing data at the relevant outcome assessment. We were alert to the potential mislabelling or non-identification of standard errors and standard deviations (SDs). Unless missing standard deviations could be derived from confidence intervals or standard errors, we planned to consider whether it was appropriate to estimate values based on comparable data included in this review in order to present these in the analyses. We imputed no data in the review. Should we impute data in future, we will make clear for which trials imputed data have been used (e.g. footnotes in the forest plots). Should data have been presented as the median (inter-quartile range), we would not have transformed these to achieve normality or to estimate the mean and SD.

***Assessment of heterogeneity***

We assessed heterogeneity by visual inspection of the forest plot (analysis) along with consideration of the $Chi^2$ test for heterogeneity and the $I^2$ statistic.[32] We considered heterogeneity statistically significant if the $I^2$ statistic was 70% or more or the P value < 0.1 for the $Chi^2$ test. We also examined studies for methodological and clinical heterogeneity, particularly if significant statistical heterogeneity was identified.

***Assessment of reporting biases***

For future updates of the review, we will explore the possibility of publication bias using a funnel plot if there are data from at least 10 trials available for pooling.[32]

***Data synthesis***

When considered appropriate, we pooled results of comparable groups of trials using both fixed-effect and random-effects models. The choice of the model to report was guided by a careful consideration of the extent of heterogeneity and whether it could be explained, in addition to other factors such as the number and size of studies that were included. The fixed-effect model was the standard. We used a random-effects model in case of statistically significant heterogeneity.

***Subgroup analysis and investigation of heterogeneity***

Where data permitted, we proposed to perform the following subgroup analyses:

- Gender
- Duration of complaints (acute (less than three months) versus chronic)
- Sport participation (athletes and/or military recruits versus the general population)

We intended to inspect the overlap of confidence intervals and perform the test for subgroup differences available in RevMan to test whether subgroups were statistically significantly different from one another. However, subgroup analysis to determine the effects of gender, duration of complaints and sports participation on the outcomes of interest was not possible due to the small number of participants in the studies and the inconsistent reporting of baseline characteristics.

***Sensitivity analysis***

Where appropriate, we performed sensitivity analyses investigating the effects of risks of bias by excluding trials with high or unclear risk of bias (such as selection bias for trials with lack of allocation concealment and lack of random sequence generation) and trials reported in abstracts only. We explored the effects of using different models (fixed-effect versus random-effects) for pooling data where there was substantial heterogeneity and retained the more conservative result (random-effects) but also explored the effects on the results of removing single trials (outliers) in analyses where there were three trials or more. We did not need to perform sensitivity analyses to explore the effects of included trials with imputed data (e.g. SDs) for this version of the review.

***'Summary of findings' tables***

Where there were sufficient data, we summarised the results for the main comparisons described in the Types of interventions in 'Summary of findings' tables (Appendix 2). We used the GRADE approach for systematic reviews[33-36] to assess the quality of evidence related to seven outcomes (pain during activity (short-term; ≤ 3 months); usual pain (short-term); pain during activity (long-term; > 3months); usual pain (long-term); func-

tional ability (short-term); functional ability (long-term); recovery (long-term); see Types of outcome measures) (Higgins[32]; *see* section 12.2).

## RESULTS

### Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies; Available online: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010387.pub2/full

### Results of the search

We found 1398 records from the following databases: Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (49 records); Cochrane Central Register of Controlled Trials (135), MEDLINE (326 records), EMBASE (491 records), AMED (178 records), CINAHL (146 records), PEDro (11 records), the WHO International Clinical Trials Registry Platform (42) and Current Controlled Trials (20). Furthermore, we identified 13 potentially eligible studies from the previous review of Heintjes et al.[10]

The search identified 107 potentially eligible studies of which 60 were clearly not eligible upon the retrieval of full-text articles. Of those remaining, 31 studies (two with data published in two reports) were included in the review. We excluded 12 studies and there is one ongoing study. One study is reported in Turkish and has been placed in Characteristics of studies awaiting classification pending translation.[37]

A flow diagram summarising the study selection process is shown in Figure 1.

### Included studies

Full details of the trials can be found in the Characteristics of included studies (online available). A summary of key patient characteristics is presented in Table 1; and in the text below.

### Design

We included 25 randomised controlled trials[17 27 29 38-60] and six quasi randomized trials.[61-66]

We extracted data for one comparison from 21 trials and for two comparisons from 10 trials.[29 39 43 46 50-53 57 65]

### Sample sizes

In total, 1690 participants from 31 trials were included in this review. The number of participants in the intervention groups in the individual studies ranged from six[58] to 65[27].

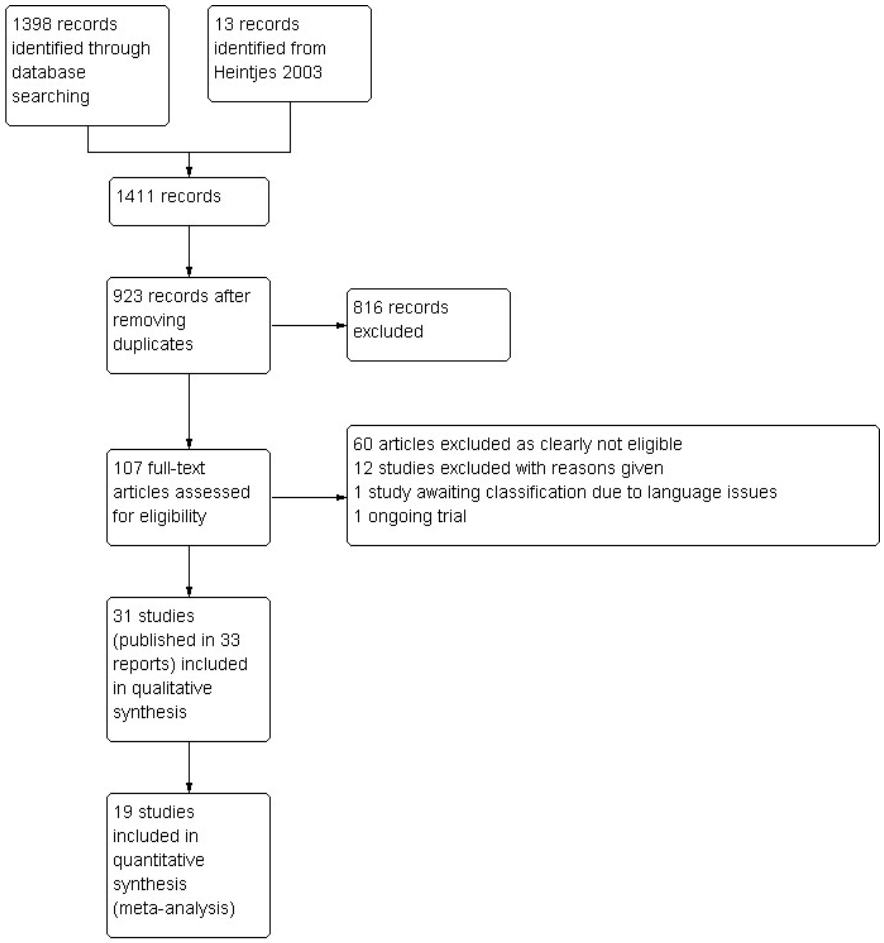



**Figure 1.** Study flow diagram

## Recruitment setting

Participants were recruited from the following settings: orthopaedic clinics[39 40 42 43 49-52 57 60 66], general practices[27 43 50 52 60 65], physiotherapy practices[38 44 53 54 62], chiropractic practices[58], rehabilitation services[46 47], athletic trainer practices[45], sports medicine practices[27], rheumatology department[43], department of community health[48], institute of sports[48], poster advertisements in public places[58], screening of all female students at the physiotherapy clinic affiliated to the rehabilitation faculty[55], or via bulletin board posters and word of mouth[52] (*see* Table 1). Seven trials recruited from more than one setting.[27 43 48 50 52 58 60] Seven trials did not report their recruitment setting.[17 29 41 56 61 63 64] Trials were undertaken in 18 different countries (Australia (two trials); Belgium (one); Brazil (four); Canada (two); Egypt (two); Germany (one); Iran (four); Israel (one); Norway (one); Saudi Arabia (one);

**Table 1.** Summary of characteristics of included studies

| | Recruitment setting, Country | Number of participants included | % female gender | Age | %bilateral complaints | Activity level | BMI |
|---|---|---|---|---|---|---|---|
| **Abd Elhafz 2011** | Physiotherapy clinic, Egypt | 30 | 30 | 35.8 | 0 | Not reported | Not reported |
| **Abrahams 2003** | Orthopaedic, UK | 78 | 50 | 29.0 | 0 | Not reported | 24.8 |
| **Avraham 2007** | Orthopaedic, Israel | 30 | Not reported | 35 | Not reported | Not reported | Not reported |
| **Bakhtiary 2008** | Not reported, Iran | 32 | 100 | 22.1 | Not reported | Not reported | Not reported |
| **Balci 2009** | Orthopaedic,Turkey | 40 | 100 | 37.6 | 0 | Not reported | 25.5 |
| **Clark 2000** | Orthopaedic, rheumatology consultants or general practice, Australia | 81 | 44 | 27.8 | 55 | Not reported | 25.0 |
| **Colón 1988** | Not reported, USA | 29 | 34 | Range: 15 to 24 | Not reported | Active[1] | Not reported |
| **De Marche 2014** | Physical therapy clinic, Brazil | 31 | 100 | 22 | Not reported | Active[2] | 21.5 |
| **Dolak 2011** | Athletic trainer, USA | 33 | 100 | 25.4 | 48 | Not reported | 25.5 |
| **Eburne 1996** | Outpatient physiotherapy department, UK | 75 | Not reported | Not reported | Not reported | Not reported | Not reported |
| **Fukuda 2010** | Rehabilitation service | 70 | 100 | 24.6 | 0 | Less active[3] | 22.0 |
| **Fukuda 2012** | Rehabilitation service | 54 | 100 | 22.5 | 0 | Less active[3] | 24.0 |
| **Gaffney 1992** | Department of community health and institute of sport, Australia | 72 | 35 | 33.9 | 50 | Not reported | 23.3 |
| **Gobelet 1992** | Not reported, Switzerland | 94 | 53 | 20.7 | Not reported | Not reported | Not reported |
| **Hafez 2012** | Orthopaedic, Egypt | 40 | 100 | 18 | Not reported | Not reported | Not reported |
| **Harrison 1999** | General practice and orthopaedic, Canada | 112 | 60 | 22.2 | 54 | Not reported | Not reported |
| **Herrington 2007** | Orthopaedic, Saudi Arabia | 45 | 0 | 26.9 | Not reported | Not reported | Not reported |
| **Khayambashi 201** | Physician, specialty not reported, Iran | 28 | 100 | 29.7 | 100 | Less active[4] | 24.3 |
| **Khayambashi 2014** | Physicians, specialty not reported, Iran | 36 | 50 | 27.8 | 61 | Less active[4] | 23.2 |

**Table 1.** Summary of characteristics of included studies (continued)

| | Recruitment setting, Country | Number of participants included | % female gender | Age | %bilateral complaints | Activity level | BMI |
|---|---|---|---|---|---|---|---|
| **Loudon 2004** | Primary care, USA | 29 | 76 | 24.7 | 0 | Active[5] | 26.9 |
| **Lun 2005** | General practice or orthopaedic or via bulletin board posters and word of mouth, Canada | 98 | 58 | 34.8 | 44 | Not reported | 24.4 |
| **Moyano 2013** | Physiotherapy clinic, Spain | 61 | 43 | 39.9 | Not reported | Less active[6] | 24.6 |
| **Nakagawa 2008** | Physiotherapy clinic, Brazil | 14 | 71 | 23.6 | Not reported | Not reported | Not reported |
| **Razeghi 2010** | Screening of all female students at the physiotherapy clinic affiliated to the rehabilitation faculty, Iran | 33 | 100 | 22.6 | 62.5 | Not reported | Not reported |
| **Schneider 2001** | Not reported, Germany | 40 | 70 | Not reported | Not reported | Active[7] | Not reported |
| **Song 2009** | Orthopaedic, Taiwan | 89 | 87 | 40.9 | Not reported | Less active[8] | 22.6 |
| **Taylor 2003** | Chiropractic clinic and poster advertisements in public places, UK | 12 | 33.3 | 30.2 | Not reported | Not reported | Not reported |
| **Thomee 1997** | Orthopaedic, Sweden | 40 | 100 | 20.2 | 68 | Not reported | Not reported |
| **Van Linschoten 2009** | General practices and sports medical centres, The Netherlands | 131 | 64.1 | 23.9 | 60.3 | Not reported | 23.1 |
| **Witvrouw 2000** | Not reported, Belgium | 60 | 66.7 | 20.3 | 45 | Not reported | Not reported |
| **Østeråsa 2013** | General practice and orthopaedics, Norway | 40 | 80 | 30.0 | 70 | Not reported | Not reported |

[1]Recreational athletes.

[2]Athletes with a minimum sport participation of 30 minutes, 3 times a week.

[3]Sedentary: not practised physical activity any day of the week, both aerobic and strengthening exercises, for at least the past six months.

[4]Patients were not physically active and did not participate in recreational sport activities or exercise beyond that of activities of daily living.

[5]Active in sports for at least 120 minutes per week.

[6]No engagement in regular sporting activities.

[7]Active amateur athletes.

[8]No engagement in regular sporting activities.

Spain (one); Sweden (one); Switzerland (one); Taiwan (one); the Netherlands (one); Turkey (one); UK (three); and USA (three) (*see* Table 1).

### Participants

All participants were diagnosed with patellofemoral pain syndrome based on clinical symptoms and, occasionally, radiological examination (Table 2).

Exceptionally, in Abrahams et al.[39], malalignment also had to be diagnosed by X-ray. The trials varied quite markedly in their inclusion criteria, such as the explicit mention of a minimum duration of symptoms and, if mentioned, the minimum required; this ranged from three weeks[52] to eight months.[39] Five trials provided no details of pain provoking activities or pain provoking functional or clinical tests used for determining eligibility (see Table 2).[29 39 43 49 56 62] Trials consisted of populations with different levels of activity. Six trials reported that they included a less active population[46 47 53 57 63 64] and four trials an active population.[44 56 61 65] 18 trials included both male and female participants.[17 27 29 38 39 43 48 50 52-54 56-58 60 61 64 65] Ten studies involved only female participants[41 42 44-47 49 55 63 66] and one included only male participants.[51] Two studies did not report the number of females and males.[40 62] The age of participants ranged from 10 to 65

years. The mean age of the participants reported in 28 trials ranged from 18 to 40.9 years. The mean body mass index (BMI), only reported in 15 trials, ranged from 21.5 to 26.9 (*see* Table 1). The duration of complaints ranged from four weeks[54] to nine years.[66] Eleven trials included both participants with unilateral- or bilateral complaints.[17 27 43 45 48 50 52 55 60 64 66] Seven trials included only participants with unilateral complaints[38 39 42 46 47 65] and one trial included only patients with bilateral complaints.[63] The remaining 13 studies did not mention the proportion of unilateral and bilateral complaints. A total of six trials excluded participants who had prior exercise therapy.[27 43 51 52 60 63]

### Interventions

A range of exercise therapy interventions were evaluated in the included trials. We distinguished three comparisons:

1. Exercise therapy versus control (no treatment, placebo or waiting list controls)
2. Exercise therapy versus different conservative interventions:
    i) Exercise therapy versus unimodal conservative interventions
    ii) Exercise therapy versus multimodal conservative interventions
3. Different types of exercise therapy
    i) Delivery of exercises or exercise programmes (e.g. supervised versus home exercise; group versus individual supervision)
    ii) Medium of exercises or exercise programmes (water versus land-based exercise)

iii) Types of exercises or exercise programmes (with the primary categorisation being by the type of kinetic chain involved)
iv) Target of exercises or exercise programmes (strengthening of hip and knee muscles versus knee muscles)
v) Duration of exercises or exercise programmes (e.g. long duration (more than three months) versus shorter duration (three months or less))
vi) Intensity of exercises or exercise programmes (e.g. high-intensity (several times per week) versus low-intensity (once weekly)

The intervention period ranged from three weeks[41] to four months[53] and participants exercised on average three times per week.

***Exercise therapy versus control (no treatment, placebo or waiting list)***

For further details, see Appendix 2.

Ten trials compared exercise therapy with a control strategy (no treatment, placebo or waiting list controls).[27 39 43 46 51-53 57 58 65] Clark et al.[43] compared exercise therapy and education versus education alone. Abrahams et al.[39] compared both a traditional exercise protocol and an exercise protocol with thigh adduction and tibia medial rotation during eccentric squat with waiting list. This study was not pooled due to clinical heterogeneity (participants in this study had to be diagnosed with malalignment and PFPS). Taylor et al.[58] compared exercise and patella mobilisation/manipulation with patella mobilisation/manipulation alone. A supervised exercise programme and a home exercise programme were both compared with a control intervention (information leaflet) by Loudon et al.[65] Lun et al.[52] compared a home exercise programme with brace versus brace alone. Herrington et al.[51] compared both weightbearing exercises (CKC) and non weightbearing exercises (OKC) with a control group without treatment. Knee exercises and knee and hip exercises were both compared with no intervention by Song et al.[57] Van Linschoten et al.[27] compared exercise therapy with usual care ('wait and see policy'). Moyano et al.[53] compared classic stretching and quadriceps exercises with education and proprioceptive neuromuscular facilitation stretching (including aerobic exercise) with education. Finally, Fukuda et al.[46] compared both a knee exercise group and a knee and hip exercise group with a group that received no treatment.

***Exercise therapy versus different conservative treatments***

For further details, see Appendix 2.

***Exercise therapy versus unimodal conservative interventions***

Four trials compared exercise therapy with different unimodal conservative interventions.[29 43 52 63] Gobelet et al.[29] compared both an isokinetic exercise programme and an isometric exercise programme with a muscle electrostimulation group. In Clark et al.[43],

**Table 2.** Summary of diagnostic inclusion criteria

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Abd Elhafz 2011** | Diffuse, unilateral anterior knee pain | At least 8 weeks | Exacerbated by activity | | Exacerbated by isometric quadriceps contraction | | |
| **Abrahams 2003** | Unilateral PFPS; retropatellar or anterior knee pain | 8-18 months | Pain on squatting | | Positive direct patellofemoral grind test | | Malalignment as diagnosed by X-ray |
| **Avraham 2007** | Anterior knee pain | | Pain related to prolonged sitting, climbing stairs, and descending stairs | | Positive sign in patellofemoral gliding test; negative McMurray test | Full knee range of motion | No relevant patellofemoral degenerative changes on imaging |
| **Bakhtiary 2008** | Chondromalacia patellae | | Pain during climbing up and down stairs and pain after sitting for a long time with the knee flexed and problem with knee extension after sitting for a long time with the knee flexed and giving away during walking | | Positive Clark test | | |
| **Balci 2009** | Patellofemoral pain | At least 2 months | Between at least 2 activities like longtime sitting, stair/slope climbing and descending, crouching, running, bouncing and jumping | | | | |
| **Clark 2000** | Anterior knee pain | > 3 months | | | | | |

**Table 2.** Summary of diagnostic inclusion criteria (continued)

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Colon 1988** | Patellofemoral chondrosis | | 2 out of the following 6 criteria: persistent aching in the knees while at rest, pain in the knees after sitting with the knees in a flexed position for more than 10 to 20 minutes, occurrence or exaggeration of pain on walking up or down stairs, crepitation in the knees with movement, snapping sensations in the knees upon extension or flexion, locking of the knees, inability to squat down without pain | | Crepitation and compression sign during physical examination | | |
| **De Marche 2014** | Anterior or retropatellar knee pain of 3 or greater on the 10 cm VAS scale | Minimum of 8 weeks | Pain during at least 3 of the following activities: ascending/ descending stairs, squatting, running, kneeling, jumping, and prolonged sitting | | | | |
| **Dolak 2011** | Anterior- or retropatellar knee | More than 1 month | Pain during at least 2 of the activities of stair climbing, hopping, running, squatting, kneeling, and prolonged sitting | | Pain with compression of the patella: pain on palpation of patellar facets | | |
| **Eburne 1996** | Anterior knee pain | | | | | | |

**Table 2.** Summary of diagnostic inclusion criteria (continued)

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Fukuda 2010** | Anterior knee pain | At least the past 3 months | Pain in 2 or more: ascending and descending stairs, squatting, kneeling, jumping, long sitting, isometric knee extension contraction at 60° of knee flexion, and pain on palpation of the medial and/or lateral facet of the patella | | Pain on palpation of the medial and/or lateral facet of the patella | | |
| **Fukuda 2012** | Anterior knee pain | At least the past 3 months | Pain in 2 or more: ascending and descending stairs, squatting, kneeling, jumping, long sitting, isometric knee extension contraction at 60° of knee flexion, and pain on palpation of the medial and/or lateral facet of the patella | | Pain on palpation of the medial and/or lateral facet of the patella | | |

**Table 2.** Summary of diagnostic inclusion criteria (continued)

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Gaffney 1992** | Patellofemoral knee pain, usually retropatellar or medially | | Pain during 1 of the following activities: ascending or descending stairs, squatting or rising from a squat, or sitting with the knee bent at 90 degrees. | | No sign of ligament damage as determined by valgus and varus stress tests, Lachman's test and the anterior drawer of the knee in neutral, internal and external rotation no sign of meniscal involvement as determined by the McMurray and Steinmann test; no involvement of structures around the patella; Patients who had tenderness around the patella either on its margins or chondral surface were included | | |
| **Gobelet 1992** | Retro-patellar chondropathy | | | | | | Without radiological lesion; with or without Wyberg dysplasia 1 or 2 |
| **Hafez 2012** | Chondromalacia patellae | | | | | | |

**Table 2.** Summary of diagnostic inclusion criteria (continued)

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Harrison 1999** | Diagnosed with PFPS | | | | 2 of the following criteria: patellar pain with manual compression of the patella against the femur, patellar tenderness with palpation of the posterior-medial and postero-lateral borders of the patella, patellar pain during resisted dynamic knee extensions, or patellar pain with manual compression of the patella against the femur during isometric knee extensor contraction (Clarke's compression test) | | |
| **Herrington 2007** | Anterior knee pain | At least 1 month | Anterior or retropatellar knee pain on at least 2 of the following activities: prolonged sitting, climbing stairs, squatting, running, kneeling, and hopping/ jumping | Average pain level of 3 or more on a 10-cm visual analogue scale during stepping up and down a 25-cm height | Presence of 2 of the following clinical criteria on assessment: pain during apprehension test, pain during the patellar compression test, and crepitation during the compression test | | |
| **Khayambashi 2012** | Diagnosis of bilateral PFP based on the location of symptoms (peripatellar and/ or retropatellar | At least 6 months | Pain with activities commonly association with this condition, such as stair descent, squatting, kneeling, and prolonged sitting | | | | |

**Table 2.** Summary of diagnostic inclusion criteria (continued)

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Khayambashi 2014** | Diagnosis of PFP based on the location of symptoms (peripatellar and/ or retropatellar | At least 6 months | Pain with activities commonly association with this condition, such as stair descent, squatting, kneeling, and prolonged sitting | | | | |
| **Loudon 2004** | Diagnosis of unilateral PFPS based on pain around or under the patella | At least a 2-month duration | 3 of the 4 criteria: pain in the patellofemoral joint during or after activity, sitting, stair climbing, squatting | | | | |
| **Lun 2005** | Atraumatic unilateral and/ or bilateral peripatellar or retropatellar knee pain | Pain for at least 3 weeks but no greater than 2 years | Patellofemoral knee pain with and/or after activity; inactivity patellofemoral pain and/or stiffness, especially with sitting with knees in a flexed position | | Peripatellar tenderness ±mild inferior patellar pole tenderness | | |
| **Moyano 2013** | Diagnosis of PFP | Pain history more than six months | | | Positive tests: patellofemoral grinding test and patellofemoral compression test | | |
| **Nakagawa 2008** | Anterior or retropatellar knee pain | Pain persistent for at least 4 weeks | Pain during at least 3 of the following activities: ascending/descending stairs, squatting, running, kneeling, hopping/jumping and prolonged sitting | Pain on stepping down from a 25-cm step, or during a double-legged squat | Pain on palpation of the patellar facets | | |

**Table 2.** Summary of diagnostic inclusion criteria (continued)

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Razeghi 2010** | Retro- or peripatellar pain | Insidious onset of pain without a history of trauma persisting for at least 4 weeks | Pain from at least 2 of the following activities: squatting, prolonged sitting, stair climbing, running, kneeling | | Pain during patellar compression test, patellar grind test or medial/ lateral patellar facet tenderness; negative patellar apprehension sign | | |
| **Schneider 2001** | Unilateral retropatellar pain | More than 6 months | | | | | |
| **Song 2009** | Anterior or retropatellar knee pain | For more than 1 month | Pain after performing at least 2 of the following activities: prolonged sitting, stair climbing, squatting, running, kneeling, hopping and jumping, and deep knee flexing | | 2 of the following positive signs of anterior knee pain during the initial physical examination: patellar crepitus, pain following isometric quadriceps femoris muscle contraction against suprapatellar resistance with the knee in slight flexion (Clarke's sign), pain following compression of the patella against the femoral condyles with the knee in full extension (patellar grind test), tenderness upon palpation of the posterior surface of the patella or surrounding structures, and pain following resisted knee extension | | |

**Table 2.** Summary of diagnostic inclusion criteria (continued)

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Taylor 2003** | Localised peri or retropatellar pain originating from the peripatellar tissue or the patellofemoral joint | At least 1 month | Pain during 2 of the following: squatting, running, ascending and/or descending stairs, isometric quadriceps femoris muscle contraction or after sitting for a prolonged period of time with the knee flexed | | | | |
| **Thomee 1997** | Pain from the patellofemoral joint | For a minimum of 6 months | 3 of the following 4 inclusion criteria were fulfilled: pain from the patellofemoral joint during or after activity, during or after sitting, during stair climbing, during squatting | | | | |
| **Van Linschoten 2009** | | Pain > 2 months and < 2 year | At least 3 of the following symptoms: pain when walking up or down stairs; pain when squatting; pain when running; pain when cycling; pain when sitting with knees flexed for a prolonged period of time; grinding of the patella | | A positive clinical patellar test (such as Clarke's test or patellar femoral grinding test) | | |

**Table 2.** Summary of diagnostic inclusion criteria (continued)

| | Inclusion criterion | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Symptom** | **Symptom duration** | **Pain provoking functional activities** | **Pain provoking functional tests** | **Pain provoking clinical tests** | **Other clinical tests** | **Imaging tests** |
| **Witvrouw 2000** | Anterior knee pain | For more than 6 weeks | | | 2 of the following criteria on initial assessment: pain on direct compression of the patella against the femoral condyles with the knee in full extension, tenderness on palpation of the posterior surface of the patella, pain on resisted knee extension, and pain with isometric quadriceps muscle contraction against suprapatellar resistance with the knee in slight flexion | | |
| **Osterasa 2012** | Anterior or retropatellar pain | For more than 2 months | Anterior or retropatellar pain from at least two of the following activities – prolonged sitting, climbing stairs, squatting, running, kneeling and hopping/ jumping | | Pain on palpation of the patellar facets or positive physical tests on grinding of the patella, Clarke's test or patellar crepitus | | |

PFP: patellofemoral pain, PFPS: patellofemoral pain syndrome, VAS: visual analogue scale

the data comparing exercise therapy versus tape were used. In Lun et al.[52], data from a structured home exercise programme were compared with a brace group. Khayambashi et al.[63] compared hip exercises with 1000 mg of Omega-3 and 400 mg of calcium daily.

***Exercise therapy versus multimodal conservative interventions***

Four trials compared exercise therapy with different multimodal conservative interventions including exercises.[48 50 56 62] Harrison et al.[50] compared both a supervised exercise programme and a home exercise programme versus a vastus medialis-specific supervised exercise programme including taping. Eburne and Bannister.[62] compared isometric quadriceps exercise versus the multimodal McConnell regimen comprising different types of exercises and taping. Gaffney et al.[48] compared concentric exercises versus a multimodal intervention comprising excentric exercises and taping. Schneider et al.[56] compared physiotherapeutic exercises based on proprioceptive neuromuscular facilitation versus a special knee resistance-controlled knee splint combined with a special exercise programme.

***Different exercises or exercise programmes***

For further details, see Appendix 2.

***Delivery of exercises or exercise programmes***

Two studies compared supervised exercise programmes with home exercise programmes (Harrison 1999; Loudon 2004).[50 65] Harrison et al.[50] compared a supervised exercise programme with a home exercise programme. Loudon et al.[65] compared a supervised exercise programme and additional home exercises with home exercises and five physiotherapy sessions. A supervised exercise programme was regarded as the intervention group.

***Medium of exercises or exercise programmes***

There were no trials eligible for this comparison.

***Types of exercise or exercise programmes***

Eleven studies compared types of exercises or exercise programmes with each other.[17 29 38 39 41 42 49 51 53 61 66] Of these, four studies compared closed kinetic chain exercises with open kinetic chain exercises.[17 38 41 51] Closed kinetic chain (CKC) exercise was regarded as the intervention group. Two studies tested variants of closed kinetic chain exercises.[39 42] The first listed CKC variant was regarded as the intervention group. Abrahams et al.[39] compared an exercise protocol with thigh adduction and tibia medial rotation during eccentric squat versus a traditional exercise protocol. This study was not pooled due to clinical heterogeneity (participants also had to be diagnosed with malalignment). Balci

et al.[42] compared closed kinetic chain exercises with internally rotated hip versus closed kinetic chain exercises with externally rotated hip. Four studies studied open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action.[29 49 61 66] The first listed kinetic chain exercise group was regarded as the intervention group. Hafez et al.[49] compared eccentric exercises versus concentric exercises. One study compared eccentric exercises versus isometric exercises.[66] One study compared isokinetic exercises versus isometric exercises.[29] One study compared combined isotonic and isometric exercises (pogo stick) versus isometric exercises.[61] One study, which is presented separately in Effects of interventions, compared proprioceptive neuromuscular facilitation stretching and aerobic exercise with classic stretching and quadriceps exercises.[53]

***Target of exercise or exercise programmes***

Nine trials compared different targets of exercises or exercises programmes with each other.[40 44-47 54 55 57 64] Seven trials compared exercises for the knee and hip with exercises for the knee.[40 44 46 47 54 55 57] Two trials compared exercises for the knee with exercises for the hip.[45 64] Since studies investigated similar exercises (i.e. quadriceps exercises or knee exercises) but named them differently, we defined them all as knee exercises. An exercise programme including hip exercises was regarded as the intervention group.

***Duration of exercises or exercise programmes***

There were no trials eligible for this comparison.

***Intensity of exercises of exercise programmes***

Østerås et al.[60] was the only trial that compared high-dose, high repetition medical exercise therapy (MET) with low-dose, low repetition exercises. The high-intensity group was regarded as the intervention group.

## Outcomes

Pain was measured by a visual analogue scale (VAS) or numerical (pain) rating scale (N(P)RS), the McGill pain score[20] and as number of patients experiencing pain. A higher score on VAS, N(P)RS or McGill means worse pain. Pain was scored in various ways: during activity, usual, worst, at rest, after exposure, least, one hour after sport activity, following 30 minutes of sitting with knees flexed, experienced at four different positions of the knee, during isometric knee extension, during triple jump test, during walking, ascending stairs, during running, during jumping, during sports, during squatting, during prolonged sitting, during the night and during isokinetic test. If multiple pain scales were reported only pain in daily life (usual pain), worst pain and pain at activities (e.g. sports, pain during descending stairs) are presented in Effects of interventions. We selected pain at descending for pooling on 'pain at activities' as this outcome measure was present in

most studies eligible for pooling of pain at activity. Functional ability was scored with the Anterior Knee Pain Scale (AKPS)[24], (Modified) Functional Index Questionnaire ((M) FIQ)[22 67], Arpège function scale, Lower Extremity Function Scale (LEFS)[68], (modified) function scale[69], patient specific function score, patellofemoral scale, Bessette and Hunter score[70], WOMAC Osteoarthritis Index [23], Patellofemoral Joint Evaluation Scale[71], Lysholm score[25]) and dichotomously as the number of patients improved in function. If multiple scales for functional ability were measured including the AKPS, we used the latter for pooling. A higher score means better function, except for WOMAC. For consistency, we have inverted the WOMAC scale, in order that a higher score means better function. Functional performance was scored with, for example, the single leg triple hop test, step (down) test, single-limb hop test, bilateral and unilateral squat, anteromedial lunge, step-down dips, leg press, balance and reach and vertical jump test. Studies including participants with bilateral complaints used the most painful side for analysis; thus avoiding unit of analysis issues. Recovery was measured with eight different measures: a Likert scale[27], number of patients no longer troubled by symptoms[43], number of patients with more than 50% improved on pain scale[61], improvement percentage[62], patients' impression of change (ordinal scale of three)[50], subjective success (yes or no)[48], number of patients participating in sports with or without pain[66], and the global rating of change on a 15-point scale.[44] Four trials reported adverse events.[45 58 61 63] Two trials reported that they actively recorded adverse events.[45 61] Most trials measured the outcomes post-intervention; however, a few studies reported on a longer term follow-up period ranging from five months[44] to a maximum of five years.[16]

### Excluded studies

We discussed and excluded 12 potentially eligible studies after consensus[28 72-82] *see* the Characteristics of excluded studies (online available). Two studies were neither randomised nor quasi-randomised.[75 77] Two trials also included patients with osteoarthritis[74 81] and Roush et al[76] also included participants with patellofemoral osteoarthritis, plica syndrome, patellar tendinitis, quadriceps tendinitis and Osgood-Schlatter's disease. Dursun et al.[28] studied the effect of electromyographic (EMG) feedback rather than our interventions of interest; and the other trials studied a combination of interventions and we were unable to extract the effect of exercise alone.[72 73 78-80 82]

### Ongoing studies

There is one ongoing study that investigates the effect of lumbo pelvic stabilisation training in women with patellofemoral pain.[83] This study includes women from 18 to 30 years with patellofemoral pain. The women allocated to the experimental group carry out strengthening exercises for the lumbo-pelvic muscles as well as functional training to correct any dynamic lower limb misalignment. The control group receives a conven-

tional treatment focusing on quadriceps strengthening and stretching of the lower limb muscles. Both groups perform the activities three times a week for eight consecutive weeks.

### Studies awaiting classification

Erel and Ozakn.[37] is reported in Turkish and is awaiting classification pending translation.

### Risk of bias in included studies

We explicitly judged all criteria using: low risk of bias; high risk of bias; and unclear risk of bias (where 'unclear' relates to a lack of information or uncertainty over the potential for bias). Full details of the risk of bias for the 31 trials are provided in Figure 2 and Figure 3.

#### *Allocation*

Random sequence generation was applied in 16 out of 31 trials and was mainly done by computer-generated lists.[17 27 41 43-47 50-54 57 58 60] Six trials were quasi randomized.[61-66] Allocation of the participants was concealed in 12 out of 31 trials mainly by using sealed and opaque envelopes.[17 27 41 44 46 47 51 53 54 57 58 60] Eight trials were at high risk of allocation bias[43 45 61-66], because of matching, because the randomization was done by the physiotherapist/investigator or because allocation concealment was highly unlikely in quasi-randomised trials. In the remaining 11 trials the process of allocation was not specified or unclear.

#### *Blinding*

Blinding of personnel was impractical due to the nature of the intervention, and while standardisation of interactions between personnel and patients (i.e. use of standardised scripts) would have been possible, none of the included studies took this approach. Five studies attempted to address performance bias by means of blinding the patients. Abd Elhafz et al.[38] stated that patients were unaware about the number of groups, randomisation technique or interventions for each group. De Marche et al.[44] and Nakagawa et al.[54] reported that patients were blinded to group allocation. In Khayambashi et al.[63], participants were aware of an alternative treatment group in the study but had no knowledge of intervention details. In Taylor et al.[58], participants were aware that they were receiving what was believed to be 'real' treatments, but were not aware of which treatment was considered better by those delivering the treatments or collecting data. As the success of these measures was uncertain, we rated all as unclear for performance bias. We rated the other studies as high risk on this criterion. The risk of detection bias is inevitably high for studies where patients who have not been blinded to interventions self report on outcomes; but we rated the risk as unclear in four of the five studies when patient blind-

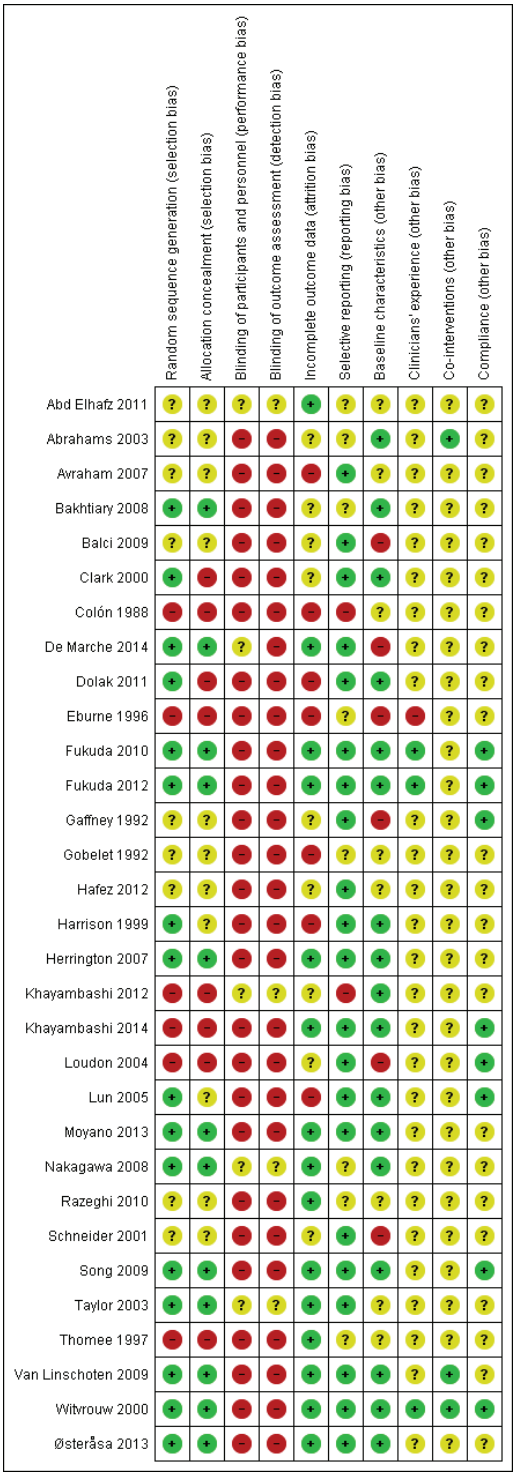



**Figure 2.** 'Risk of bias' summary: review authors' judgement about each risk of bias item for each included study

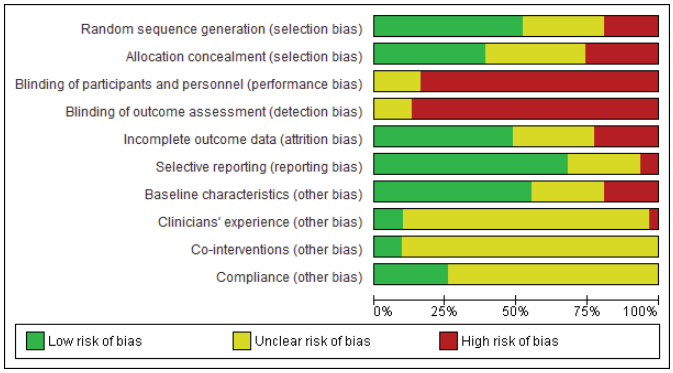



**Figure 3.** 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentage across all included studies

ing had been attempted.[38 54 58 63] We rated the other study reporting patient blinding at high risk because assessor blinding was not done for functional performance.[44]

***Incomplete outcome data***

We judged incomplete outcome data on three items. We considered a dropout rate greater than 20% in the short-term or greater than 30% on follow-up at 12 months or longer, cross-over or dropout due to adverse events to be high risk criteria if no reliable intention-to-treat analysis was carried out. We rated 15 trials low risk since they reported no cross-overs and low dropout rates.[17 27 38 44 46 47 51 53-55 57 58 60 64 66] We rated six trials high risk as they reported a high dropout rate, cross-overs or dropouts due to adverse events and did not report an intention-to treat-analysis.[29 40 50 52 61 62] Avraham et al.[40] reported 29% dropout in the short-term and no intention-to-treat analysis. In Colón et al.[61], a patient dropped out due to increased pain after the intervention, and no intention-to-treat analysis was reported. Eburne and Bannister.[62] reported 29% dropout in the short-term and no intention-to-treat analysis. Gobelet et al.[29] reported 22% dropout, not equally distributed among groups: 12 patients stopped because of ineffectiveness of treatment and no intention-to-treat analysis was reported. Harrison et al.[50] reported a 33% dropout in the short-term, 48% dropout at 12 months and no intention-to-treat analysis. Lun et al.[52] reported that two participants crossed over to another treatment group before three months. These were considered to be withdrawals from the study and no intention-to-treat analysis was reported. We rated one trial high risk because they reported an 18% dropout rate in the short-term, a withdrawal by the investigators for increased pain and an unreliable imputation method.[45] They carried out the last available measure moved forward method, which is generally considered conservative, but there are more reliable methods such as multiple imputation.[84] We rated the remaining nine trials unclear as no further details were reported.

***Selective reporting***

None of the trials, except Van Linschoten et al.[27], published a study protocol. We considered any outcomes of pain and functional ability to be expected outcomes and they had to be reported at all time points in order to get a low risk rating. One study did not report any of these expected outcomes and we therefore rated it high risk.[61] Khayambashi et al.[63] did not provide long-term (six months) results on pain or functional ability for the comparator group and we also rated it high risk. We rated eight studies unclear risk.[29 38 39 41 54 55 62 66] Two studies did not report pain data[29 39] and six studies did not report functional ability data.[38 41 54 55 62 66] The remaining 21 trials did report pain and functional ability data at all time points listed in their methods and we therefore rated them low risk.

***Other potential sources of bias***

We judged all studies on four potential other sources of bias: difference in baseline characteristics, comparability in clinician's experience with the interventions under test, differences in care other than the interventions and compliance with therapy. We rated a total of 17 trials low risk. Twelve trials reported no significant statistical difference in demographic variables and outcome variables.[17 41 43 46 47 51 53 54 57 60 63 64] Five trials reported no statistical significant difference in demographic variables, but did not statistically test the difference in outcome variables.[27 39 45 50 52] Their outcome values seemed similar and therefore we also rated them low risk. We rated six trials high risk since demographics or outcome variables were statistically different or did not seem to be similar.[42 44 48 56 62 65] In Balci et al.[42], the groups differed in height. BMI was not statistically tested, but the difference between groups was 2.3 points. Gaffney et al.[48] reported a significant difference in BMI attributed to the fact that there were slightly more females and some 11 to 13 years old in the concentric group. Eburne and Bannister.[62] reported a significant difference between groups for age. The duration of complaints between groups in the study of De Marche et al.[44] seemed to be rather different with a remarkably higher duration of complaints in the stabilisation group. The VAS in the physiotherapy group was higher compared with the other two groups in the study of Loudon et al.[65] In Schneider et al.[56], there was a difference in VAS at rest across groups. Hafez et al.[49] did report comparable baseline outcome data, but did not report demographics and we rated it unclear. The remaining seven trials did not report on demographics or outcome variables and we therefore rated them unclear. Only Fukuda et al.[46 47] and Witvrouw et al.[17] reported that the therapists were trained and we therefore rated them low risk. We rated Eburne and Bannister.[62] high risk as there were two changes of therapist in the McConnell and three in the isometric quadriceps group. The remaining trials did not report comparability of clinician's experience with the interventions under test. We rated three studies low risk as they reported on co-interventions and the comparability across groups in individual

studies. Abrahams et al.[39] excluded participants who started a co-intervention. Van Linschoten et al.[27] reported that other interventions, like the use of bandages or braces, insoles or ice application, or consumption of medication other than simple analgesics, were allowed in both groups (despite from exercise therapy in the control group) and equally used. Witvrouw et al.[17] reported that no medication was prescribed as part of their treatment. No brace or tape was used by any patient in this study. We rated the remaining trials unclear. Compliance was adequately reported in eight trials and we rated these low risk.[17] Gaffney et al.[48] reported a self reported compliance of 86% in eccentric and 88% in concentric programmes. Fukuda et al.[46 47] excluded patients if they missed treatment sessions. In Khayambashi et al.[64], all participants were required to complete at least 19 out of the 24 treatment sessions (= 80%) to remain in the study. In addition, if a patient missed three consecutive treatment sessions, their participation in the study was terminated. All participants completed the required number of treatment sessions. Loudon et al.[65] asked participants to keep a diary and excluded those who did not complete 90% of the exercise programme. Lun et al.[52] asked participants to document in a journal when the exercises were done and/or when the brace or sleeve was worn. These journals were submitted to the second research assistant on a monthly basis. Overall, the compliance was very good and similar among all treatment groups. Song et al.[57] reported that all exercise intervention participants except one attended all scheduled exercise sessions. One participant in the knee exercises only group completed only half of the intervention and subsequently dropped out of the study due to work commitments. Witvrouw et al[17] reported that every patient followed the exercise programme for the required period of five weeks. Four trials reported a method for aiding compliance but did not report the actual compliance at the end of the intervention.[27 41 43 45] The remaining nine trials did not report on compliance.

### Effects of interventions

See: Summary of findings for the main comparison (Appendix 2). Exercise therapy compared with a control strategy (no treatment, placebo or waiting list controls) for patellofemoral pain syndrome; Summary of findings 2 (Appendix 2) Supervised exercises compared with home exercises for patellofemoral pain syndrome; Summary of findings 3(Appendix 2) Closed kinetic chain exercises compared with open kinetic chain exercises for patellofemoral pain syndrome; Summary of findings 4(Appendix 2) Target of exercise: hip + knee versus knee exercises for treating patellofemoral pain syndrome; Summary of findings 5(Appendix 2) Target of exercise: hip versus knee exercises for treating patellofemoral pain syndrome; Summary of findings 6(Appendix 2) High-intensity versus low intensity exercise programmes for patellofemoral pain syndrome.

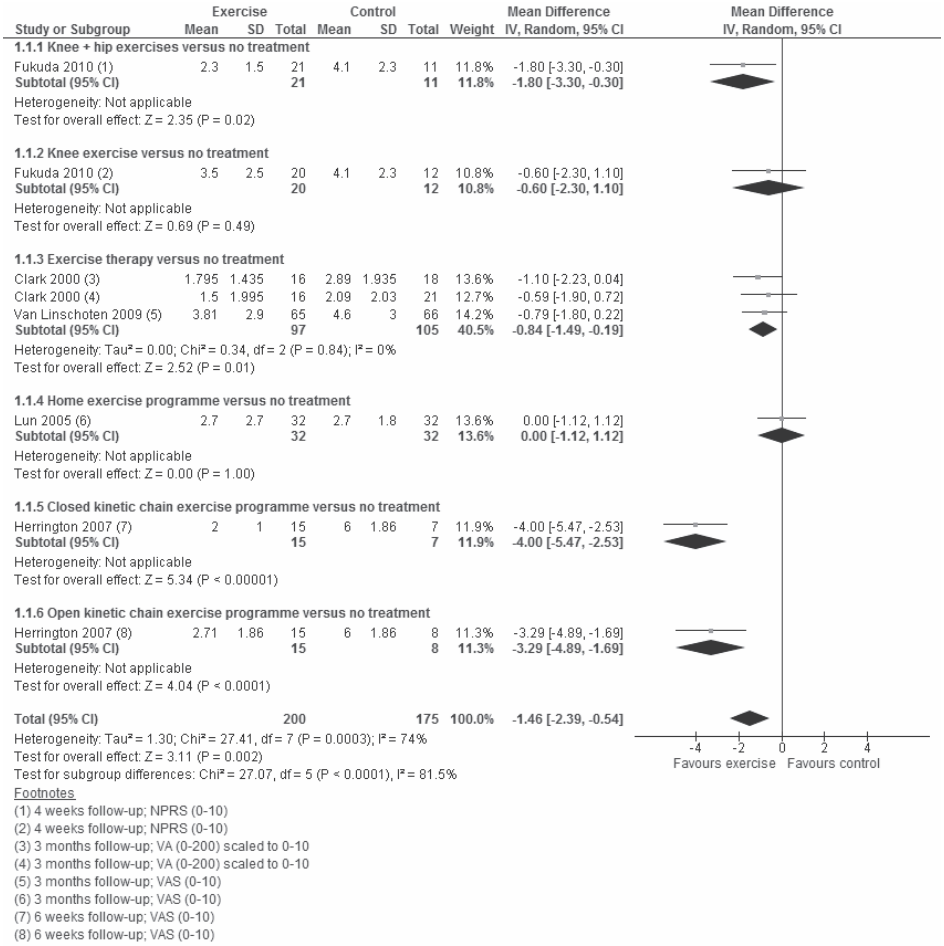
***Exercise therapy versus control (no treatment, placebo or waiting list controls)***

Ten studies compared exercise therapy with a control strategy (no treatment, placebo or waiting list controls).[27 39 43 46 51-53 57 58 65] In the analyses, these are subgrouped according to the main characteristic of exercise therapy. Although, with the exception of Abrahams et al.[39], we have pooled the results of these heterogeneous studies, the pooled result should be taken as illustrative, especially where the heterogeneity is statistically significant. We presented Abrahams et al.[39] in a separate analysis (malalignment group) because of clear clinical heterogeneity since participants also had to be diagnosed with malalignment. Where a trial tested two separate exercise interventions and one control group, we split the data in the control group so that the individual results of the each intervention could be presented while avoiding double counting of those in the control group.[46 51 57] We extracted standard deviations for pain and function[51] from error bars, which we interpreted to be standard deviations (SDs), in graphs presented in the publications of this trial.

***Knee pain in the short term***

*During activity (0 to 10 scale; higher scores mean worse pain)*

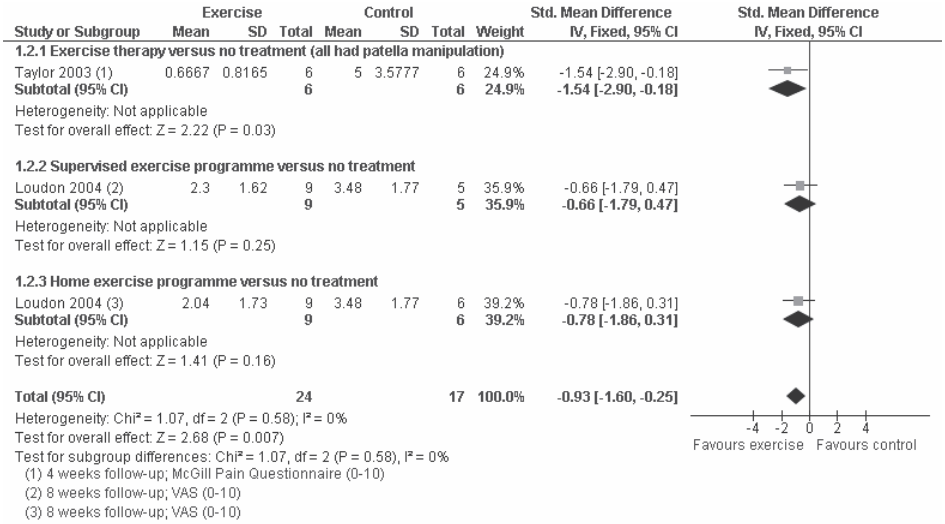
Pooled data from five studies[27 43 46 51 52] (375 participants) showed a mean difference (MD) of -1.46 favouring exercise therapy, 95% confidence interval (CI) -2.39 to -0.54, P value = 0.002, random-effects model used due to statistical heterogeneity (P value = 0.0003; $I^2$ = 74%); very low quality evidence due to risk of bias, imprecision and inconsistency; *see* Analysis 1.1. The results were homogeneous (P value = 0.55 and I2 = 0%) upon removal of Herrington et al.[51], but with a reduced effect size (MD -0.76, 95% CI -1.26 to -0.25, P value = 0.003).




**ANALYSIS 1.1** Exercise therapy versus control, outcome: 1.1 Sum: pain during activity continuous short-term

*Usual pain (0 to 10 scale; higher scores mean worse pain)*

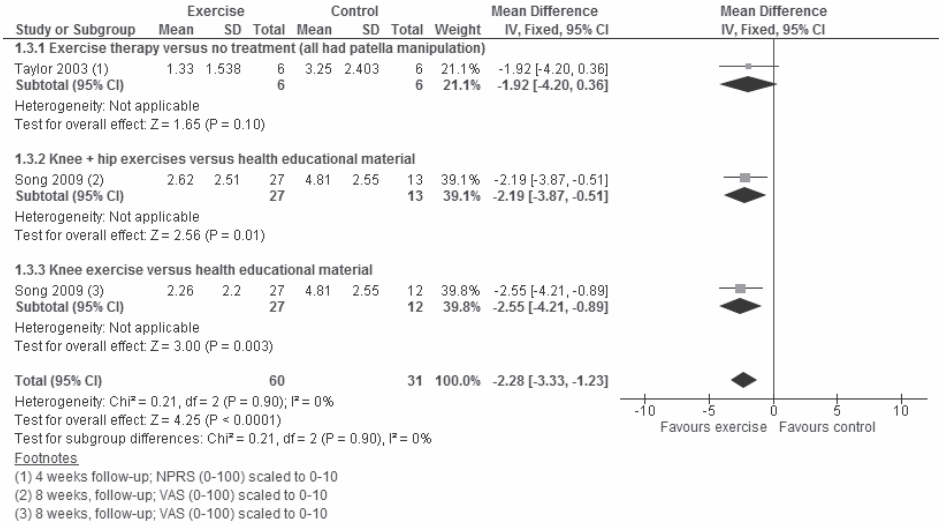
Pooled data from two studies[58 65] (41 participants) showed a standardised mean difference (SMD) of -0.93 favouring exercise therapy, 95% CI -1.60 to -0.25, P value = 0.007; very low quality evidence due to serious risk of bias and imprecision; *see* Analysis 1.2.




**ANALYSIS 1.2** Comparison I Exercise therapy versus control, outcome 2 Usual pain (short term)

*Worst pain (0 to 10 scale; higher scores mean worse pain)*

Pooled data from two studies[57 58] (91 participants) resulted in a MD of -2.28 favouring exercise therapy, 95% CI -3.33 to -1.23, P value < 0.0001; low quality evidence due to risk of bias and imprecision; *see* Analysis 1.3.

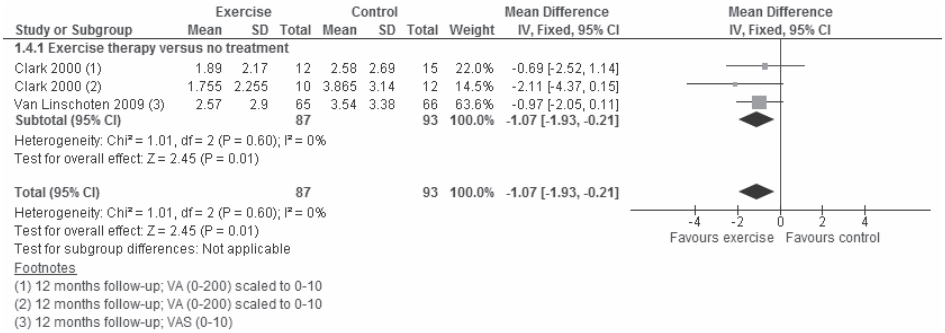



**ANALYSIS 1.3** Comparison I Exercise therapy versus control, outcome 3 Worst pain (short term)

***Knee pain in the long term***

*During activity (0 to 10 scale; higher scores mean worse pain)*

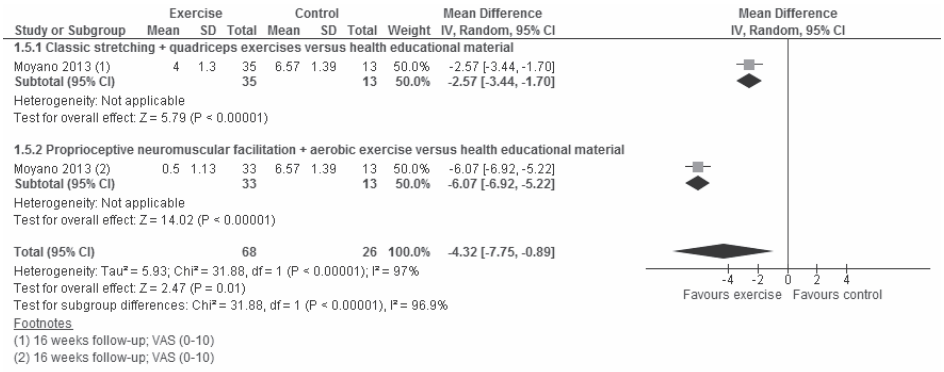
Pooled data from two studies[27 43] (180 participants) resulted in a MD of -1.07 favouring exercise therapy, 95% CI -1.93 to -0.21, P value = 0.01; very low quality evidence due to serious risk of bias and imprecision; *see* Analysis 1.4.




**ANALYSIS 1.4** Comparison I Exercise therapy versus control, outcome 4 Pain during activity (short term)

*Usual pain (visual analogue scale (VAS) 0 to 10; higher scores mean worse pain)*

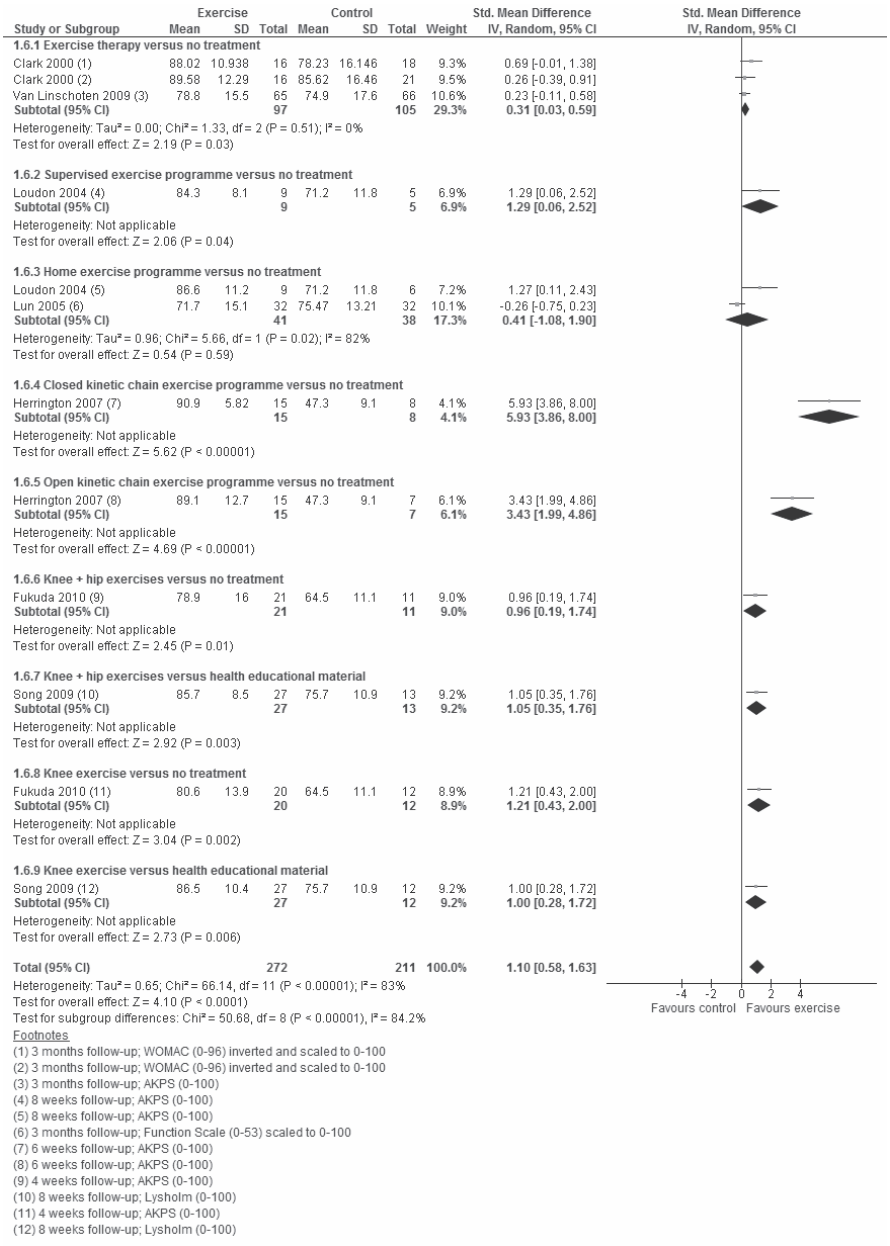
Pooled data from two exercise interventions tested by one study[53] (94 participants) showed a MD of -4.32 favouring exercise therapy, 95% CI -7.75 to -0.89, P value < 0.00001; random-effects model used due to statistical heterogeneity (heterogeneity P value < 0.00001, $I^2$ = 97%); very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 1.5.




**ANALYSIS 1.5** Comparison I Exercise therapy versus control, outcome 5 Usual pain (long term)

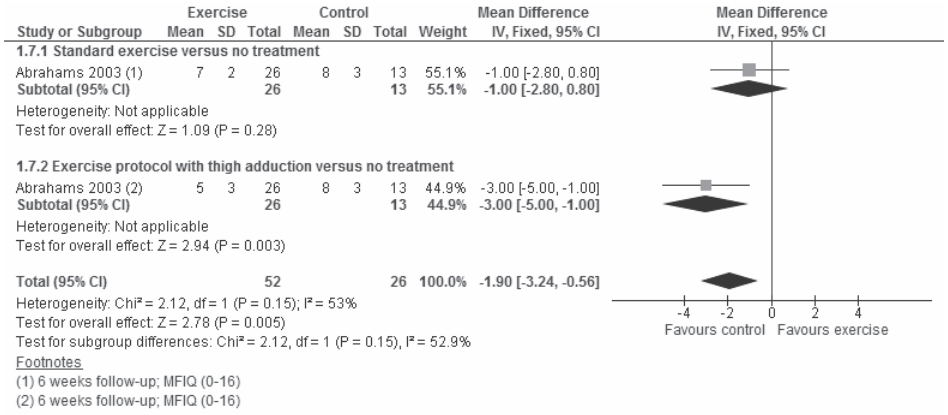
***Functional ability in the short term (0 to 100 scale; modified Functional Index Questionnaire (MFIQ) 0 to 16; higher scores mean better function)***

Based on a 0 to 100 scale (higher scores mean better function), pooled data from seven studies[27 43 46 51 52 57 65] (483 participants) showed a SMD of 1.10 favouring exercise therapy, 95% CI 0.58 to 1.63, P value < 0.0001, random-effects model used due to statistical heterogeneity (P value < 0.00001, $I^2$ = 83%); very low quality evidence due to risk of bias and serious inconsistency; *see* Analysis 1.6. The results did not became homogeneous after excluding any single study.




**ANALYSIS 1.6** Comparison I Exercise therapy versus control, outcome 6 Functional ability (short term)

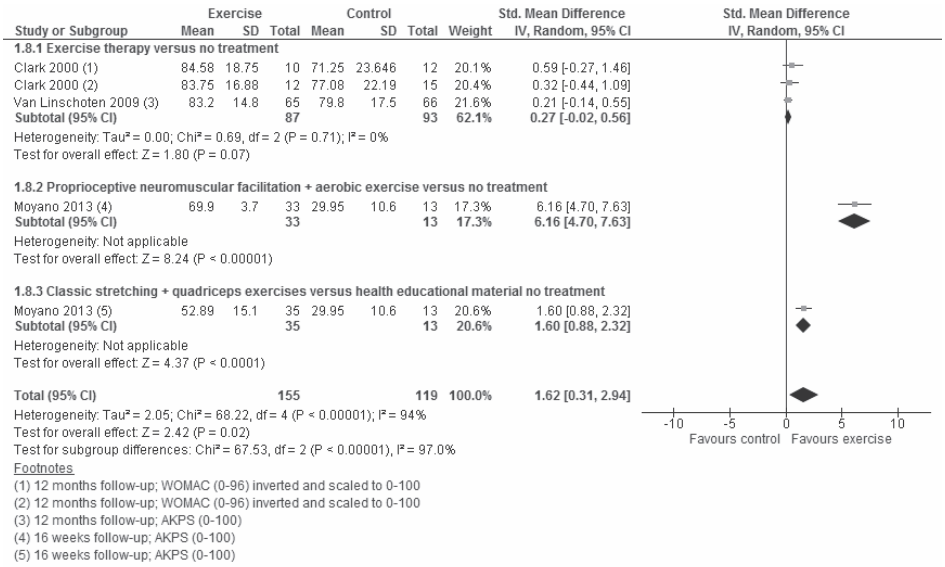
Based on the MFIQ (0 to 16), Abrahams et al.[39] (78 participants) reported a MD of -1.90, favouring a control strategy, 95% CI -3.24 to -0.56, P value = 0.005; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 1.7.




**ANALYSIS 1.7** Comparison I Exercise therapy versus control, outcome 7 Functional ability (short term), all participants had malalignment

***Functional ability in the long term (0 to 100 scale; patient specific function scale; higher scores mean better function)***

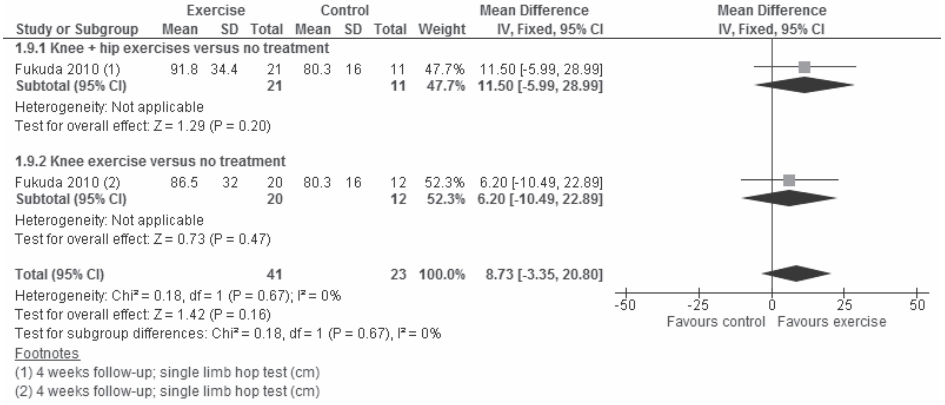
Pooled data from three studies[27 43 53] (274 participants) resulted in a SMD of 1.62, favouring exercise therapy, 95% CI 0.31 to 2.94, P value = 0.02; random-effects model used due to statistical heterogeneity (heterogeneity P value < 0.00001, $I^2$ = 94%); very low quality evidence due to risk of bias, imprecision and inconsistency; *see* Analysis 1.8. The results were homogeneous ($I^2$ = 0%) upon removal of Moyano et al.[53], but smaller in effect size (SMD0.27, 95%CI -0.02 to 0.56, P value = 0.07). Taylor et al.[58] (12 participants) reported that there were no statistically significant differences between groups for patient specific function scale scores for three different activities.




**ANALYSIS 1.8** Comparison I Exercise therapy versus control, outcome 8 Functional ability (long term)

***Functional performance in the short term (single-limb hop test; bilateral squat)***

Fukuda et al.[46] (64 participants) reported for the single-limb hop test a MD of 8.73 cm favouring exercise therapy, 95% CI -3.35 to 20.80, P value = 0.16; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 1.9.

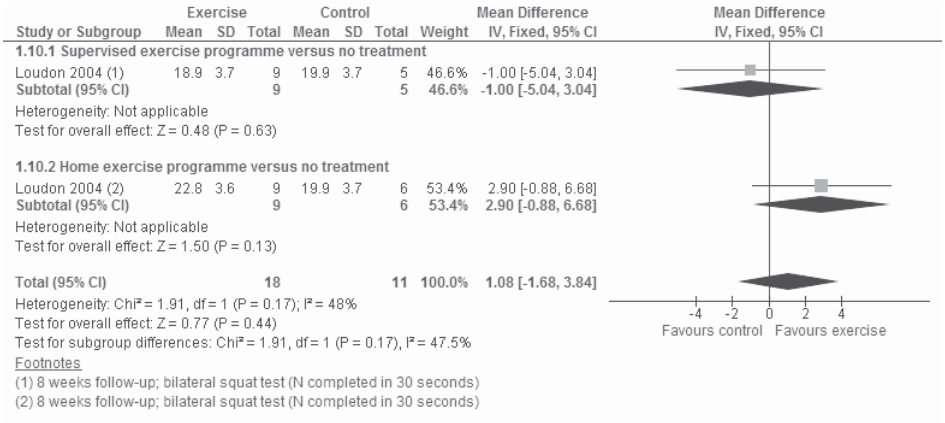



**ANALYSIS 1.9** Comparison I Exercise therapy versus control, outcome 9 Functional performance (short term), single leg hop test

Loudon et al.[65] (29 participants) reported for the bilateral squat test (number completed in 30 seconds) a MD of 1.08 favouring exercise therapy, 95% CI -1.68 to 3.84, P value =

0.44; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 1.10.

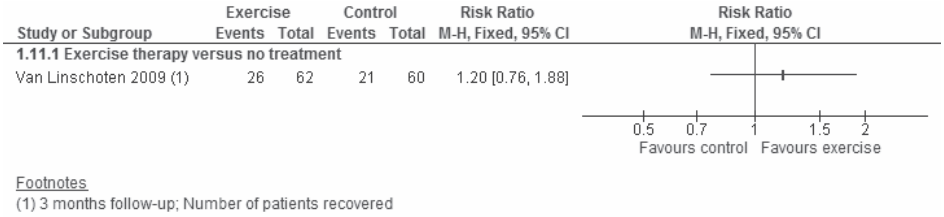
Full data were not available for the four other functional performance tests, based on limb symmetry index, measured by Loudon et al.[65] (29 participants): anteromedial lunge, step-down dip, leg press, and balance and reach.




**ANALYSIS 1.10** Comparison I Exercise therapy versus control, outcome 10 Functional performance (short term), bilateral squat test

***Recovery in the short term (number of participants no longer troubled by symptoms)***

Van Linschoten et al.[27] (122 participants) reported that 26/62 participants in the exercise group versus 21/60 participants in the tape group were no longer troubled by pain at three months; risk ratio (RR) 1.20 favouring exercise therapy, 95% CI 0.76 to 1.88, P value = 0.43; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 1.11.

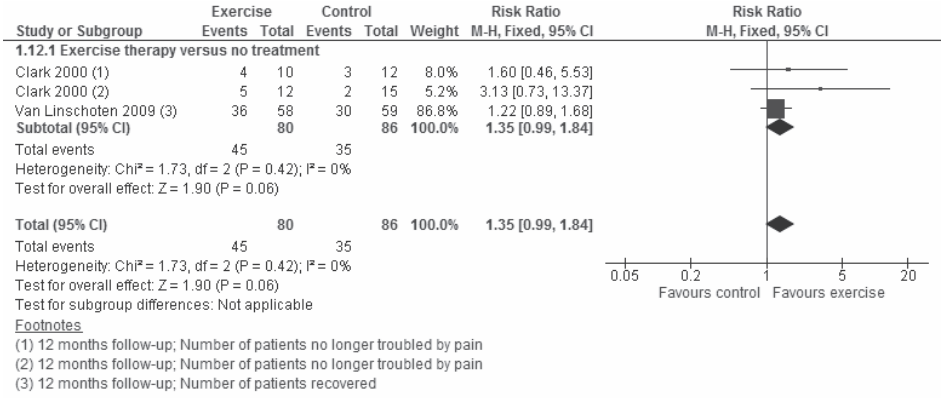



**ANALYSIS 1.11** Comparison I Exercise therapy versus control, outcome 11 Recovery (short term)

***Recovery in the long term (number of patients recovered and number of patients no longer troubled by symptoms)***

Pooled data from two studies[27 43] (166 participants) reported that 45/80 participants in the exercise group versus 35/86 participants in the tape group were no longer troubled

by pain at 12months;RR1.35 favouring exercise therapy, 95% CI 0.99 to 1.84, P value = 0.06; very low quality evidence due to serious risk of bias and imprecision; *see* Analysis 1.12.




**ANALYSIS 1.12** Comparison I Exercise therapy versus control, outcome 12 Recovery (long term)

### *Adverse events*

Taylor et al.[58] reported no harmful side effects.

### ***Exercise therapy versus different conservative treatments: exercise therapy versus unimodal conservative interventions***

For convenience, the available data for five different comparisons, tested within four trials[29 43 52 63], are presented together in Analyses 2.1 to 2.5 but without pooling. The five comparisons are presented in turn below. None of the four trials reported on functional performance or adverse events.

### ***Hip exercises versus 1000 mg of Omega-3 and 400 mg of calcium***

One study evaluated this comparison.[63] It did not report on functional performance or aspects of recovery and did not provide long-term (six months) results on pain or functional ability for the comparator group.

### *Knee pain in the short term*

*During activity (VAS 0 to 10; higher scores mean worse pain)*

Khayambashi et al.[63] (28 participants) reported a MD of -5.30 favouring hip exercises, 95%CI -6.90 to -3.70, P value < 0.00001; very low quality evidence due to serious risk of bias and serous imprecision; *see* Analysis 2.1.

***Functional ability in the short term (WOMAC 0 to 96) (inverted score; higher scores mean better function)***

Khayambashi et al.[63] (28 participants) reported a MD of 49.20 favouring hip exercises, 95%CI 38.49 to 59.91, P value < 0.00001; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 2.3.

***Adverse events***

Khayambashi et al.[63] stated that no adverse effects were reported.

***Home exercise programme versus brace***

The one study making this comparison did not report on long-term outcome, functional performance, aspects of recovery or adverse events.[52]

***Knee pain in the short term***

*During activity (VAS 0 to 10; higher scores mean worse pain)*

Lun et al.[52] (66 participants) reported a MD of 0.20 favouring bracing, 95% CI -0.82 to 1.22, P value = 0.70; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 2.1.

***Functional ability in the short term (function scale 0 to 53; higher scores mean better function)***

Lun et al.[52] (66 participants) reported a MD of 2.00 favouring a home exercise programme, 95% CI -1.88 to 5.88, P value = 0.31; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 2.3.

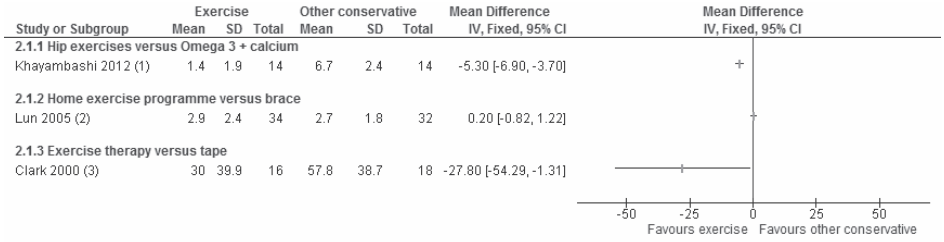
***Exercise therapy versus tape***

One study made this comparison.[43] It did not report on functional performance or adverse events.

***Knee pain in the short term***

*During activity (VAS 0 to 200; higher scores mean worse pain)*

Clark et al.[43] (34 participants) reported a MD of -27.80 favouring exercise therapy, 95%CI -54.29 to -1.31, P value = 0.04; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 2.1.



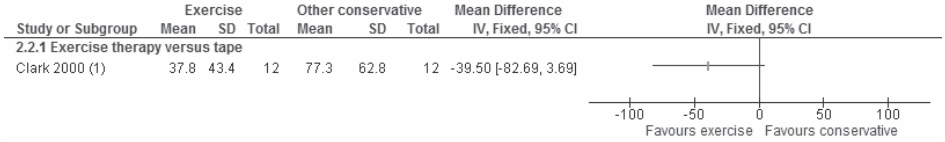

Footnotes
(1) 8 weeks follow-up; VAS (0-10)
(2) 3 months follow- up; VAS (0-10)
(3) 3 months follow-up; VA (0-200)

**ANALYSIS 2.1** Comparison 2 Exercise therapy versus unimodal conservative interventions, Outcome 1 pain during activity (short term)

### *Knee pain in the long term*

*During activity (VAS 0 to 200; higher scores mean worse pain)*

Clark et al.[43] (24 participants) reported a MD of -39.50 favouring exercise therapy, 95% CI -82.69 to 3.69, P value = 0.07; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 2.2.

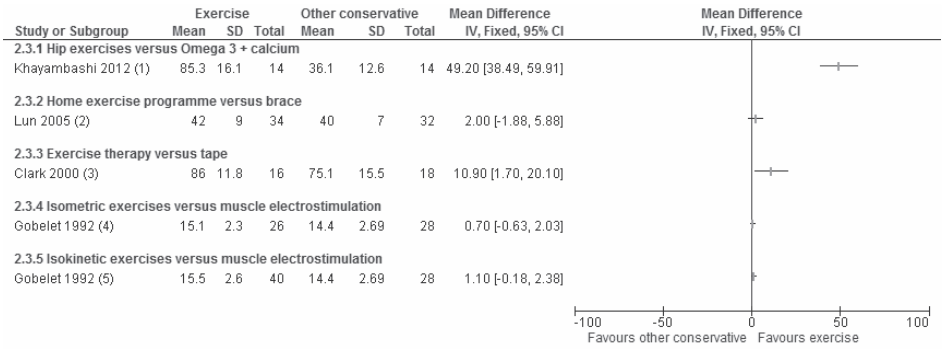



Footnotes
(1) 12 months follow-up; VA (0-200)

**ANALYSIS 2.2** Comparison 2 Exercise therapy versus unimodal conservative interventions, Outcome 2 pain during activity (long term)

### *Functional ability in the short term (WOMAC 0 to 96) (inverted score; higher scores mean better function)*

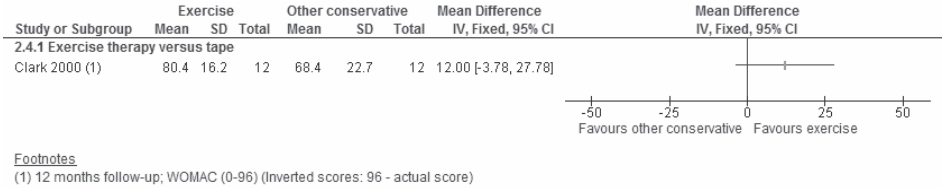
Clark et al.[43] (34 participants) reported a MD of 10.90 favouring exercise therapy, 95% CI 1.70 to 20.10, P value = 0.02; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 2.3.




**ANALYSIS 2.3** Comparison 2 Exercise therapy versus unimodal conservative interventions, Outcome 3 Functional ability in the short term (short term)

### *Functional ability in the long term (WOMAC 0 to 96) (inverted scores; higher scores mean better function)*

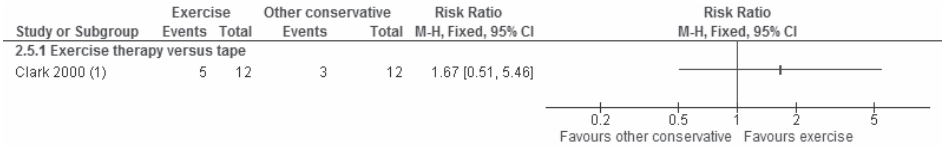
Clark et al.[43] (24 participants) reported a MD of 12.00 favouring exercise therapy, 95% CI -3.78 to 27.78, P value = 0.14; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 2.4.




**ANALYSIS 2.4** Comparison 2 Exercise therapy versus unimodal conservative interventions, Outcome 4 Functional ability (long term)

### *Recovery (number of participants no longer troubled by symptoms)*

Clark et al.[43] reported that 5/12 participants in the exercise group versus 3/12 participants in the tape group were no longer troubled by pain at 12 months; RR 1.6 favouring exercise therapy, 95% CI 0.51 to 5.46, P value = 0.40; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 2.5.




Footnotes
(1) 12 months follow-up; Number of patients no longer troubled by pain

**ANALYSIS 2.5** Comparison 2 Exercise therapy versus unimodal conservative interventions, Outcome 5 Recovery (long term)

***Isometric exercises versus muscle electrostimulation***

The one study making this comparison did not report on long-term outcome, knee pain (during activity, usual or worse), functional performance, aspects of recovery or adverse events.[29]

***Functional ability in the short term (Arpège function scale 0 to 18; higher scores mean better function)***

Gobelet et al.[29] (54 participants) reported a MD of 0.70 favouring isometric exercises, 95%CI -0.63 to 2.03, P value = 0.30; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 2.3.

***Isokinetic exercises versus muscle electrostimulation***

The one study making this comparison did not report on long-term outcome, knee pain (during activity, usual or worse), functional performance, aspects of recovery or adverse events.[29]

***Functional ability in the short term (Arpège function scale 0 to 18; higher scores mean better function)***

Gobelet et al.[29] (68 participants) reported a MD of 1.10 favouring isokinetic exercises, 95%CI -0.18 to 2.38, P value = 0.09; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 2.3

***Exercise therapy versus different conservative treatments: exercise therapy versus multimodal conservative interventions***

For convenience, the available data for five different comparisons, tested within four trials[48 50 56 62], are presented together in Analyses 3.1 to 3.5 but without pooling. The five comparisons are presented in turn below. None of the four trials reported on functional performance. Only Eburne and Bannister.[62] reported on adverse events but did not report on denominators. Harrison et al.[50] presented functional ability via a Functional Index Questionnaire (FIQ) modified score and a non-validated patellofemoral scale. Therefore the FIQ is presented.

***Isometric quadriceps exercises versus McConnell regimen including exercises and tape***

One study made this comparison.[62] It did not report on long-term outcome, knee pain during activity, usual pain or worse pain, functional ability or functional performance.

***Knee pain in the short term***

*Pain experienced at four different positions of the knee*

Eburne and Bannister.[62] (53 participants) reported that a positive McConnell critical test (pain experienced at four different positions of the knee) was "abolished" in 25% of participants in the isometric exercises group and 30% in the McConnell regimen group; very low quality evidence due to serious risk of bias and imprecision.

***Recovery in the short term***

Eburne and Bannister.[62] concluded that there was improvement in 50% of each group; very low quality evidence due to serious risk of bias, indirectness and imprecision.

***Adverse events***

Eburne and Bannister.[62] (75 participants) did not report the numbers assigned. However one participant was withdrawn from the trial for surgery (group not stated) and "three due to severe allergy to the strapping" (presumably in the McConnell regimen group); very low quality evidence due to serious risk of bias and imprecision.

***Supervised exercise programme versus vastus medius specific exercise programme plus taping***

The one study making this comparison did not report on adverse events.[50]

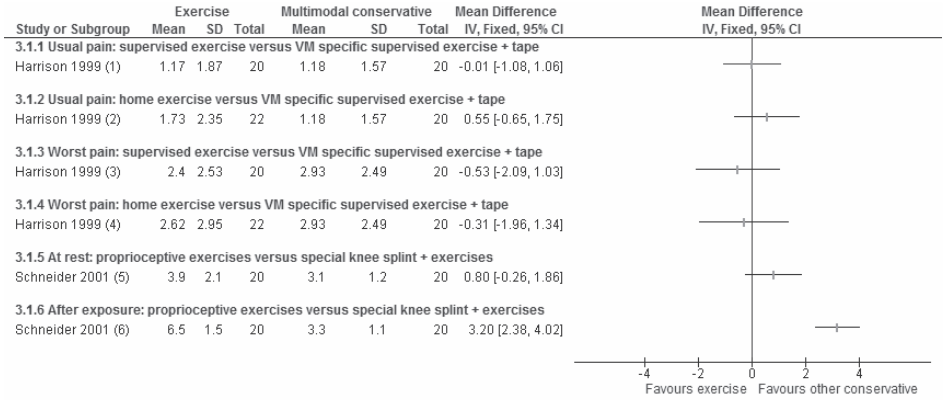
***Knee pain in the short term***

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (40 participants) reported a MD of -0.01 favouring supervised exercise, 95% CI -1.08 to 1.06, P value = 0.99; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.1.

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (40 participants) reported a MD of -0.53 favouring supervised exercise, 95% CI -2.09 to 1.03, P value = 0.50; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.1.




**ANALYSIS 3.1** Comparison 3 Exercise therapy versus multimodal conservative interventions, Outcome 1 Pain (short term)

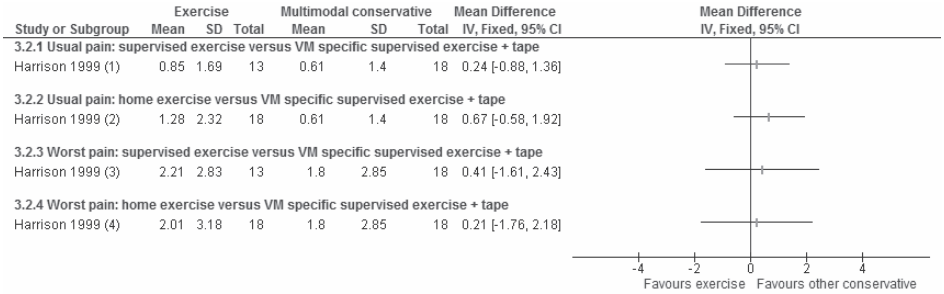
### *Knee pain in the long term*

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (31 participants) reported a MD of 0.24 favouring vastus medius specific supervised exercise plus tape, 95%CI -0.88 to 1.36, P value = 0.68; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.2.

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (31 participants) reported a MD of 0.41 favouring vastus medius specific supervised exercise plus tape, 95%CI -1.61 to 2.43, P value = 0.69; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.2.

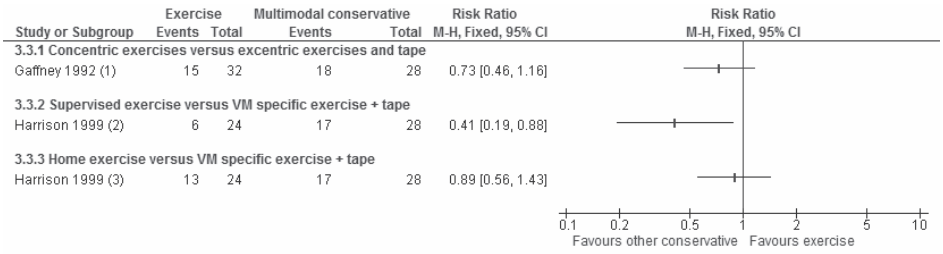



Footnotes
(1) 12 months follow-up; VAS (0-10)
(2) 12 months follow-up; VAS (0-10)
(3) 12 months follow-up; VAS (0-10)
(4) 12 months follow-up; VAS (0-10)

**ANALYSIS 3.2** Comparison 3 Exercise therapy versus multimodal conservative interventions, Outcome 2 Pain (long term)

***Functional ability in the short term (FIQ modified 0 to 16 scale; higher scores mean better function)***

Harrison et al.[50] (54 participants) presented the numbers of participants with scores split into four FIQ categories (0 to 4, 5 to 8, 9 to 12, 13 to 16). Although we present the data for those in the top (13 to 16, best function) category, the ordinal nature of the data and extent of the loss to follow-up in both groups raises serious questions as to the validity of these results (6/24 versus 17/28; RR 0.41 favouring a vastus medius specific exercise programme plus taping, 95% CI 0.19 to 0.88, P value = 0.02; very low quality evidence due to risk of bias, indirectness and serious imprecision; *see* Analysis 3.3.

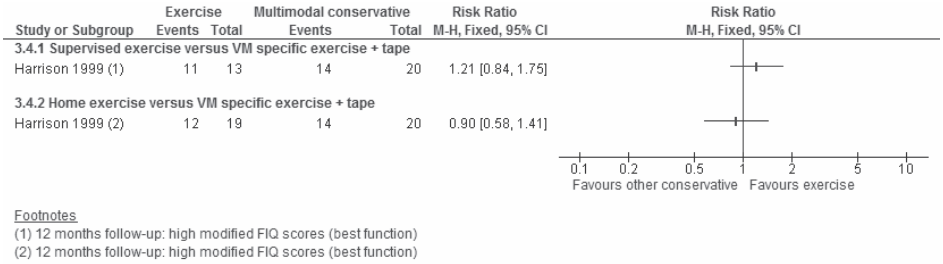



Footnotes
(1) 8 weeks follow-up; Number of patients improved
(2) 1 month follow-up: high modified FIQ scores (best function)
(3) 1 month follow-up: high modified FIQ scores (best function)

**ANALYSIS 3.3** Comparison 3 Exercise therapy versus multimodal conservative interventions, Outcome 3 Functional ability (short term)

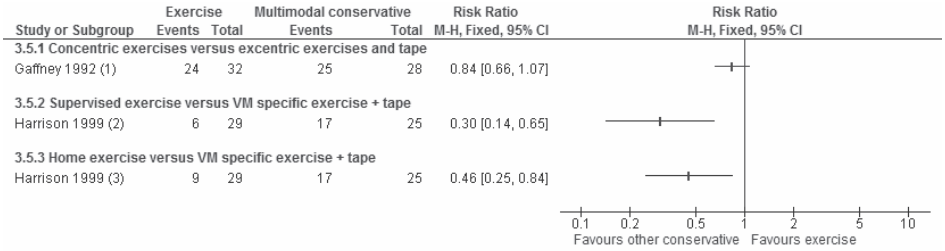
***Functional ability in the long term (FIQ modified 0 to 16 scale; higher scores mean better function)***

As described above, Harrison et al.[50] (33 participants) presented modified FIQ data split into four categories. The results for participants in the best function category (13 to 16) were: 11/13 versus 14/20; RR 1.21 favouring a supervised exercise programme, 95% CI 0.84 to 1.75, P value = 0.31; very low quality evidence due to risk of bias, indirectness and serious imprecision; *see* Analysis 3.4.




Footnotes
(1) 12 months follow-up: high modified FIQ scores (best function)
(2) 12 months follow-up: high modified FIQ scores (best function)

**ANALYSIS 3.4** Comparison 3 Exercise therapy versus multimodal conservative interventions, Outcome 4 Functional ability (long term)

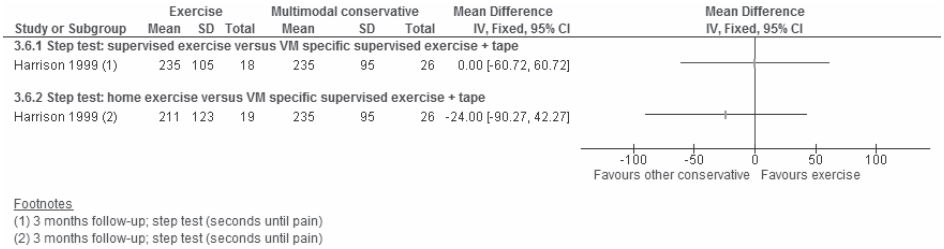



Footnotes
(1) 8 weeks follow-up; Number of participants rating treatment a success
(2) 1 month follow-up: participants' rating of significant improvement
(3) 1 month follow-up: participants' rating of significant improvement

**ANALYSIS 3.5** Comparison 3 Exercise therapy versus multimodal conservative interventions, Outcome 5 Recovery (short term)

***Functional performance in the short term (step test)***

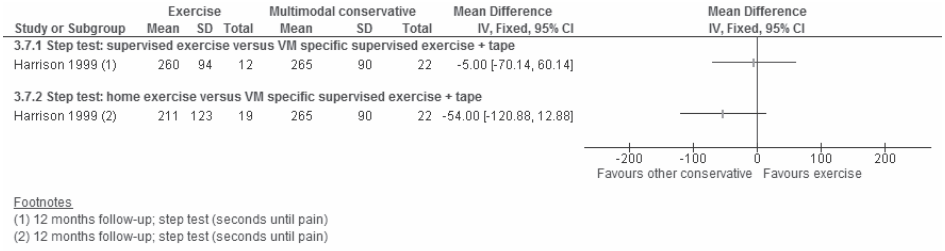
Harrison et al.[50] (44 participants) performed a step test (time until pain) and reported a MD of 0.00 seconds favouring neither intervention, 95%CI -60.72 to 60.72, P value = 1.00; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.6.




**ANALYSIS 3.6** Comparison 3 Exercise therapy versus multimodal conservative interventions, Outcome 6 Functional performance (short term)

### *Functional performance in the long term (step test)*

Harrison et al.[50] (34 participants) performed a step test (time until pain) and reported a MD of -5.00 seconds favouring a vastus medius specific exercise programme plus taping, 95% CI -70.14 to 60.14, P value = 0.88; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.7.




**ANALYSIS 3.7** Comparison 3 Exercise therapy versus multimodal conservative interventions, Outcome 7 Functional performance (long term)

### *Recovery in the short term*

Harrison et al.[50] (54 participants) reported that 6/29 participants in the supervised exercise programme versus 17/25 participants in the vastus medius specific exercise programme plus taping reported significant improvement; RR 0.30 favouring the vastus medius specific exercise programme plus taping, 95% CI 0.14 to 0.65, P value = 0.002; very low quality evidence due to serious risk of bias, indirectness and imprecision; *see* Analysis 3.5.

### ***Home exercise programme versus vastus medius specific exercise programme plus taping***

The one study making this comparison did not report on adverse events.[50]

***Knee pain in the short term***

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (42 participants) reported a MD of 0.55 favouring vastus medius specific supervised exercise plus tape, 95%CI -0.65 to 1.75, P value = 0.37; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.1.

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (42 participants) reported a MD of -0.31 favouring home exercise, 95% CI -1.96 to 1.34, P value = 0.71; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.1.

***Knee pain in the long term***

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (36 participants) reported a MD of 0.67 favouring vastus medius specific supervised exercise plus tape, 95%CI -0.58 to 1.92, P value = 0.29; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.2.

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (36 participants) reported a MD of 0.21 favouring vastus medius specific supervised exercise plus tape, 95%CI -1.76 to 2.18, P value 0.83; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.2.

***Functional ability in the short term (FIQ modified 0 to 16 scale; higher scores mean better function)***

Harrison et al.[50] (52 participants) presented the numbers of participants with scores split into four FIQ categories (0 to 4, 5 to 8, 9 to 12, 13 to 16). Although we present the data for those in the top (13 to 16, best function) category, the ordinal nature of the data and extent of the loss to follow-up in both groups raises serious questions as to the validity of these results (13/24 versus 17/28; RR 0.89 favouring the vastus medius specific exercise programme plus taping, 95% CI 0.56 to 1.43, P value = 0.64; very low quality evidence due to risk of bias, indirectness and serious imprecision; *see* Analysis 3.3.

***Functional ability in the long term (FIQ modified 0 to 16 scale; higher scores mean better function)***

As described above, Harrison et al.[50] (39 participants) presented modified FIQ data split into four categories. The results for participants in the best function category (13 to 16) were: 12/19 versus 14/20; RR 0.90 favouring the vastus medius specific exercise programme plus taping, 95%CI 0.58 to 1.41, P value = 0.65; very low quality evidence due to risk of bias, indirectness and serious imprecision; *see* Analysis 3.4.

***Functional performance in the short term (step test)***

Harrison et al.[50] (45 participants) performed a step test (time until pain) and reported a MD of -24.00 seconds favouring the vastus medius specific exercise programme plus taping, 95% CI -90.27 to 42.27, P value = 0.48; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.6.

***Functional performance in the long term (step test)***

Harrison et al.[50] (31 participants) performed a step test (time until pain) and reported a MD of -54.00 seconds favouring the vastus medius specific exercise programme plus taping, 95% CI -120.88 to 12.88, P value = 0.11; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 3.7.

***Recovery in the short term***

Harrison et al.[50] (54 participants) reported that 9/29 participants in the home exercise programme versus 17/25 participants in the vastus medius specific exercise programme plus taping reported significant improvement; RR 0.46 favouring the vastus medius specific exercise programme plus taping, 95% CI 0.25 to 0.84, P value = 0.001; very low quality evidence due to serious risk of bias, indirectness and imprecision; *see* Analysis 3.5.

***Concentric exercises versus eccentric exercises and tape***

One study made this comparison.[48] It did not report on long-term outcome, functional performance or adverse events.

***Knee pain in the short term***

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Gaffney et al.[48] (60 participants) reported no significant between group difference in mean maximum pain values (concentric 2.64 versus eccentric 2.86); very low quality evidence due to serious risk of bias and imprecision.

***Functional ability in the short term (number of patients improved)***

Gaffney et al.[48] (60 participants) reported that 15/32 in the concentric exercises and 18/28 in the eccentric plus tape group had improved function; RR 0.73 favouring the eccentric plus tape group, 95% CI 0.46 to 1.16, P value = 0.18; very low quality evidence due to serious risk of bias and imprecision; *see* Analysis 3.3.

***Recovery in the short term (participant-rated success)***

Gaffney et al.[48] (60 participants) reported that 24/32 in the concentric exercises and 25/28 in the eccentric plus tape group rated their outcome as a success; RR 0.84 favour-

ing the eccentric plus tape group, 95% CI 0.66 to 1.07, P value = 0.15; very low quality evidence due to serious risk of bias, indirectness and imprecision; *see* Analysis 3.3.

***Physiotherapeutic exercises based on proprioceptive neuromuscular facilitation versus special knee splint combined with exercises***

One study (40 participants) made this comparison.[56] It did not report on long-term outcome, knee pain during activity, usual pain or worse pain, functional performance, aspects of recovery or adverse events.

***Knee pain in the short term***

*Pain at rest and pain after exposure (VAS 0 to 10; higher scores mean worse pain)*

Schneider et al.[56] (40 participants) reported on knee pain at rest and "after exposure" to some muscle tests. Schneider et al.[56] reported a MD of 0.80 favouring special knee splint and exercises for pain at rest, 95% CI -0.26 to 1.86, P value = 0.83; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 3.1

For pain after exposure, Schneider et al.[56] reported a MD of 3.20 favouring special knee splint and exercises for pain at rest, 95% CI 2.38 to 4.02, P value < 0.00001; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 3.1.

***Functional ability in the short term (Bessette and Hunter score: 0 to 100; higher scores mean better function)***

Schneider et al.[56] (40 participants) reported significant improvements in both groups from53 to 69 points in the physiotherapeutic exercises based on proprioceptive neuromuscular facilitation group and from 53 to 72 points in the group receiving a special knee splint combined with exercises. However, Schneider et al.[56] did not report SDs for the Bessette and Hunter score; very low quality evidence due to serious risk of bias and lack of data.

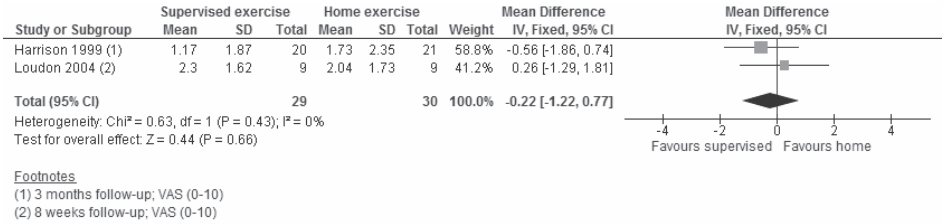
***Different modes of delivery of exercises or exercise programmes: Supervised versus home exercise programmes***

Two studies compared supervised with home exercise programmes.[50 65] Harrison et al.[50] reported functional ability using a modified FIQ and a non-validated patellofemoral scale; only the modified FIQ is presented below. Neither study reported on adverse events. We obtained missing standard deviations for pain and function for Loudon et al.[65]

***Knee pain in the short term***

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

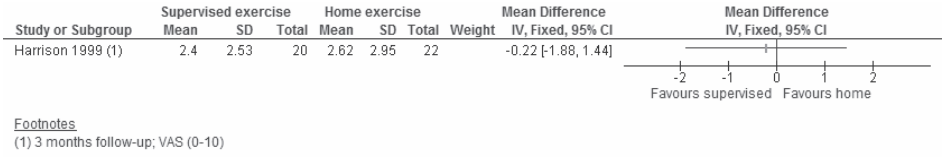
Pooled data from two studies[50 65] (59 participants) showed a MD of -0.22 favouring a supervised exercise programme, 95%CI -1.22 to 0.77, P value = 0.66; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 4.1.




**ANALYSIS 4.1** Comparison 4 Delivery of exercise: supervised versus home exercise program, Outcome 1 Usual pain (short term)

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (42 participants) reported a MD of -0.22 favouring a supervised exercise programme, 95% CI -1.88 to 1.44, P value = 0.79; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 4.2.

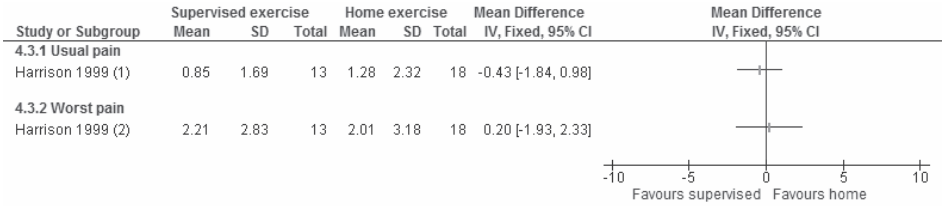



**ANALYSIS 4.2** Comparison 4 Delivery of exercise: supervised versus home exercise program, Outcome 2 Worst pain (short term)

***Knee pain in the long term***

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (31 participants) reported a MD of -0.43 favouring a supervised exercise programme, 95% CI -1.84 to 0.98, P value = 0.55; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 4.3.




Footnotes
(1) 12 months follow-up; VAS (0-10)
(2) 12 months follow-up; VAS (0-10)

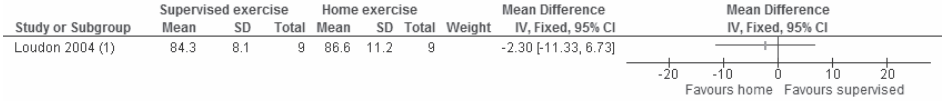
**ANALYSIS 4.3** Comparison 4 Delivery of exercise: supervised versus home exercise program, Outcome 3 Pain (long term)

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Harrison et al.[50] (31 participants) reported a MD of 0.20 favouring a home exercise programme, 95% CI -1.93 to 2.33, P value = 0.85; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 4.3.

***Functional ability in the short term (Anterior Knee Pain Score (AKPS) 0 to 100; modified FIQ 0 to 16; higher scores mean better function)***

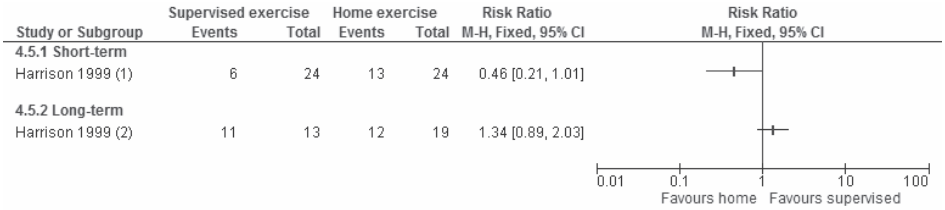
Loudon et al.[65] (18 participants) measured the AKPS (higher scores mean better function) and reported a MD of -2.30 favouring a home exercise programme, 95% CI -11.33 to 6.73, P value = 0.62; very low quality evidence due to serious risk of bias and imprecision; *see* Analysis 4.4.




Footnotes
(1) 8 weeks follow-up; AKPS (0-100)

**ANALYSIS 4.4** Comparison 4 Delivery of exercise: supervised versus home exercise program, Outcome 4 Functional ability (short term)

Harrison et al.[50] (48 participants) presented the numbers of participants with scores split into four FIQ categories (0 to 4, 5 to 8, 9 to 12, 13 to 16). Although we present the data for those in the top (13 to 16, best function) category, the ordinal nature of the data and extent of the loss to follow-up in both groups raises serious questions as to the validity of these results (6/24 versus 13/ 24); RR 0.46 favouring the home exercise group, 95% CI 0.21 to 1.01, P value = 0.05; very low quality evidence due to risk of bias, indirectness and serious imprecision; *see* Analysis 4.5.



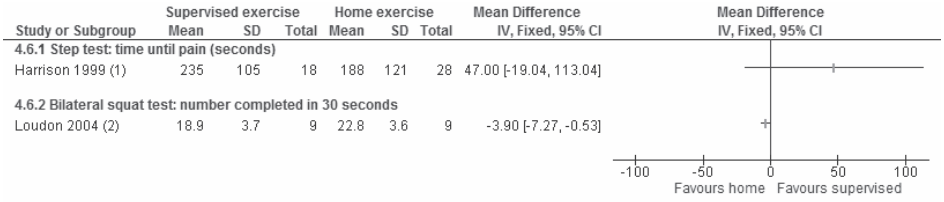

**ANALYSIS 4.5** Comparison 4 Delivery of exercise: supervised versus home exercise program, Outcome 5 Functional ability (short and long term)

### *Functional ability in the long term (modified FIQ 0 to 16; higher scores mean better function)*

As described above, Harrison et al.[50] presented modified FIQ data split into four categories. They reported a significant improvement in function scores for both groups but for even fewer participants at 12 months follow-up. The results for participants in the best function category (13 to 16) were: 11/13 versus 12/19; RR 1.34, 95%CI 0.89 to 2.03, P value = 0.17; very low quality evidence due to risk of bias, indirectness and serious imprecision; *see* Analysis 4.5.

### *Functional performance in the short term (step test, bilateral squat)*

Harrison et al.[50] (46 participants) performed a step test (time until pain) and reported a MD of 47.00 seconds favouring a supervised exercise programme, 95% CI -19.04 to 113.04, P value = 0.16; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 4.6.



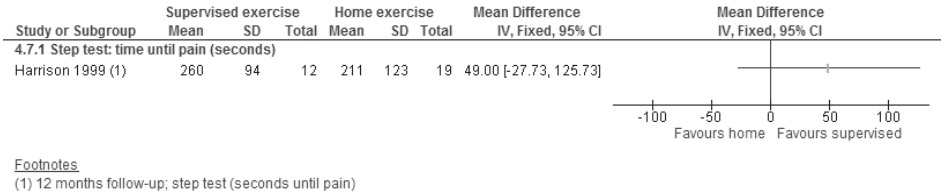

**ANALYSIS 4.6** Comparison 4 Delivery of exercise: supervised versus home exercise program, Outcome 6 Functional performance (short term)

Loudon et al.[65] (18 participants) performed the bilateral squat test (number completed in 30 seconds) and reported a MD of -3.90 favouring a home exercise programme, 95% CI -7.27 to -0.53, P value = 0.02; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 4.6.

Full data were not available for the four other functional performance tests, based on limb symmetry index, measured by Loudon et al.[65] (18 participants): anteromedial lunge, step-down dip, leg press, and balance and reach.

***Functional performance in the long term (step test: time until pain)***

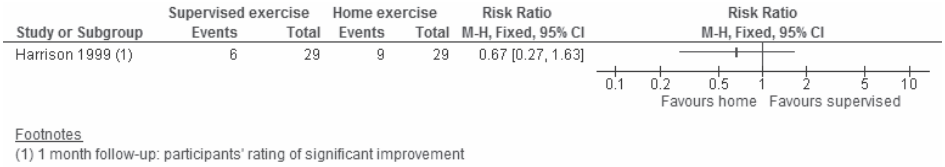
Harrison et al.[50] (31 participants) reported a MD of 49.00 seconds favouring a supervised exercise programme, 95% CI -27.73 to 125.73 seconds, P value = 0.21; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 4.7.




**ANALYSIS 4.7** Comparison 4 Delivery of exercise: supervised versus home exercise program, Outcome 7 Functional performance (long term)

***Recovery in the short term***

Harrison et al.[50] (58 participants) reported that 9/29 participants in the home exercise programme versus 6/29 participants in the supervised exercise programme reported significant improvement; RR 0.67 favouring a home exercise programme, 95% CI 0.27 to 1.63, P value = 0.37; very low quality evidence due to serious risk of bias, indirectness and imprecision; *see* Analysis 4.8.




**ANALYSIS 4.8** Comparison 4 Delivery of exercise: supervised versus home exercise program, Outcome 8 Recovery (short term)

***Medium of exercises or exercise programmes***

There were no trials evaluating this comparison, i.e. water- versus land-based exercise.

***Different types of exercise or exercise programmes***

Eleven studies compared different types of exercises or exercise programmes.[17 29 38 39 41 42 49 51 53 61 66] We grouped the seven different comparisons into three groups defined according to type of kinetic chain exercise: closed kinetic chain exercises versus open kinetic chain exercises; variants of closed kinetic chain exercises; and open,

mixed or unspecified kinetic chain exercises subgrouped by type of muscle action. For convenience, these are presented subgrouped in the same forest plots, but without overall pooling. A comparison of proprioceptive neuromuscular facilitation stretching and aerobic exercise versus classic stretching and quadriceps exercises is presented separately.[53]

Recovery was not reported in any study making these comparisons.

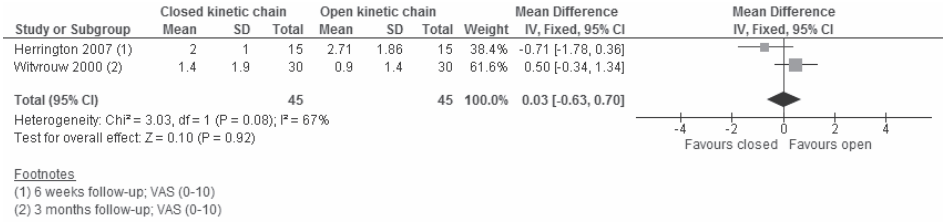
***Closed kinetic chain exercises versus open kinetic chain exercises***

Four studies compared closed kinetic chain exercises versus open kinetic chain exercises.[17 38 41 51] None of the four studies reported on aspects of recovery or adverse events. We extracted standard deviations for pain and function[51] and function[17] from error bars, which we interpreted to be SDs, in graphs presented in the publications of these two trials.

***Knee pain in the short term***

*Pain during activity (VAS 0 to 10; higher scores mean worse pain)*

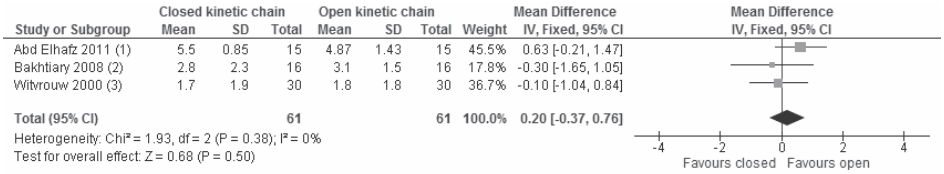
Pooled data from two studies[17 51]; (90 participants) showed a MD of 0.03 favouring open kinetic chain exercises, 95% CI -0.63 to 0.70, P value = 0.92; very low quality evidence due to risk of bias, inconsistency and serious imprecision; *see* Analysis 5.1.




**ANALYSIS 5.1** Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 1 Pain during activity (short term)

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

Pooled data from three studies[17 38 41]; (122 participants) showed a MD of 0.20 favouring open kinetic chain exercises, 95% CI -0.37 to 0.76, P value =0.38; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.2.

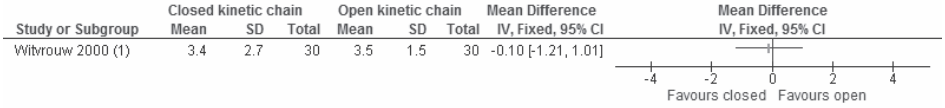



Footnotes
(1) 4 weeks follow-up; VAS (0-10)
(2) 5 weeks follow-up; VAS (0-10)
(3) 3 months follow-up; VAS (0-10)

**ANALYSIS 5.2** Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 2 Usual pain (short term)

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Witvrouw et al.[17] (60 participants) reported a MD of -0.10 favouring closed kinetic chain exercises, 95% CI -1.21 to 1.01, P value = 0.86; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.3.



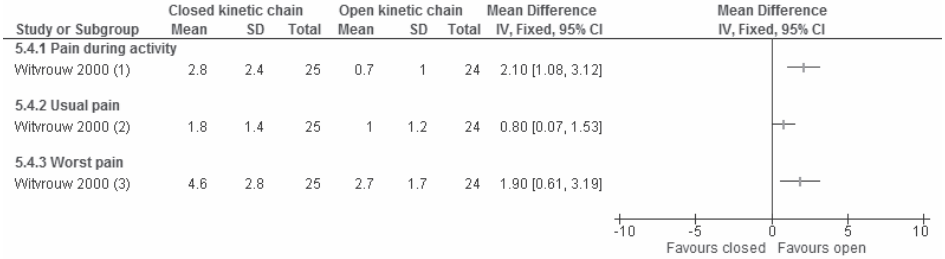

Footnotes
(1) 3 months follow-up; VAS (0-10)

**ANALYSIS 5.3** Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 3 Worst pain (short term)

***Knee pain in the long term (five years follow-up)***

*Pain during activity (VAS 0 to 10; higher scores mean worse pain)*

Witvrouw et al.[17] (49 participants) showed a MD of 2.10 favouring open kinetic chain exercises, 95% CI 1.08 to 3.12, P value <0.0001; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.4.




**ANALYSIS 5.4** Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 4 Pain (long term)

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

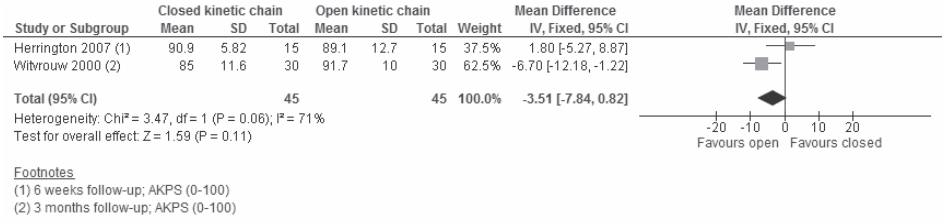
Witvrouw et al.[17] (49 participants) reported a MD of 0.80 favouring open kinetic chain exercises, 95% CI 0.07 to 1.53, P value 0.03; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.4.

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Witvrouw et al.[17] (49 participants) reported a MD 1.90 favouring open kinetic chain exercises, 95% CI 0.61 to 3.19, P value 0.004; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.4.

***Functional ability in the short term (AKPS 0 to 100; higher scores mean better function)***

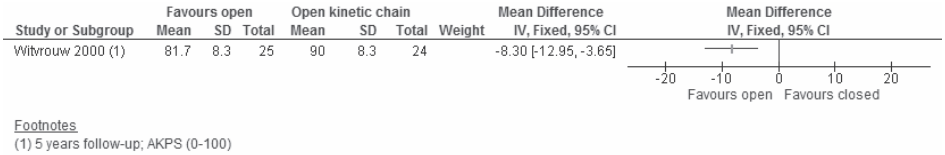
Pooled data from two studies[17 51]; (90 participants) showed a MD of -3.51 favouring open kinetic chain exercises, 95% CI -7.84 to 0.82, P value = 0.11; very low quality evidence due to risk of bias, imprecision and inconsistency; *see* Analysis 5.5.




**ANALYSIS 5.5** Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 5 Functional ability (short term)

***Functional ability in the long term (AKPS 0 to 100; higher scores mean better function)***

Data from Witvrouw et al.[17] (49 participants) showed a MD of -8.30 favouring open kinetic chain exercises, 95% CI -12.95 to -3.65, P value = 0.0005; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.6.




**ANALYSIS 5.6** Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 6 Functional ability (long term)

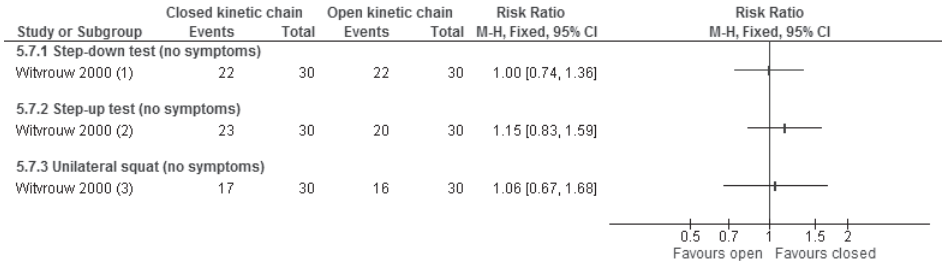
***Functional performance in the short term (step-up, stepdown, unilateral squat)***

Witvrouw et al.[17] (60 participants) reported that 22/30 participants in each group were without symptoms during the step-up test; RR 1.00 favouring neither intervention, 95%CI 0.32 to 3.14, P value = 1.00; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.7.

Witvrouw et al.[17] (60 participants) reported that 23/30 participants in the closed kinetic chain exercise group and 20/30 participants in the open kinetic chain exercise group were without symptoms during the step-down test; RR of 1.15 favouring closed kinetic chain exercises, 95% CI 0.83 to 1.59, P value = 0.39; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.7

Witvrouw et al.[17] (60 participants) reported that 17/30 participants in the closed kinetic chain exercise group and 16/30 participants in the open kinetic chain exercise group were without symptoms during the unilateral squat test; RR 1.06 favouring closed kinetic chain exercises, 95% CI 0.67 to 1.68, P value = 0.80; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.7.

Witvrouw et al.[17] also reported there were no significant differences between treatment groups for the triple jump test but did not provide supporting data.




Footnotes
(1) 3 months follow-up; step up (N of patients without symptoms)
(2) 3 months follow-up; step down (N of patients without symptoms)
(3) 3 months follow-up; unilateral squat (N of patients without symptoms)

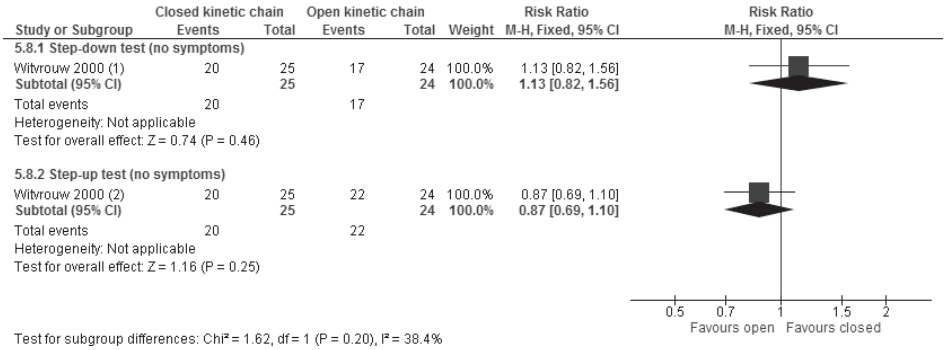
**ANALYSIS 5.7** Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 7 Functional performance(short term)

***Functional performance in the long term (triple jump test (cm), step-up (N of patients without symptoms) and stepdown (N of patients without symptoms))***

Witvrouw et al.[17] (49 participants) reported that 20/25 participants in the closed kinetic chain exercise group and 17/24 participants in the open kinetic chain exercise group were without symptoms during the step-down test; RR 1.13, favouring closed kinetic chain exercises, 95% CI 0.82 to 1.56, P value = 0.46; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.8.

Witvrouw et al.[17] (49 participants) reported that 20/25 participants in the closed kinetic chain exercise group and 22/24 participants in the open kinetic chain exercise group were without symptoms during the step-up test; RR 0.87, favouring open kinetic chain exercises, 95% CI 0.69 to 1.10, P value = 0.25; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 5.8.

Witvrouw et al.[17] also reported that there were no significant differences between treatment groups for the triple jump test but did not provide supporting data.




**ANALYSIS 5.8** Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 8 Functional performance (long term)

***Variants of closed kinetic chain exercises***

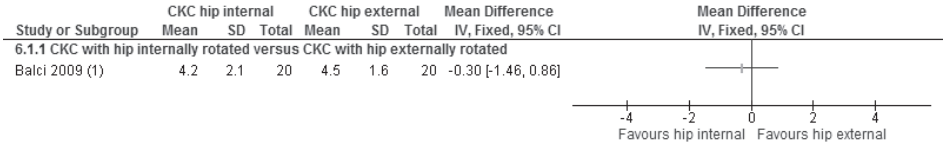
Two studies tested variants of closed kinetic chain exercises. Abrahams et al.[39] compared an exercise protocol with thigh adduction and tibiamedial rotation during eccentric squat versus a traditional exercise protocol. Balci et al.[42] compared closed kinetic chain exercises with internally rotated hip versus closed kinetic chain exercises with externally rotated hip. For convenience, these two heterogeneous studies are presented subgrouped in the same forest plots, but without overall pooling. Neither trial reported on long-term outcomes, functional performance, aspects of recovery or adverse events.

***Knee pain in the short term***

This outcome was not reported in Abrahams et al.[39]

*Pain during activity (VAS 0 to 10; higher scores mean worse pain)*

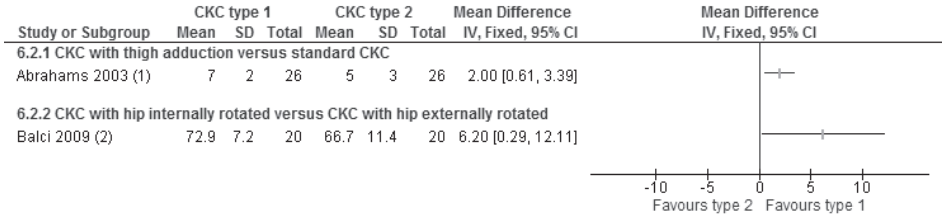
Balci et al.[42] (40 participants) showed a MD of -0.30 favouring closed kinetic chain exercises with internal hip rotation, 95% CI -1.46 to 0.86, P value = 0.61; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 6.1.




**ANALYSIS 6.1** Comparison 6 Types of exercise: variants of closed kinetic chain exercises, Outcome 1 Pain during activity (short term)

***Functional ability in the short term (MFIQ 0 to 16, AKPS 0 to 100; higher scores mean better function)***

Based on the MFIQ (0 to 16) score, Abrahams et al.[39] (52 participants) reported a MD of -2.00 favouring the novel exercise protocol, 95% CI -3.39 to -0.61, P value = 0.005; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 6.2. Based on the AKPS 0 to 100 score, Balci et al.[42] (40 participants) showed a MD of 6.20 favouring closed kinetic chain exercises with internal hip rotation, 95% CI 0.29 to 12.11, P value = 0.04; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 6.2.




Footnotes
(1) 6 weeks follow-up; MFIQ (0-16)
(2) 4 weeks follow-up; AKPS (0-100)

**ANALYSIS 6.2** Comparison 6 Types of exercise: variants of closed kinetic chain exercises , Outcome 2 Functional ability (short term)

***Open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action***

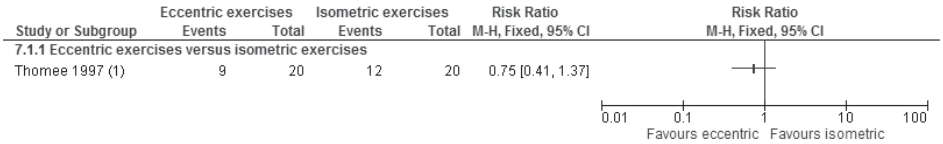
The comparisons undertaken by four studies fell into this category. One study compared eccentric exercises versus concentric exercises.[49] One study compared eccentric exercises versus isometric exercises.[66] One study compared isokinetic exercises versus isometric exercises.[29] One study compared combined isotonic and isometric exercises (pogo stick) versus isometric exercises.[61]

***Knee pain in the short term***

This was not reported in Colón et al.[61] or Gobelet et al.[29]

*Pain during activity (number of patients with pain)*

Thomee et al.[66] (40 participants) reported that 9/20 participants in the eccentric exercise group and 12/20 participants in the isometric exercise group had pain during jogging; RR of 0.75 favouring eccentric exercises, 95% CI 0.41 to 1.37, P value = 0.35; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 7.1.

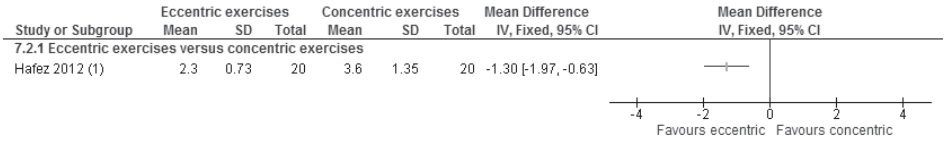



Footnotes
(1) 3 months follow-up; Number of patients with pain during jogging

**ANALYSIS 7.1** Comparison 7 Types of exercise: open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action, Outcome 1 Pain during activity (short term)

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

Hafez et al.[49] (40 participants) reported a MD of -1.30 favouring eccentric exercise, 95% CI -1.97 to -0.63, P value = 0.0002; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 7.2.




Footnotes
(1) 12 weeks follow-up: VAS (0-10)

**ANALYSIS 7.2** Comparison 7 Types of exercise: open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action, Outcome 2 Usual pain continuous (short term)

***Knee pain in the long term***

This was not reported in Colón et al.[61], Gobelet et al.[29] or Hafez et al.[49]

*Pain during activity (number of patients with pain)*

Thomee et al.[66] (40 participants) reported that 4/20 participants in the eccentric exercise group and 6/20 participants in the isometric exercise group had pain during jogging; RR of 0.67 favouring eccentric exercises, 95% CI 0.22 to 2.01, P value = 0.47; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 7.3.

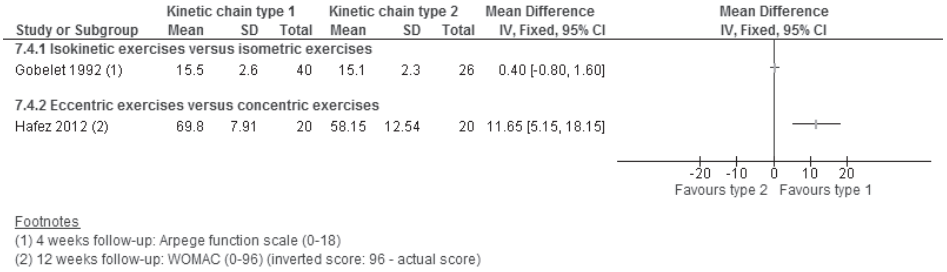

Footnotes
(1) 12 months follow-up; Number of patients with pain during jogging

**ANALYSIS 7.3** Comparison 7 Types of exercise: open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action, Outcome 3 Pain during activity (long term)

***Functional ability in the short term (WOMAC 0 to 96 (inverted scores; higher scores mean better function), Arpège function scale 0 to 18; higher scores mean better function)***

This was not reported in Colón et al.[61] or Thomee et al.[66] Based on the WOMAC (0 to 96) score, Hafez et al.[49] (40 participants) reported a MD of 11.65 favouring eccentric exercises, 95% CI 5.15 to 18.15, P value = 0.0004; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 7.4.

Based on the Arpège scale (0 to 18),Gobelet et al.[29] (66 participants) reported a MD of 0.40 favouring isometric exercises, 95% CI -0.80 to 1.60, P value = 0.51; very low quality evidence due to serious risk of bias and imprecision; *see* Analysis 7.4.




**ANALYSIS 7.4** Comparison 7 Types of exercise: open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action, Outcome 4 Functional ability (short term)

***Functional ability in the long term***

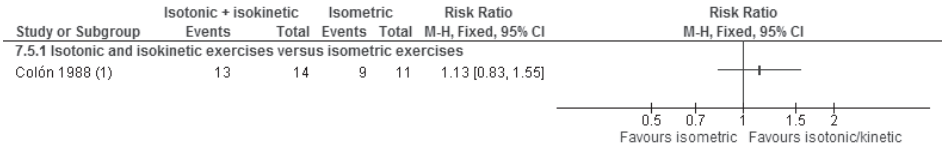
This was not reported in any of the four trials.

***Functional performance in the short term (vertical jump test)***

Only Thomee et al.[66] reported on functional performance, using the vertical jump test; however, only the overall data for the trial population were provided.

***Recovery in the short and long term***

Colón et al.[61] reported that 13/14 participants in the isotonic and isokinetic group versus 9/11 participants in the isometric exercise group had 50% or higher pain relief at eight weeks follow-up; RR 1.13 favouring isotonic and isokinetic exercises, 95% CI 0.83 to 1.55, P value = 0.43; very low quality evidence due to serious risk of bias, indirectness and imprecision; *see* Analysis 7.5.



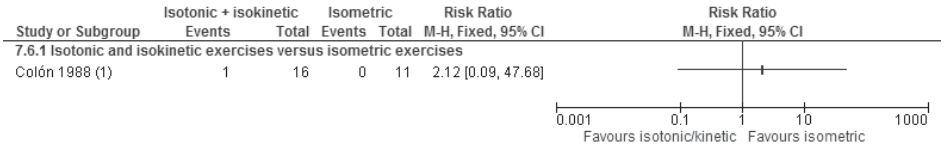

Footnotes
(1) 8 weeks follow-up; Number of patients with 50+% pain relief

**ANALYSIS 7.5** Comparison 7 Types of exercise: open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action, Outcome 5 Recovery (short term)

Thomee et al.[66] (40 participants) reported that all participant except one (group not identified) rated their knee function as excellent at 12 months; the exception rated her knee function as improved although still poor; very low quality evidence due to serious risk of bias, indirectness and imprecision. Two participants, one in each group, had chosen to undergo surgery at nine months.

***Adverse events (number of patients with increased pain)***

Colón et al.[61] reported that 1/16 participants in the isotonic and isokinetic group versus 0/11 participants in the isometric exercise group had an adverse event; RR 2.12 favouring isometric exercises, 95% CI 0.09 to 47.68, P value = 0.64; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 7.6.




Footnotes
(1) 8 weeks follow-up; Number of patients with increased pain

**ANALYSIS 7.6** Comparison 7 Types of exercise: open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action, Outcome 6 Adverse events

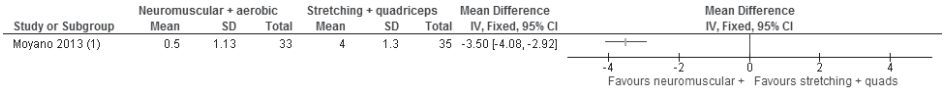
***Proprioceptive neuromuscular facilitation stretching and aerobic exercise versus classic stretching and quadriceps exercises***

The one study making this comparison (68 participants) reported on long-term (16 weeks) pain and function only.[53]

***Knee pain in the long term***

*Usual pain (VAS 0 to 10)*

Moyano et al.[53] reported a MD of -3.50, favouring proprioceptive neuromuscular facilitation stretching and aerobic exercise, 95% CI -4.08 to -2.92, P value < 0.00001; very low quality evidence due to risk of bias and serious imprecision; see Analysis 8.1.

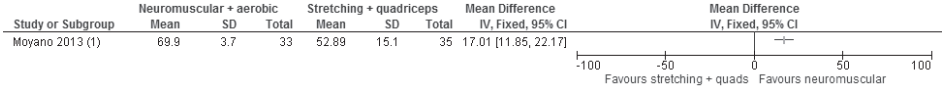



Footnotes
(1) 16 weeks follow-up; VAS (0-10)

**ANALYSIS 8.1** Comparison 8 Types of exercise: open proprioceptive neuromuscular facilitation + aerobic exercise versus classic stretching + quadriceps exercises, Outcome 1 Usual pain (long term)

### *Functional ability in the long term (0 to 100 AKPS scale; higher scores mean better function)*

Moyano et al.[53] reported a MD of 17.01, favouring proprioceptive neuromuscular facilitation stretching and aerobic exercise, 95% CI 11.85 to 22.17, P value < 0.00001; very low quality evidence due to risk of bias and serious imprecision; see Analysis 8.2.




Footnotes
(1) 16 weeks follow-up; AKPS (0-100)

**ANALYSIS 8.2** Comparison 8 Types of exercise: open proprioceptive neuromuscular facilitation + aerobic exercise versus classic stretching + quadriceps exercises, Outcome 2 Functional ability (long term)

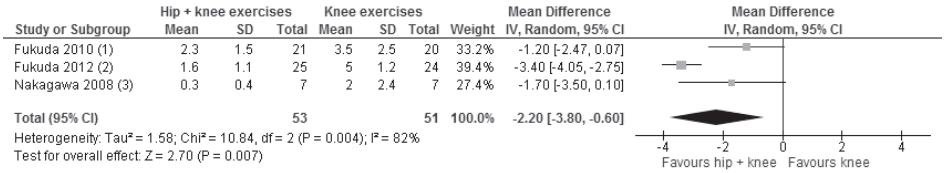
### ***Target of exercises or exercise programmes: Knee and hip exercises versus knee exercises alone***

Seven studies compared knee and hip exercises versus knee exercises alone.[40 44 46 47 54 55 57] Only De Marche et al.[44] reported on aspects of recovery, which was assessed via a global rating of improvement (15-point scale). None of the trials reported on adverse events. Avraham et al.[40], which provided very low quality evidence reflecting very serious risk of bias and imprecision, only presented P values in a graph for the comparisons of three groups of which two were knee and hip exercises and one was knee exercises.

#### *Knee pain in the short term*

*Pain during activity (0 to 10 scale; higher scores mean worse pain)*

Pooled data from three studies[46 47 54] (104 participants) showed a MD of -2.02 favouring knee and hip exercises, 95%CI -3.80 to -0.60, P value = 0.007; very low quality evidence due to risk of bias, serious inconsistency and imprecision (significant heterogeneity: P value = 0.004, I2 = 82%); *see* Analysis 9.1. The results were homogeneous (P value = 0.66 and I2 = 0%) upon removal of Fukuda et al.[47], but smaller in effect size (MD -1.37, 95% CI -2.40 to -0.33, P value = 0.010).

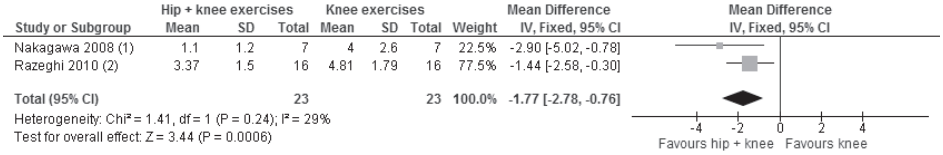



Footnotes
(1) 4 weeks follow-up; NPRS (0-10)
(2) 3 months follow-up; NPRS (0-10)
(3) 6 weeks follow-up; VAS (0-10)

**ANALYSIS 9.1** Comparison 9 Target of exercise: hip + knee versus knee exercises , Outcome 1 Pain during activity (short term)

*Usual pain (VAS 0 to 10; higher scores mean worse pain)*

Pooled data from two studies[54 55] (46 participants) showed a MD of -1.77 favouring knee and hip exercises, 95%CI -2.78 to -0.76, P value = 0.0006; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 9.2.



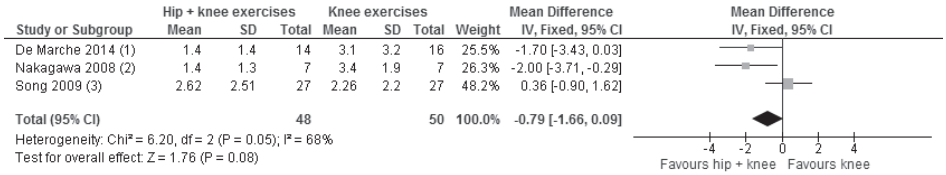

Footnotes
(1) 6 weeks follow-up; VAS (0-10)
(2) 4 weeks follow-up; VAS (0-10)

**ANALYSIS 9.2** Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 2 Usual pain (short term)

Avraham et al.[40] (30 participants) reported that no significant between-group differences were found for pain (reported P value =0.11 and P value = 0.72, P values extracted from graph).

*Worst pain (0 to 10 scale; higher scores mean worse pain)*

Pooled data from three studies[44 54 57] (98 participants) showed a MD of -0.79 favouring knee and hip exercises, 95% CI -1.66 to 0.09, P value = 0.08; very low quality evidence due to risk of bias, inconsistency and imprecision; *see* Analysis 9.3.



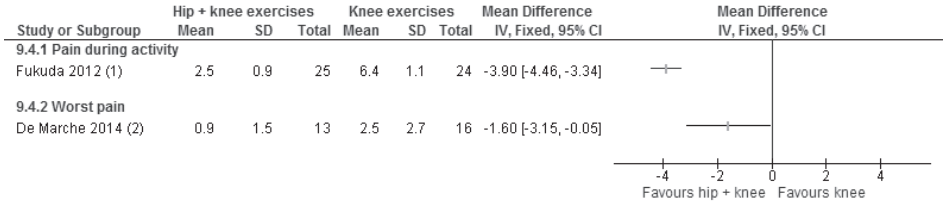

Footnotes
(1) 8 weeks follow-up; VAS (0-10)
(2) 6 weeks follow-up; VAS (0-10)
(3) 8 weeks follow-up; VAS (0-100) scaled to 0-10

**ANALYSIS 9.3** Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 3 Worst pain (short term)

### *Knee pain in the long term*

*Pain during activity (numerical pain rating scale (NPRS) 0 to 10; higher scores mean worse pain)*

Fukuda et al.[47] (49 participants) reported a MD of -3.90 favouring knee and hip exercises, 95% CI -4.46 to -3.34, P value < 0.00001; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 9.4.




Footnotes
(1) 12 months follow-up; NPRS (0-10)
(2) 5 months follow-up; VAS (0-10)

**ANALYSIS 9.4** Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 4 Pain (long term)

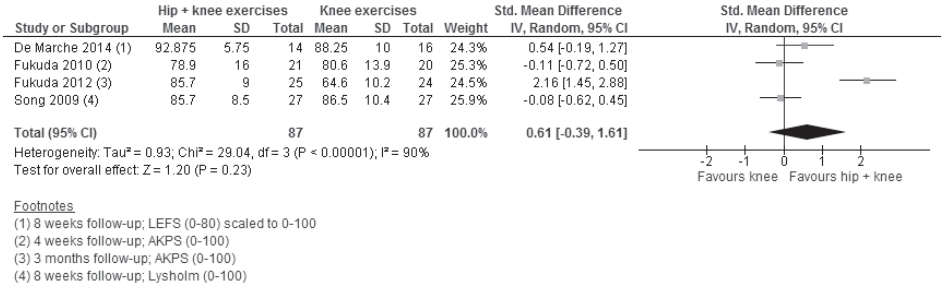
*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

De Marche et al.[44] (29 participants) reported a MD of -1.60 favouring knee and hip exercises, 95% CI -3.15 to -0.05, P value = 0.04; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 9.4.

### *Functional ability in the short term (0 to 100 scale; higher scores mean better function)*

Pooled data from four studies[44 46 47 57] (174 participants) showed a SMD of 0.61 favouring knee and hip exercises, 95% CI -0.39 to 1.61, P value = 0.23; very low quality evidence due to risk of bias, imprecision and serious inconsistency (significant heterogeneity: P value < 0.00001, I2 = 90%); *see* Analysis 9.5. Upon removal of Fukuda et al.[47], the results were homogeneous (P value = 0.33 and $I^2$ = 11%) with little difference between the two groups (SMD 0.06, 95% CI -0.32 to 0.43, P value = 0.76).

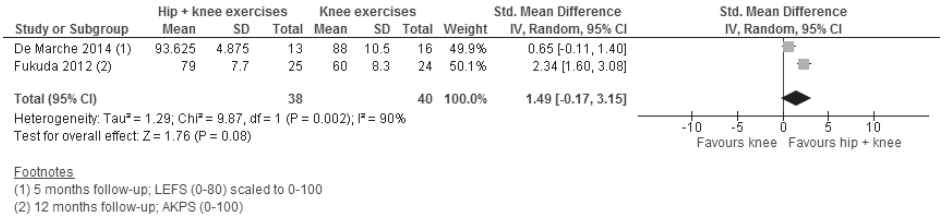
Avraham et al.[40] (20 participants) reported no significant between group differences were found for function assessed using the patellofemoral joint evaluation scale (0 to 100) (reported P value = 0.74 and P value = 0.70; P values extracted from graph).




**ANALYSIS 9.5** Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 5 Functional ability (short term)

***Functional ability in the long term (0 to 100 scale; higher scores mean better function)***

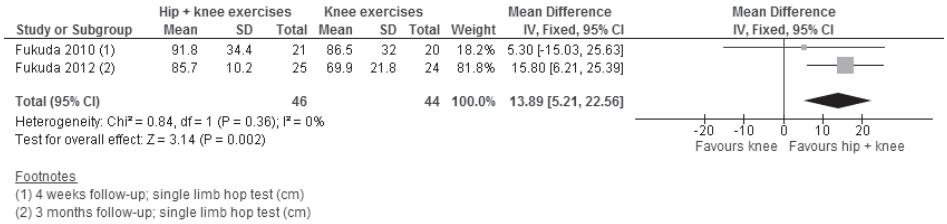
Pooled data from two studies[44 47] (78 participants) showed a SMD of 1.49 favouring knee and hip exercises, 95% CI -0.17 to 3.15, P value = 0.08; very low quality evidence due to risk of bias, imprecision and serious inconsistency (significant heterogeneity: P value = 0.002, $I^2$ = 90%); *see* Analysis 9.6.




**ANALYSIS 9.6** Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 6 Functional ability (long term)

***Functional performance in the short term (single-limb hop test)***

Pooled data from two trials[46 47] (90 participants) reporting the single-limb hop test showed a MD of 13.89 cm favouring knee and hip exercises, 95% CI 5.21 to 22.56, P value = 0.002; low quality evidence due to risk of bias and imprecision; *see* Analysis 9.7.

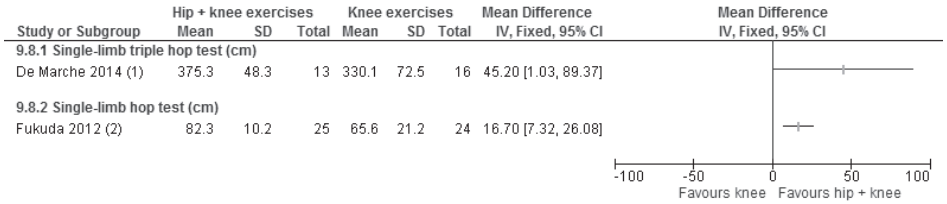



**ANALYSIS 9.7** Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 7 Functional performance (short term)

***Functional performance in the long term (single-leg triple hop test and single-limb hop test)***

De Marche et al.[44] (29 participants) reported for the single-leg triple hop test a MD of 45.20 cm favouring knee and hip exercises, 95% CI 1.03 to 89.37, P value = 0.04; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 9.8.

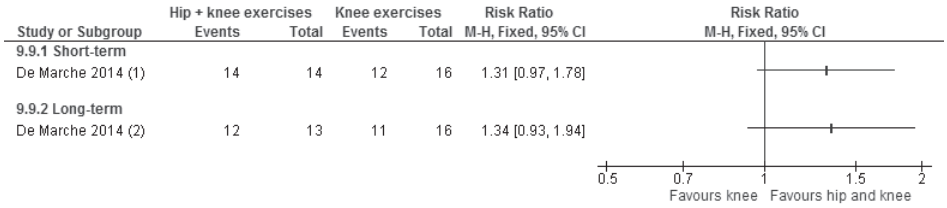
Fukuda et al.[47] (49 participants) reported for the single-limb hop test a MD of 16.70 cm favouring knee and hip exercises, 95% CI 7.32 to 26.08, P value = 0.001; low quality evidence due to risk of bias and imprecision; *see* Analysis 9.8.




**ANALYSIS 9.8** Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 8 Functional performance (long term)

***Recovery in the short and long term (number of participants at least moderately better)***

De Marche et al.[44] (30 participants in the short term, 29 participants in the long term) reported on the number of participants who perceived themselves as at least moderately better in the short term (14/14 versus 12/16), RR 1.31 favouring hip and knee exercises, 95% CI 0.97 to 1.78, P value = 0.07; very low quality evidence due to risk of bias, indirectness and serious imprecision) and in the long term (12/13 versus 11/16), RR 1.34 favouring hip and knee exercises, 95% CI 0.93 to 1.94, P value = 0.11; very low quality evidence due to risk of bias, indirectness and serious imprecision), *see* Analysis 9.9.




Footnotes
(1) 8 weeks follow-up; at least moderately better
(2) 5 months follow-up; at least moderately better

**ANALYSIS 9.9** Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 9 Recovery (short and long term)

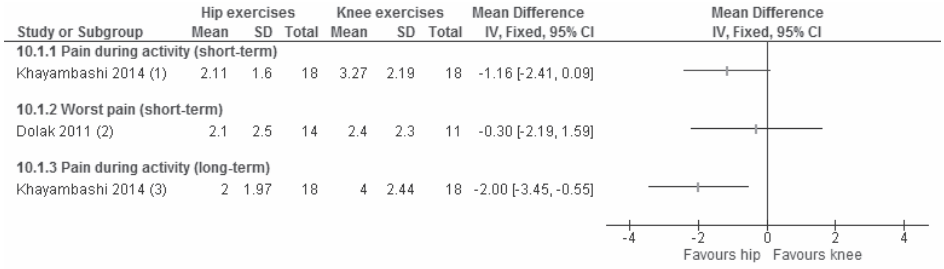
***Target of exercises or exercise programmes: Hip exercises versus knee exercises***

Two studies compared hip versus knee exercises.[45 64] Dolak et al.[45] did not report on long-term outcome. Neither study reported on aspects of recovery.

***Knee pain in the short term***

*During activity (VAS 0 to 10; higher scores mean worse pain)*

Khayambashi et al.[64]2014 (36 participants) reported a MD of -1.16 favouring hip exercises, 95% CI -2.41 to 0.09, P value = 0.07; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 10.1.




Footnotes
(1) 8 weeks follow-up; VAS (0-10)
(2) 3 months follow-up; VAS (0-10)
(3) 6 months follow-up; VAS (0-10)

**ANALYSIS 10.1** Comparison 10 Target of exercise: hip versus knee exercises, Outcome 1 Pain (short and long term)

*Worst pain (VAS 0 to 10; higher scores mean worse pain)*

Dolak et al.[45] (25 participants) reported a MD of -0.30 favouring hip exercises, 95% CI -2.19 to 1.59, P value = 0.76; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 10.1.

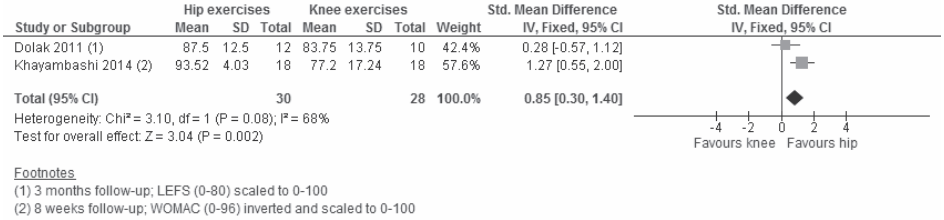
***Knee pain in the long term***

*During activity (VAS 0 to 10; higher scores mean worse pain)*

Khayambashi et al.[64] (36 participants) reported a MD of -2.00 favouring hip exercises, 95% CI -3.45 to -0.55, P value = 0.007; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 10.1.

***Functional ability in the short term (0 to 100 scale; higher scores mean better function)***

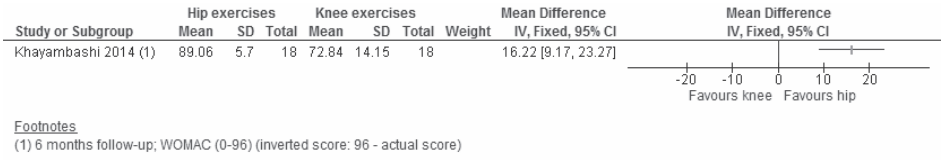
Pooled data from two studies[45 64] (58 participants) showed a SMD of 0.85 favouring hip exercises, 95% CI 0.30 to 1.40, P value = 0.002, which was statistically heterogeneous (P value = 0.08; I2 = 68%); very low quality evidence due to serious risk of bias, imprecision and inconsistency; *see* Analysis 10.2.




**ANALYSIS 10.2** Comparison 10 Target of exercise: hip versus knee exercises, Outcome 2 Functional ability (short term)

***Functional ability in the long term (WOMAC 0 to 96, score inverted so that higher scores mean better function)***

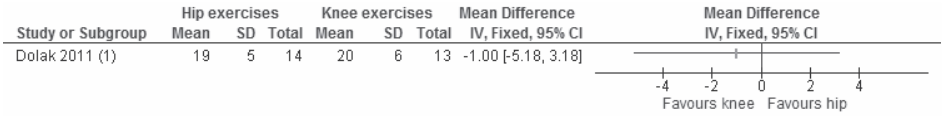
Khayambashi et al.[64] (36 participants) reported a MD of 16.22 favouring hip exercises, 95%CI 9.17 to 23.27, P value < 0.00001; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 10.3.




**ANALYSIS 10.3** Comparison 10 Target of exercise: hip versus knee exercises , Outcome 3 Functional ability (long term)

***Functional performance in the short term (step-down test (N of repetitions in 30 seconds))***

Dolak et al.[45] (27 participants) performed the step-down test (number of repetitions in 30 seconds) and reported a MD of -1.00 favouring quadriceps exercises, 95% CI -5.18 to 3.18, P value = 0.64; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 10.4.

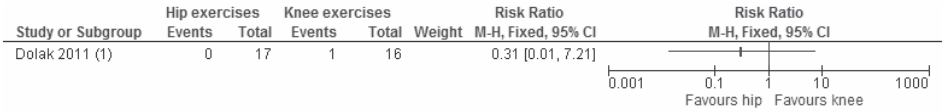



Footnotes
(1) 8 weeks follow-up; step down test (number of repetitions in 30 seconds)

**ANALYSIS 10.4** Comparison 10 Target of exercise: hip versus knee exercises, Outcome 4 Functional performance (short term)

### *Adverse events*

Dolak et al.[45] (31 participants) reported that 0/17 participants in the hip exercise group versus 1/16 participants in the knee exercise group had an adverse event; RR of 0.31 favouring hip exercises, 95% CI 0.01 to 7.21, P value = 0.47; very low quality evidence due to serious risk of bias and serious imprecision; *see* Analysis 10.5.




Footnotes
(1) 3 months follow-up; number of patients with increased pain

**ANALYSIS 10.5** Comparison 10 Target of exercise: hip versus knee exercises, Outcome 5 Adverse events

### ***Duration of exercises or exercise programmes***

There were no trials testing duration of exercise therapy.

### ***Intensity of exercises or exercise programmes: High- versus low-intensity exercise programme***

One study compared high-dose, high-repetition medical exercise therapy (MET) with low-dose, low-repetition exercises.[60] Østerås et al.[60] did not report on aspects of recovery or adverse events.

### ***Knee pain in the short term***

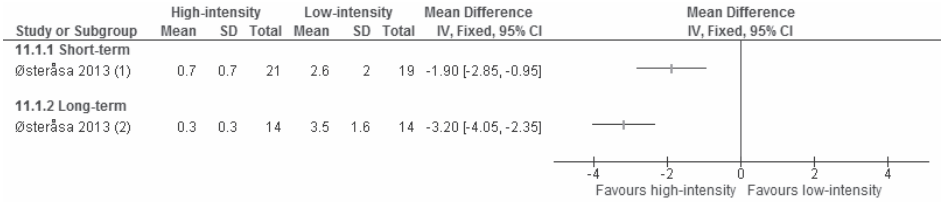
*Usual pain (0 to 10 scale; higher scores mean worse pain)*

Østerås et al.[60] (40 participants) reported a MD of -1.90 favouring a high-intensity programme, 95% CI -2.85 to -0.95, P value <0.0001; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 11.1.

***Knee pain in the long term***

*Usual pain (0 to 10 scale; higher scores mean worse pain)*

Østerås et al.[60] (28 participants) reported a MD of -3.20 favouring a high-intensity programme, 95% CI -4.05 to -2.35, P value <0.00001; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 11.1.

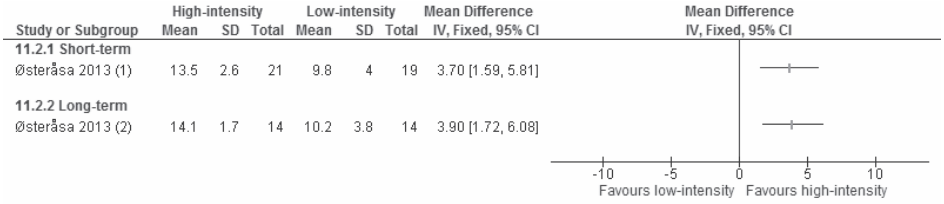



Footnotes
(1) 3 months follow-up; VAS (0-10)
(2) 12 months follow-up; VAS (0-10)

**ANALYSIS 11.1** Comparison 11 Intensity of exercise: high- versus low-intensity exercise programme, Outcome 1 Usual pain (short and long term)

***Functional ability in the short term (FIQ 0 to 16 scale; higher scores mean better function)***

Østerås et al.[60] (40 participants) reported a MD of 3.70 favouring a high-intensity programme, 95% CI 1.59 to 5.81, P value = 0.0006; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 11.2.




Footnotes
(1) 3 months follow-up; FIQ (0-16)
(2) 12 months follow-up; FIQ (0-16)

**ANALYSIS 11.2** Comparison 11 Intensity of exercise: high- versus low-intensity exercise programme, Outcome 2 Functional ability (short and long term)

***Functional ability in the long term (FIQ 0 to 16 scale; higher scores mean better function)***

Østerås et al.[60] (28 participants) reported a MD of 3.90 favouring a high-intensity programme, 95% CI 1.72 to 6.08, P value = 0.0005; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 11.2.

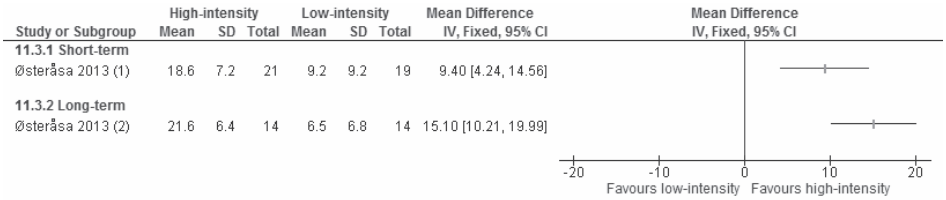
***Functional performance in the short term (step-down test)***

Østerås et al.[60] (40 participants) performed the step-down test (number of repetitions in 30 seconds) and reported a MD 9.40 favouring a high-intensity programme, 95% CI

4.24 to 14.56, P value = 0.0004; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 11.3.

***Functional performance in the long term (step-down test)***

Østerås et al.[60] (28 participants) performed the step-down test (number of repetitions in 30 seconds) and reported a MD of 15.10 favouring a high-intensity programme, 95% CI 10.21 to 19.99,P value < 0.00001; very low quality evidence due to risk of bias and serious imprecision; *see* Analysis 11.3.




Footnotes
(1) 3 months follow-up; step down test (N of repetitions in 30 seconds)
(2) 12 months follow-up; step down test (N of repetitions in 30 seconds)

**ANALYSIS 11.3** Comparison 11 Intensity of exercise: high- versus low-intensity exercise programme, Outcome 3 Functional performance (short and long term)

### Subgroup analyses for patient characteristics

We did not perform subgroup analyses to determine the effects of patient characteristics (gender, duration of complaints and sports participation) on outcome. This reflected the lack of data and the inconsistent and incomplete reporting of baseline characteristics.

### Sensitivity analysis excluding trials at high risk of selection bias

The results of pooled studies were robust when excluding trials with a high risk of bias of selection bias: Clark et al.[43]; Colón et al.[61]; Dolak et al.[45]; Eburne and Bannister.[62]; Khayambashi et al.[63 64 85]; Loudon et al.[65]; and Thomee et al.[66] (results not shown).

## DISCUSSION

### Summary of main results

This systematic review assessed the effects (benefits and harms) of exercise therapy aimed at reducing knee pain and improving knee function for people with patellofemoral pain syndrome.

This review comprises 31 heterogeneous trials including 1690 participants with a diagnosis of patellofemoral pain syndrome. As well as variation in the patient characteristics and diagnostic criteria for study inclusion, the exercise interventions tested in the trials

varied considerably. We assessed the evidence as being very low quality (*see* Quality of the evidence (online available)).

We based our assessment of clinical relevance on the following minimal clinically important differences: 1.3 points on a visual analogue scale (VAS) for pain during activity; 2.0 points on a VAS for usual and worst pain; 10.0 points on the Anterior Knee Pain Score (AKPS) and 2.0 points on the modified Functional Index Questionnaire (FIQ) (0 to 16)[21]; and 15.0 points for the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[86]. In our summary of the main results for each comparison, we restrict our report to seven outcomes (pain during activity (short-term: ≤ 3 months); usual pain (short-term); pain during activity (long-term: > 3 months); usual pain (long-term); functional ability (short-term); functional ability (long-term); and recovery (long-term)).

***Exercise therapy versus control (no treatment, placebo or health educational material)***

Although 10 studies compared exercise therapy versus control, we do not discuss the findings from Abrahams et al.[39] here because this trial also required participants to have patella malalignment and was thus presented separately in Effects of interventions.

All nine trials stipulated a minimum duration of symptoms; this ranged from three weeks to six months. We assessed the quality of the available evidence as being of very low quality for each outcome (*see Appendix 2* Summary of finding table for the main comparison).

Pooled data from five studies (375 participants) for pain during activity in the short term(four weeks to three months) favoured exercise therapy; the confidence interval, which did not cross the line of no effect, included the minimal clinically important difference pointing to the possibility of a clinically important effect. The same finding applied for pooled data from two studies (41 participants) for usual pain in the short term (four to eight weeks); for pooled data from two studies (180 participants) for pain during activity in the long term (12 months) and for data from a single study (94 participants) for usual pain in the long term(16 weeks). Pooled data from seven studies (483 participants) for functional ability in the short term (four weeks to three months) also favoured exercise therapy.

In order to interpret the standardised mean difference results, we converted these to AKPS; the resulting confidence interval, which did not cross the line of no effect, included the minimal clinically important difference pointing to the possibility of a clinically important effect. The same finding applied to pooled data from three studies (274 participants) for functional ability in the long term (16 weeks to 12 months). Pooled data from two studies (166 participants) indicated that, based on the recovery of 250 per 1000 in the control group, 88 more (95%confidence interval (CI) 2 fewer to 210 more) participants per 1000 recovered in the long term(12 months) as a result of exercise therapy. It is important to note the very significant heterogeneity in the contributing

trials and in the results for pain during activity and functional ability in the short term. However, sensitivity analyses did retain the positive findings for both of these outcomes, although the effect sizes were reduced.

***Exercise therapy versus different unimodal or multimodal conservative interventions***

All comparisons in this category are represented by single trials only, with no pooling undertaken because of the heterogeneity in the control groups (other conservative intervention).

***Exercise therapy versus different unimodal interventions***

Four trials provided very low quality and incomplete evidence for five comparisons of exercise therapy versus different unimodal conservative interventions.

One study (28 less active female participants; bilateral symptoms of at least six months duration) comparing hip exercises versus 1000 mg of Omega-3 and 400 mg of calcium daily found a clinically important and highly statistically significant difference favouring the hip exercises group for pain during activity and functional ability in the short term (eight weeks).

One study (66 participants; symptoms of at least three weeks duration) comparing home exercises versus brace reporting on short-term( three months) results found slightly lower pain during activity in the brace group and better functional ability in the exercises group. However, the confidence interval for pain during activity crossed the line of no effect and did not include the minimal clinically important difference. The confidence interval for functional ability also crossed the line of no effect but may have included a clinically important effect for exercise as well as a non-clinically important effect for bracing.

One study (24 participants with symptoms of at least three months) comparing exercise therapy versus tape found lower pain during activity in the short term (three months) in the exercises group; the confidence interval, which did not cross the line of no effect, included a clinically important effect. A similar finding applied to pain during activity in the long term (12 months); however the confidence interval also crossed the line of no effect and a small but clinically irrelevant effect in favour of tape cannot be ruled out. The same pattern, in favour of exercise, applied to functional ability at short- and long-term follow-up. Slightly more participants in the exercise group had recovered by 12months; the confidence interval crossed the line of no effect and thus a result in favour of taping cannot be ruled out.

One study (54 participants) comparing isometric exercises versus muscle electrostimulation found better functional ability in the short term(four weeks) in the exercise group; the confidence interval included a clinically important effect but also crossed the line of no effect and thus included a non-clinically important effect in favour of muscle

electrostimulation. The same observation applies to short-term functional ability results from the comparison of isokinetic exercises versus muscle electrostimulation made in the same trial (68 participants).

***Exercise therapy versus multimodal conservative interventions***

Four trials provided very low quality and incomplete evidence for five comparisons of exercise therapy versus different multimodal conservative interventions. One quasi-randomised study (53 participants), which compared isometric quadriceps exercise versus the multimodal McConnell regimen comprising different types of exercises and taping, provided no usable quantitative data. It concluded that there was improvement in 50%of each group in the short term (three months). It also reported that three participants withdrew because of "severe allergy to the strapping" (presumably in the McConnell regimen group).

One study, which compared a supervised exercise programme versus a vastus medialis-specific supervised exercise programme including taping found no clinically important difference between the two groups in usual pain in the short term (three months; 40 participants) or long term (12 months; 31 participants). In both cases the confidence intervals crossed the line of no effect and did not include the minimal clinically important difference. This study found over twice as many participants in the multimodal group had best function in the short term (52 participants overall). Conversely, the result at 12 months (33 participants) favoured the exercise group; however, the confidence intervals crossed the line of no effect.

The same study as above also compared a home exercise programme versus a vastus medialis-specific supervised exercise programme including taping. For usual pain and functional ability at both short (42 and 52 participants respectively) and long-term follow-up (36 and 39 participants respectively), the confidence intervals crossed the line of no effect and, for usual pain, did not include the minimal clinically important difference.

One study (60 participants), which compared concentric exercises versus a multimodal intervention comprising excentric exercises and taping, found better functional ability (expressed in terms of the number of participants with improved function) and recovery in the short term(eight weeks follow-up) in the multimodal group. In both cases, the confidence intervals crossed the line of no effect and thus a greater benefit from concentric exercises alone cannot be ruled out.

One study (40 active participants with symptoms for at least six months), which compared physiotherapeutic exercises based on proprioceptive neuromuscular facilitation versus a special knee resistance-controlled knee splint combined with a special exercise programme, provided no data on the selected pain measures and incomplete data for functional ability at short-term (eight weeks) follow-up. It did not find a statistically or

clinically significant difference between the two groups in pain at rest or functional ability.

***Different exercises or exercise programmes***

***Delivery of exercises or exercise programmes: supervised versus home exercise***

Two trials, one of which stipulated a minimum duration of symptoms of two months, provided very low quality evidence for this comparison (*see* Summary of findings table (Appendix 2)). Pooled data (59 participants) for usual pain in the short term (eight weeks or three months) marginally favoured supervised exercises but the confidence interval crossed the line of no effect and did not include the minimal clinically important difference for usual pain. The same observation applied to data from one study (31 participants) for usual pain in the long term (12 months). One study (18 active participants) found functional ability in the short term (eight weeks) slightly favoured home exercise; however, although the confidence interval included the minimal clinically important difference, it also crossed the line of no effect. The other trial (31 participants) reported higher numbers of participants with best function in the home group in the short term (one month; 48 participants) but the converse in the long term (12 months). In both cases, the confidence intervals crossed the line of no effect and thus a benefit from supervised exercises in the short term and home exercises in the long term cannot be ruled out.

***Types of exercises or exercise programmes: closed kinetic chain exercises versus open kinetic chain exercises***

This comparison was tested in four trials; the three providing quantitative data stipulated a minimum duration of symptoms (four, six and eight weeks respectively). We assessed all evidence for this comparison as being of very low quality (*see* Summary of findings table (Appendix 2)). Recovery was not reported. Although pooled data from two studies (90 participants) for pain during activity in the short term (six weeks or three months) marginally favoured open kinetic exercises, the confidence interval crossed the line of no effect and did not include the minimal clinically important difference. The same observation applied to pooled data from three studies (122 participants) for usual pain in the short term (four weeks to three months). In the long term (five years), one study (49 participants) found less pain during activity and usual pain in the open kinetic chain group; the confidence interval included a clinically important effect for the first outcome but not the second.

Although pooled data from two studies (90 participants) for functional ability in the short term (six weeks or three months) marginally favoured open kinetic exercises, the confidence interval crossed the line of no effect and did not include the minimal

clinically important difference. In the long term (five years), one study (49 participants) found better function in the open kinetic chain group; the confidence interval included a clinically important effect. It is important to note that data for long-term effect were from one trial only and that data for functional ability were extracted from graphs for both trials reporting these data.

***Types of exercises or exercise programmes: variants of closed kinetic chain exercises***

Two trials provided very low quality and incomplete evidence for two different comparisons of variants of closed kinetic chain exercises. Neither trial reported on long-term outcomes or recovery.

One trial (52 participants with a minimum duration of symptoms of eight months plus patella malalignment) comparing an exercise protocol with thigh adduction and tibia medial rotation during eccentric squat versus a traditional exercise protocol found better functional ability in the short term (six weeks) in the first intervention group; the confidence interval, which did not cross the line of no effect, included a clinically important effect.

One trial (40 female participants with symptoms for at least two months) comparing closed kinetic chain exercises with internally rotated hip versus closed kinetic chain exercises with externally rotated hip reported less pain during activity in the short term (four weeks) in the internally rotated group; the confidence interval included a clinically important effect but also crossed the line of no effect and included a non-clinically important effect in favour of the externally rotated group. This trial reported better functional ability in the short term in the internally rotated group; the confidence interval, which did not cross the line of no effect, included a clinically important effect.

***Types of exercises or exercise programmes: open, mixed or unspecified kinetic chain exercises subgrouped by type of muscle action***

Four trials provided very low quality and incomplete evidence for four different comparisons. One study (40 female participants) comparing eccentric exercises versus concentric exercises found lower usual pain in the short term (12 weeks) for eccentric exercises; however, the confidence interval, which did not cross the line of no effect, excluded a clinically important effect. This study found better WOMAC scores in the short term for eccentric exercises; in this case the confidence interval, which did not cross the line of no effect, included a clinically important effect.

One study (40 female participants; symptoms for a minimum of six months) comparing eccentric exercises versus isometric exercises reported slightly fewer participants in the eccentric exercise group had pain during activity (jogging) in the short term(three months) and long term (12 months); the confidence intervals crossed the line of no effect and thus included the potential for an effect in favour of isometric exercises. All

participants except one (group not identified) rated their knee function as excellent at 12 months.

One study (66 participants) comparing isokinetic exercises versus isometric exercises found a small and clinically non-relevant between-group difference in favour of isometric exercises in functional ability in the short term (four weeks). The confidence interval crossed the line of no effect and thus included the possibility of a better but probably not clinically important result after isokinetic exercises.

One study comparing combined isotonic and isometric exercises (pogo stick) versus isometric exercises reported only on recovery (more in the first group reported 50%or higher pain relief at eight weeks; 25 active participants) and adverse events (one person in the first group had increased pain; 27 active participants). Although favouring isotonic and isokinetic exercises, the confidence interval for recovery crossed the line of no effect and thus also included the possibility of a better result after isometric exercises.

***Types of exercises or exercise programmes: proprioceptive neuromuscular facilitation stretching and aerobic exercise versus classic stretching and quadriceps exercises***

Very low quality evidence from one trial (68 less active participants with a minimum duration of pain of six months) that reported only on usual pain and functional ability in the long term (16 weeks) showed a strong clinically important effect on both outcomes in favour of proprioceptive neuromuscular facilitation stretching and aerobic exercise compared with classic stretching and quadriceps exercises. The confidence intervals for both outcomes were located beyond the minimal clinically important differences.

***Target of exercises or exercise programmes: hip and knee exercises compared with knee exercises***

This comparison was tested in seven trials; the six providing quantitative data stipulated a minimum duration of symptoms (one month (three studies), two months (one study), three months (two studies)) (*see* Summary of findings table (Appendix 2)). Very low quality evidence pooled from three studies (104 participants) showed lower pain during activity in the short term (four weeks to three months) in the hip and knee exercise group compared with the knee exercises group; the confidence interval, which did not cross the line of no effect, included a clinically important effect. Very low quality evidence pooled from two studies (46 participants) showed lower usual pain in the short term (four or six weeks) in the hip and knee exercise group; the confidence interval, which did not cross the line of no effect, included a clinically important effect. Very low quality evidence pooled from one study (49 less active female participants) showed lower pain during activity in the long term (12months) in the hip and knee exercise group compared with the knee exercise group; the confidence interval was located beyond the minimal clinically important difference of 1.3 points on a 0 to 10 scale. No study

reported on usual pain in the long term. Very low quality evidence for functional ability in both the short term (four weeks to three months; four studies, 174 participants) and long term (5 or 12 months; two studies, 78 participants) was in favour of hip and knee exercises. However, both confidence intervals crossed the line of no effect and while including a clinically important effect in favour of hip and knee exercises there was also the potential for a non-clinically important effect in favour of knee exercises. Very low quality evidence from one trial (29 active female participants) showed that long-term (five months) recovery was greater in the hip and knee exercises group; however, the confidence interval also included the possibility of better recovery in the knee exercises group.

***Target of exercises or exercise programmes: hip exercises compared with knee exercises***

This comparison was tested in two studies, both of which stipulated a minimum duration of symptoms (one and six months respectively). Neither trial reported on usual pain or recovery (*see* Summary of findings table (Appendix 2)). Very low quality evidence from one quasi randomized trial (36 less active participants) showed that hip exercises may reduce pain during activity to a greater extent compared with knee exercise in the short term (eight weeks) and long term (six months); the confidence intervals at both time points included a clinically important effect. The short-term result also included the potential for a small clinically non-relevant difference in favour of knee exercises, whilst the confidence interval for the long-term result did not cross the line of no effect. Very low quality evidence from two studies (58 participants) showed that hip exercises may improve functional ability in the short term (eight weeks or three months) compared with knee exercises; the confidence interval, which did not cross the line of no effect, included a clinically important effect. Very low quality evidence from one quasi-randomised trial (36 less active participants) showed that hip exercises may improve functional ability in the long term (six months) compared with knee exercises; the confidence interval, which did not cross the line of no effect, included a clinically important effect.

***Intensity of exercises***

There is very low quality evidence from one trial (40 participants with untreated patellofemoral pain syndrome (PFPS) of over two months in duration) that a 12-week long high-intensity exercise programme is more effective than a 12-week long low-intensity exercise programme in reducing usual pain and improving functional ability in the short term (three months) and the long term (12 months) (*see* of findings table (Appendix 2)).However, the confidence intervals for usual pain (short-term) and functional ability (short and long-term), which did not cross the line of no effect, included both a non-clinically important effect and a clinically important effect. The confidence interval for

usual pain (long-term) was located beyond the minimal clinically important difference of 2.0 points on a 0 to 10 scale. Pain during activity and recovery were not reported.

***Overall completeness and applicability of evidence***

This multi-comparison review comprised 31 heterogeneous trials including 1690 participants with a diagnosis of patellofemoral pain syndrome. The largest comparison (exercise versus control (no exercise)) was tested in 10 trials but the largest analysis in this review, which was for this comparison, included data from only 483 participants (Analysis 1.6). There were no trials testing the medium of exercise or duration of exercises. Many other comparisons, notably those comparing exercise with other conservative interventions and different intensities of exercise were tested in small single trials only. The inclusion criteria of the included trials were diverse. In the majority of trials, the diagnosis of PFPS was based on a set of clinical criteria and most trials excluded other knee pathologies (*see* Table 2 (online available)). The clinical diagnosis was made by a variety of clinical practitioner disciplines and together with the absence of a gold standard diagnostic test, differences in examination and judgements of suitability for inclusion are inevitable. Nonetheless, we judged that it was very likely that there was sufficient similarity in the underlying condition (i.e. all had PFPS) in participants recruited into all trials to warrant pooling where data were available. A notable exception was Abrahams et al.[39], since participants of this trial also had to be diagnosed with malalignment. We presented data for this trial separately. Otherwise, we made the decision to pool data despite the heterogeneity in the characteristics of the trial populations. Most trials studied the general population, but some focused on specific populations, such as sedentary individuals[46 47 63], and people who did not engage in regular sports activity[53 57], compared with more active patients who participated in sports for at least 120 minutes/week[65] and recreational athletes[44 56 61]. Some studies included only males or females or people who had not undergone previous physiotherapy. The minimum duration of the compliant or symptoms was specified as an inclusion criterion in the majority of trials but varied from a few weeks to several months. This diversity in baseline characteristics of the trial participants hampers the applicability of the results but the main assumption that these trials were testing the effects of exercise for the same underlying condition is key to consideration of applicability. The variety of the exercises tested by different trials for the same comparison is shown by an inspection of Analysis 1.1, where six different types of exercise, tested in five trials, were compared with no treatment. The heterogeneity in the types of exercise together with the lack of or insufficient data available for direct comparisons of different types of exercise means that the interpretation of the applicability of the results should be levelled at generic exercise and not at specific types of exercise.

***Outcome measures***

Although there was also considerable heterogeneity in outcome measurement, most trials reported scores for pain during activity, usual pain (pain in daily life) and worst pain. We selected 'pain during descending' when pooling pain during activities because this again was frequently reported. Most studies reported functional ability with the Anterior Knee Pain Score (AKPS), (modified) FIQ or Lower Extremity Function Scale (LEFS). If multiple measures were reported, including the AKPS score, we used the latter for pooling as this score is reliable, valid and responsive when measuring the effect of therapy for PFPS.[21] Some studies reported function with scores initially designed for other purposes, such as knee instability (Lysholm score) or osteoarthritis (WOMAC).

When assessing the quality of the evidence from these different measures of functional ability, whether presented alone or pooled in a meta-analysis, we did not downgrade the evidence for indirectness because all of these measures, when presented as continuous outcomes, can be considered to be directly related to functional ability for people with PFPS. This is in contrast to recovery, which was assessed in different ways by the eight studies that reported on recovery. Notably, Van Linschoten et al.[27] found the effects of exercise on pain and function scores were not reflected in the effect on self reported recovery between groups. Van Linschoten et al.[27] commented on the difficulties in "understanding what exactly comprises recovery from the patient's point of view". Furthermore, incomplete recovery might reflect the true nature of PFPS.[87-89] Hence, self reported recovery can give additional insights on the natural course of PFPS or the effects of therapeutic interventions, since it cannot be fully understood by pain and function outcomes alone. Functional performance tests might also contribute in assessing a patient's 'recovery', as the ultimate goal of rehabilitation is return to the highest functional level. These tests are widely used in other sport-related injuries[26] and could be of use in patellofemoral pain research. However, standardisation is needed since the studies that performed these tests could not be pooled because they did not perform similar tests.

***Applicability***

The implications of pooling data from trials with different inclusion criteria and different exercise therapies, in particular for the comparison of exercise therapy versus control, means that only a general interpretation should be made in terms of the population (people diagnosed with PFPS) and the intervention (exercise therapy). This does not rule out that some subgroups of patients may benefit from a certain intervention while others may not[90], nor that some exercise interventions may be more effective or, indeed, that some may not be effective. Direct comparisons of different exercise interventions should help inform this issue but, although several trials have compared different exercises, the current evidence is very poor quality and does not provide definitive an-

swers. The studies on exercise therapy reflect the changing opinions through the years concerning preferred treatment strategy. For example, in the late 1970s and mid 1980s questions arose about the effect and possible side effects of open and closed kinetic chain exercises for PFPS. The very low quality evidence available in this review generally favoured open kinetic exercise but did not establish there being a clinically important difference between these two approaches. Around the turn of the 21st century there was increased interest in the delivery of exercises, in particular supervised versus home exercises. The very low quality evidence available on this comparison did not establish a difference between these two approaches. In the last decade, attention has shifted to hip exercises with or without knee exercises. Again there is only very low quality evidence to inform on the choice of hip plus knee versus knee only exercises or hip versus knee exercises. The available evidence tends to favour hip plus knee exercises or hip exercises with the potential for a clinically important effect on pain and function; but again is not definitive. Lastly, although one study provides evidence that a high-intensity exercise programme is more effective than a low intensity exercise programme for patients with untreated PFPS of over two months in duration[60], such a finding needs verification by further research and in a more general population.

Besides exercise, many other interventions are used for PFPS. Only very poor quality and generally incomplete evidence from single trials was available for comparisons of exercise therapy versus different unimodal or multimodal conservative treatment strategies. In terms of applicability, the focus should be on conservative treatment strategies in common use; the evidence base for such treatments, such as taping, also needs consideration.[9]

This review did not aim to investigate the additional value of other strategies when they are combined with exercise therapy.

***Quality of the evidence***

In the previous systematic review by Heintjes et al.[10], the authors pointed to the need for higher quality in study methodology and reporting. This need continues as several of the newly included studies were at high or unclear risk of bias for multiple domains (Figure 2), including selection bias reflecting the use of quasi-randomisation methods in two recently published trials. We assessed most trials as being at high risk of performance bias and detection bias; although blinding is generally impractical for exercise trials, some measures such as standardisation of interactions between personnel and patients can still be taken to reduce bias.

Overall, the quality of the evidence, expressed using GRADE terminology, varies between 'low quality' ("Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate") and 'very low quality' ("We are very uncertain about the estimate"). All the evidence for the outcomes

presented in our 'Summary of findings' tables was very low quality. In our assessment of the quality of the evidence according to the GRADE guidelines, downgrading resulted from risk of bias (primarily relating to sequence generation, allocation concealment and assessor blinding), imprecision (wide confidence intervals and small sample size), inconsistency (significant heterogeneity) and indirectness (here this was used only for inadequate outcome measures). In some cases we downgraded our assessment of the quality of the evidence by two levels for serious risk of bias, serious imprecision and/or serious inconsistency. In assessing imprecision, we planned to downgrade one level where there were fewer than 400 cases for continuous data or fewer than 300 cases for dichotomous data. More often, however, downgrading was based on an assessment of the spread of the 95% confidence interval or that the evidence was available solely from one small study, often with a large effect size. We did not downgrade for indirectness relating to patient characteristics because the results are 'direct' when the focus is on patients with PFPS. We avoided the problem of indirectness associated with Abrahams et al.[39], which focused on a different population by including only patients with a diagnosed malalignment, by not pooling this study with other studies comparing exercise versus a control strategy. Some studies focused on different predefined activity-based populations (less active or active) or included only males or females or patients without previous physiotherapy. Where studies included a more specific population, we took this into consideration by stating the specific population in the case of single studies and checking for heterogeneity in the case of pooled studies.

***Potential biases in the review process***

With some exceptions, as detailed in Differences between protocol and review (online available), we conducted this review in accordance with our previously published protocol[31]. Although the changes to the protocol were often prompted by our review of the evidence (for example, the division of the comparison 'exercise therapy versus different conservative interventions' into two separate comparisons), we strived to avoid bias by establishing the new rules and methods prior to our interpretation of the evidence. Although we conducted a comprehensive literature search and were systematic and over-inclusive in our screening process, it is likely that we failed to identify some, particularly unpublished, small single-centre trials. It is not possible to determine the bias resulting from this but it is notable that we have found only one ongoing trial; another small trial awaits classification pending translation.

***Agreements and disagreements with other studies or reviews***

We have found four recently published systematic reviews investigating the effects of exercise therapy for PFPS.[91-93] The scopes and inclusion criteria of all four reviews differed substantively from our review. For example, Bolgla and Boling[91]. and Frye et

al.[93] also included cohort and case-control studies. Harvie et al.[94] set out to examine the "parameters of exercise programs reported in primary research", and thus excluded randomised controlled trials (RCTs) that did not show an effect of exercise therapy. Collins et al.[92] included RCTs comparing all types of non-surgical interventions, including acupuncture, electromyography and taping.

Checks of the RCTs included in the four reviews did not reveal any that were missing from our review. Moreover, our review includes more trials, which also reflects our more up-to-date search. All four reviews assessed the quality of their included studies with a quality scale. Frye et al.[93] and Harvie et al.[94] used the PEDro scale. Collins et al[92] used a modified version of the PEDro scale, and Bolgla and Boling[91] used the Strength of Recommended Taxonomy.[95] However, the use of quality scales is not recommended, because these scales are inconsistent and unpredictable.[32] Other choices, such as pooling and presentation of the results and transparency of the reporting (for instance, it was unclear which studies were pooled in Frye et al.[93] also differed amongst the four reviews and with our review. Inspection of all four reviews mainly revealed the diversity in the approaches taken by the investigators and did not yield additional insights relating to exercise therapy.

## AUTHORS' CONCLUSION

### Implications for practice

This review has found very low quality but consistent evidence that exercise therapy for patellofemoral pain syndrome (PFPS) may result in clinically important reduction in pain and improvement in functional ability, as well as enhancing long-term recovery. However, the best form of exercise therapy and whether this result would apply to all people with PFPS are unknown.

There is insufficient evidence to draw conclusions about the relative effects of exercise versus other conservative interventions, either unimodal (e.g. taping) or multimodal (combinations of interventions that may include different exercises to the exercise intervention).

The very low quality evidence for each comparison examined by the included trials was from small single trials only.

The very low quality evidence available for comparisons of different exercises was insufficient to draw conclusions on the relative effects of supervised versus home exercises; closed versus open kinetic chain exercises; different variants of closed kinetic chain exercises; other comparisons of other types of kinetic chain exercises; proprioceptive neuromuscular facilitation stretching and aerobic exercise versus classic stretching and quadriceps exercises; hip versus knee exercises; and high- versus low-intensity exercises.

There is some very low quality evidence that hip plus knee exercises may be more effective in reducing pain than knee exercise alone, but the relative effect of these two exercise types on functional ability is uncertain.
There is a lack of evidence from randomised controlled trials on exercise medium (land versus water) and duration of exercises.

**Implications for research**

Further randomised trials, which conform to international standards in their design, conduct and reporting, are needed. However, to optimise research effort and underpin the large multicenter randomised trials that are required to inform practice, it is preferable to precede this with research that aims to identify priority questions and attain agreement on these and, where practical, standardisation regarding diagnostic criteria and measurement of outcome. The selection of priority areas for research should take into account the current coverage of the evidence, current practice and differences in practice, and should involve consultation with patients as to their preferences and values. Achieving professional consensus on treatment uncertainties should facilitate sufficient centre recruitment into multicentre trials and also implementation of their findings.
Although the identification of priority topics requires input from others, we make a few suggestions drawing from the evidence in this review.
First, although we accept that the underpinning evidence for the effectiveness of exercise therapy, while consistent in effect direction, is of very poor quality, we suggest that research should be directed at comparisons of different exercises rather than comparisons of exercise therapy versus control. In our perception, recent trends in clinical practice for patellofemoral pain syndrome are moving towards protocols featuring combined knee and hip exercise programmes and high-intensity exercise programmes. Both trends are insufficiently evidenced and thus further evaluation by randomised trials on these seems warranted.
Linked with this is the need to determine whether there are important differences in the effectiveness of exercise or different types of exercise in different patient populations. This points to the need for clear definitions of patient characteristics and pre-specified subgroups in trials, such as by pre-PFPS activity level, which can help to inform on potential variation in the effects of exercise therapy.
In terms of outcomes, we suggest that consideration is given to standardising pain during a patient-nominated activity and, until a better instrument is developed, using the Anterior Knee Pain Score (AKPS)[24] to assess functional ability in future studies. The natural course of patellofemoral pain syndrome varies considerably and more research is needed to identify the risk factors for prolonged pain and functional deficit, and the potential association with degenerative joint disease. As evidenced in this review, not all

patients show full recovery and thus the development of a validated outcome measure that captures patient-rated recovery seems warranted.

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## APPENDIX

### Appendix 1 Search strategies

#### Cochrane Central Register of Controlled Trials (Wiley Online Library)

#1 MeSH descriptor: [Patellofemoral Pain Syndrome] this term only (68)
#2 MeSH descriptor: [Patella] this term only (243)
#3 MeSH descriptor: [Knee Joint] explode all trees (2304)
#4 MeSH descriptor: [Knee] this term only (573)
#5 #2 or #3 or #4 (2957)
#6 MeSH descriptor: [Arthralgia] this term only (466)
#7 MeSH descriptor: [Pain] explode all trees (32936)
#8 #6 or #7 (32936)
#9 #5 and #8 (710)
#10 anterior knee pain:ti,ab,kw (353)
#11 (patell* or femoropatell* or femoro-patell* or retropatell*) near/2 (pain or syndrome or dysfunction):ti,ab,kw (284)
#12 ((lateral compression or lateral facet or lateral pressure or odd facet) near/2 syndrome):ti,ab,kw (0)
#13 (chondromalac* or chondropath* or chondrosis) near/2 (knee* or patell* or femoropatell* or femoro-patell* or retropatell*):ti,ab,kw (31)
#14 MeSH descriptor: [Chondromalacia Patellae] this term only (5)
#15 #1 or #9 or #10 or #11 or #12 or #13 or #14 (1185)
#16 MeSH descriptor: [Exercise Therapy] explode all trees (7116)
#17 MeSH descriptor: [Exercise] explode all trees (13885)
#18 exercis* or strengthen* or stretch* or train* or physiotherapy or physical therap*:ti,ab,kw (70701)
#19 #16 or #17 or #18 (71833)
#20 #9 and #15 and #19 in Trials (148)

#### MEDLINE (Ovid Online)

1 Patellofemoral Pain Syndrome/ (453)
2 Patella/ or exp Knee Joint/ or Knee/ (56364)
3 Arthralgia/ or Pain/ (112939)
4 2 and 3 (3290)
5 anterior knee pain.tw. (1003)
6 ((patell* or femoropatell* or femoro-patell* or retropatell*) adj2 (pain or syndrome or dysfunction)).tw. (1766)

7 ((lateral compression or lateral facet or lateral pressure or odd facet) adj2 syndrome).tw. (20)
8 ((chondromalac* or chondropath* or chondrosis) adj2 (knee*1 or patell* or femoropatell* or femoro-patell* or retropatell*)).tw. (513)
9 Chondromalacia Patellae/ (59)
10 or/1,4-9 (5753)
11 exp Exercise Therapy/ or exp Exercise/ (140226)
12 (exercis* or strengthen* or stretch* or train* or physiotherapy or physical therap*).tw. (595688)
13 or/11-12 (655179)
14 Randomized controlled trial.pt. (373732)
15 Controlled clinical trial.pt. (88369)
16 randomized.ab. (293610)
17 placebo.ab. (153908)
18 Drug therapy.fs. (1698370)
19 randomly.ab. (212608)
20 trial.ab. (304899)
21 groups.ab. (1353578)
22 or/14-21 (3335964)
23 exp Animals/ not Humans/ (3938734)
24 22 not 23 (2860785)
25 and/10,13,24 (343)

**EMBASE (Ovid Online)**

1 Patellofemoral Pain Syndrome/ (678)
2 Patella/ or Patellofamoral Joint/ (6639)
3 Arthralgia/ or Pain/ (229980)
4 2 and 3 (518)
5 Knee Pain/ (7720)
6 anterior knee pain.tw. (1178)
7 ((patell* or femoropatell* or femoro-patell* or retropatell*) adj2 (pain or syndrome or dysfunction)).tw. (2017)
8 ((lateral compression or lateral facet or lateral pressure or odd facet) adj2 syndrome).tw. (25)
9 ((chondromalac* or chondropath* or chondrosis) adj2 (knee*1 or patell* or femoropatell* or femoro-patell* or retropatell*)).tw. (601)
10 Patella Chondromalacia/ (581)
11 or/1,4-10 (11083)
12 exp Exercise/ or exp Kinesiotherapy/ (228968)

13 (exercis* or strengthen* or stretch* or train* or physiotherapy or physical therap*).tw. (700876)
14 12 or 13 (777358)
15 exp Randomized Controlled Trial/ or exp Single Blind Procedure/ or expDouble Blind Procedure/ or Crossover Procedure/ (384984)
16 (random* or RCT or placebo or allocat* or crossover* or 'cross over' or trial or (doubl* adj1 blind*) or (singl* adj1 blind*)).ti,ab. (1230960)
17 15 or 16 (1303210)
18 (exp Animal/ or Animal.hw. or Nonhuman/) not (exp Human/ or Human Cell/ or (human or humans).ti.) (5041638)
19 17 not 18 (1144157)
20 11 and 14 and 19 (471)

**CINAHL (EBSCO)**

S1 (MH "Patellofemoral Pain Syndrome") (915)
S2 (MH "Patella") OR (MH "Knee") OR (MH "Knee Joint") (15,082)
S3 (MH "Arthralgia") and (MH "Pain") (60)
S4 S2 AND S3 (10)
S5 TX anterior knee pain (436)
S6 TX ((patell* or femoropatell* or femoro-patell* or retropatell*) n2 (pain or syndrome or dysfunction)) (1,263)
S7 TX ((lateral compression or lateral facet or lateral pressure or odd facet) n2 syndrome) (7)
S8 TX ((chondromalac* or chondropath* or chondrosis) n2 (knee* or patell* or femoropatell* or femoro-patell* or retropatell*)) (107)
S9 (MH "Chondromalacia Patella") (61)
S10 S1 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 (1,626)
S11 (MH "Therapeutic Exercise+") and (MH "Exercise+") (18,366)
S12 (exercis* or strengthen* or stretch* or train* or physiotherapy or physical therap*) (249,334)
S13 S11 OR S12 (249,543)
S14 PT clinical trial (75,963)
S15 (MH "Clinical Trials+") (174,859)
S16 TI clinical trial* OR AB clinical trial* (41,307)
S17 TI ( (single blind* or double blind*) ) OR AB ( (single blind* or double blind*) ) (19,881)
S18 TI random* OR AB random* (136,297)
S19 S14 OR S15 OR S16 OR S17 OR S18 (255,533)
S20 S10 AND S13 AND S19 (147)

**AMED (Ovid Online)**

1 Patellofemoral pain syndrome/ (58)
2 Patella/ or Knee/ or Knee Joint/ (4479)
3 Pain/ or Arthralgia/ (10265)
4 2 and 3 (631)
5 anterior knee pain.tw. (128)
6 ((patell* or femoropatell* or femoro-patell* or retropatell*) adj2 (pain or syndrome or dysfunction)).tw. (449)
7 ((lateral compression or lateral facet or lateral pressure or odd facet) adj2 syndrome).tw. (1)
8 ((chondromalac* or chondropath* or chondrosis) adj2 (knee*1 or patell* or femoropatell* or femoro-patell* or retropatell*)).tw. (29)
9 or/1,4-8 (905)
10 Randomized controlled trial.pt. (2931)
11 Controlled clinical trial.pt. (70)
12 Randomized Controlled Trials/ (1658)
13 Random Allocation/ (311)
14 Double-Blind Method/ (506)
15 or/10-14 (5218)
16 exp Animals/ not Humans/ (7553)
17 15 not 16 (5189)
18 Clinical trial.pt. (1160)
19 exp Clinical trials/ (3368)
20 (clinic* adj25 trial*).tw. (5872)
21 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind*)).tw. (2343)
22 Placebos/ (547)
23 placebo*.tw. (2655)
24 random*.tw. (14183)
25 exp Research design/ (17924)
26 (latin adj square).tw. (24)
27 or/18-26 (31604)
28 27 not 16 (31059)
29 28 not 17 (26011)
30 9 and 29 (174)

**Summary of findings table for comparison 1.** Exercise therapy compared with a control strategy (no treatment, placebo or waiting list controls) for patello-femoral pain syndrome

**Patient or population:** patients with patellofemoral pain syndrome (symptoms > 3 weeks (1 study); symptoms > 1 month (3 studies); symptoms > 2 months (2 studies); symptoms > 3 months (2 studies; symptoms > 6 months (1 study). (Data from a study including participants with patella malalignment are not included here.)
**Settings:** various: orthopaedic clinics, rheumatology consultants, general practices, rehabilitation service, physiotherapy practices, sports medical practices, chiropractor practices
**Intervention:** exercise therapy (various descriptions in the included trials, including knee exercises, hip and knee exercises, home exercises, supervised exercises, closed kinetic chain, open kinetic chain)
**Comparison:** control (no treatment, waiting list, health educational material)

| | Illustrative comparative risks* (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
| Outcomes | Control strategy | Exercise therapy | | | | |
| **Pain during activity (short-term)**<br>**Scale (0 to 10; higher scores mean worse pain)[1]**<br>**Follow-up range: 4 weeks to 3 months** | The mean pain in the control group ranged from 2.1 to 6.0 points[2] | The mean pain during activity (short-term) in the exercise group was 1.46 lower (2.39 to 0.54 lower) | MD -1.46 (-2.39 to -0.54) | 375 (5 studies) | ⊕⊖⊖⊖ very low[3] | |
| **Usual pain (short-term)**<br>**Scale (0 to 10; higher scores mean worse pain)[4]**<br>**Follow-up: 4 or 8 weeks** | | The mean difference in usual pain (short-term) in the exercise group was 0.93 standard deviations lower (1.60 to 0.25 lower) | SMD -0.93 (-1.60 to -0.25) | 41 (2 studies) | ⊕⊖⊖⊖ very low[5] | In order to interpret these results in terms of the VAS (0 to 10), the SMD was multiplied by the median SD of VAS usual pain (1.55)<br>The mean usual pain (short-term) in the exercises group was an estimated 1.44 lower (2.48 to 0.39 lower) |

**Summary of findings table for comparison 1.** (continued)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control strategy | Exercise therapy | | | | |
| **Pain during activity (long-term)**<br>**Scale (0 to 10; higher scores mean worse pain)[6]**<br>**Follow-up: 12 months** | The mean pain in the control group ranged from 2.6 to 3.9 points[2] | The mean pain during activity (long-term) in the exercise group was 1.07 lower (1.93 to 0.21 lower) | MD -1.07 (-1.93 to -0.21) | 180 (2 studies) | ⊕⊖⊖⊖ very low[5] | |
| **Usual pain (long-term)**<br>**VAS (0 to 10; higher scores mean worse pain)**<br>**Follow-up: 16 weeks** | The mean pain in the control group was 6.6 points[2] | The mean usual pain (long-term) in the exercise group was 4.32 lower (7.75 to 0.89 lower) | MD -4.32 (-7.75 to -0.89) | 94 (1 study) | ⊕⊖⊖⊖ very low[7] | |
| **Functional ability (short-term)**<br>**Scale (0 to 100; higher scores mean better function)[8]**<br>**Follow-up range: 4 weeks to 3 months** | | The mean difference in functional ability (short-term) in the exercise group was 1.10 standard deviations higher (0.58 to 1.63 higher) | SMD 1.10 (0.58 to 1.63) | 483 (7 studies) | ⊕⊖⊖⊖ very low[9] | In order to interpret these results in terms of the AKPS, values were scaled to 0 to 100 and the SMD was multiplied by the median SD of the AKPS (11.1)<br>The mean functional ability (short-term) in the exercises group was an estimated 12.21 higher (6.44 to 18.09 higher) |

**Summary of findings table for comparison 1.** (continued)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control strategy | Exercise therapy | | | | |
| **Functional ability (long-term) Scale (0 to 100; higher scores mean better function)[10] Follow-up range: 16 weeks to 12 months** | | The mean difference in functional ability (long-term) in the exercise group was 1.62 standard deviations higher (0.31 to 2.94 higher) | SMD 1.62 (0.31 to 2.94) | 274 (3 studies) | ⊕⊖⊖⊖ very low[11] | In order to interpret these results in terms of the AKPS, values were scaled to 0 to 100 and the SMD was multiplied by the median SD of the AKPS (11.1) The mean functional ability (long-term) in the exercises group was an estimated 17.98 higher (3.44 to 32.63 higher) |
| **Recovery (long-term) Number of patients who had recovered or number of patients no longer troubled by symptoms Follow-up: 12 months** | 250 per 1000[12] | 338 per 1000 (248 to 460) | RR 1.35 (0.99 to 1.84) | 166 (2 studies) | ⊕⊖⊖⊖ very low[13] | These data equate to 88 more (95% CI 2 fewer to 210 more) participants per 1000 who would recover in the long term as a result of exercise therapy |

*The basis for the assumed risk is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

AKPS: Anterior Knee Pain Score; CI: confidence interval; MCID: minimal clinically important difference; MD: mean difference; NPRS: numerical pain rating scale; RR: risk ratio; SMD: standardised mean difference; VAS: visual analogue scale/score

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

[1]Data were from VAS (0 to 10), NPRS (0 to 10) and VAS (0 to 200). Values were scaled to 0 to 10 (higher is worse). These measures are comparable and thus we calculated MDs.

[2]The basis for the assumed risk is the range of the control group risk of the studies.

[3]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (primarily relating to lack of assessor blinding), one level for imprecision (wide confidence intervals and small sample size) and one level for serious inconsistency (heterogeneity: P value = 0.0003, $I^2$ = 74%).

[4]Data were from VAS (0 to 10) and the McGill pain questionnaire (0 to 10).

[5]In our assessment of the quality of the evidence for this outcome, we downgraded two levels for serious risk of bias (relating to lack of allocation concealment and lack of assessor blinding) and one level for imprecision (small sample size).

[6]Data were from VAS (0 to 10) and VAS (0 to 200). Values were scaled to 0 to 10 (higher is worse). These measures are comparable and thus we calculated MDs.

[7]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (primarily relating to lack of assessor blinding) and two levels for serious imprecision (wide confidence intervals and small sample size).

[8]Data were from the AKPS (0 to 100), Lysholm (0 to 100), Function Scale (0 to 53) and WOMAC Osteoarthritis Index (0 to 96). We rescaled data from the Function Scale and WOMAC to 0 to 100; we inverted those from WOMAC first.

[9]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (primarily relating to lack of assessor blinding) and two levels for serious inconsistency (P value < 0.00001, $I^2$ = 83%).

[10]Data were from the AKPS (0 to 100) and WOMAC Osteoarthritis Index (0 to 96). We inverted data from WOMAC and rescaled data to 0 to 100.

[11]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (primarily relating to lack of assessor blinding), one level for imprecision (small sample size) and one level for serious inconsistency (heterogeneity: P value < 0.00001, $I^2$ = 94%).

[12]The basis for the assumed risk is the median control group risk of the studies.

[13]In our assessment of the quality of the evidence for this outcome, we downgraded two levels for serious risk of bias (relating to lack of allocation concealment and lack of assessor blinding) and one level for imprecision (small sample size).

**Summary of findings table for comparison 3a.** Supervised exercises compared with home exercises for patellofemoral pain syndrome

**Patient or population:** patients with patellofemoral pain syndrome (symptoms > 2 months (1 study); not stated (1 study))
**Settings:** orthopaedic clinics, general practices
**Intervention:** supervised exercises
**Comparison:** home exercises

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Home exercises | Supervised exercises | | | | |
| **Pain during activity (short-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in either of the 2 studies for this comparison |
| **Usual pain (short-term) VAS (0 to 10; higher scores mean worse pain) Follow-up: 8 weeks or 3 months** | The mean pain in the home exercises group ranged from 1.7 to 2.0 points[1] | The mean usual pain (short-term) in the supervised exercises group was 0.22 lower (1.22 lower to 0.77 higher) | MD -0.22 (-1.22 to 0.77) | 59 (2 studies) | ⊕⊖⊖⊖ very low[2] | |
| **Pain during activity (long-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in either of the 2 studies for this comparison |
| **Usual pain (long-term) VAS (0 to 10; higher scores mean worse pain) Follow-up: 12 months** | The mean pain in the home exercises group was 1.3 points[1] | The mean usual pain (long-term) in the supervised exercises group was 0.43 lower (1.84 lower to 0.98 higher) | MD -0.43 (-1.84 to 0.98) | 31 (1 study) | ⊕⊖⊖⊖ very low[2] | The confidence interval excludes the MCID for usual pain of 2.0 points[3] |
| **Functional ability (short-term) AKPS (0 to 100; higher scores mean better function) Follow-up: 8 weeks (1 month)** | The mean AKPS score in the home exercises group was 86.6 points[1] | The mean functional ability (short-term) in the supervised exercises group was 2.30 lower (11.33 lower to 6.73 higher) | MD -2.30 (-11.33 to 6.73) | 18 (1 study) | ⊕⊖⊖⊖ very low[3] | The other study making this comparison (28 participants) found a greater number of people in the home exercises group with high (13 to 16) FIQ scores indicating best function[4]: RR 0.46, 95% CI 0.21 to 1.01; very low quality evidence[5] |

**Summary of findings table for comparison 3a** (continued)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Home exercises | Supervised exercises | | | | |
| **Functional ability (long-term) FIQ (number of patients in top (best function) category 13 to 16)[4] Follow-up: 12 months** | 632 per 1000[1] | 847 per 1000 (563 to 1000) | RR 1.34 (0.89 to 2.03) | 31 (1 study) | ⊕⊖⊖⊖ very low[5] | These data equate to 215 more (95% CI 69 fewer to 468 more) participants per 1000 who would have best function in the long term as a result of supervised exercise |
| **Recovery (long-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in either of the 2 studies for this comparison |

*The basis for the assumed risk is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

AKPS: Anterior Knee Pain Score; CI: confidence interval; FIQ: Functional Index Questionnaire; MD: mean difference; RR: risk ratio; VAS: visual analogue scale/score

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

[1]The basis for the assumed risk is the range of the control group risk of the studies.

[2]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding) and two levels for serious imprecision (small sample size).

[3]In our assessment of the quality of the evidence for this outcome, we downgraded two levels for serious risk of bias (relating to lack of allocation concealment and lack of assessor blinding) and one level for imprecision (small sample size).

[4]This trial presented the numbers of participants with scores split into four FIQ categories (0 to 4, 5 to 8, 9 to 12, 13 to 16). We present the data for those in the top (13 to 16, best function) category.

[5]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding), one level of indirectness (reflecting the inadequateness of the outcome) and one level for imprecision (small sample size).

**Summary of findings table for comparison 3c.** Closed kinetic chain exercises compared with open kinetic chain exercises for patellofemoral pain syndrome

**Patient or population:** patients with patellofemoral pain syndrome (symptoms > 4 weeks (1 study); symptoms > 6 weeks (1 study); symptoms > 8 weeks (1 study); not stated (1 study))
**Settings:** orthopaedic clinics, physiotherapy practices
**Intervention:** closed kinetic chain exercises
**Comparison:** open kinetic chain exercises

| | Illustrative comparative risks* (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| Outcomes | Open kinetic chain (OKC) exercises | Closed kinetic chain (CKC) exercises | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
| **Pain during activity (short-term)**<br>**VAS (0 to 10; higher scores mean worse pain)**<br>**Follow-up: 6 weeks or 3 months** | The mean pain in the OKC exercises group ranged from 0.9 to 2.7 points[1] | The mean pain during activity (short-term) in the CKC group was 0.03 higher (0.63 lower to 0.70 higher) | MD 0.03 (-0.63 to 0.70) | 90 (2 studies) | ⊕⊖⊖⊖ very low[2] | |
| **Usual pain (short-term)**<br>**VAS (0 to 10; higher scores mean worse pain)**<br>**Follow-up range: 4 weeks to 3 months** | The mean pain in the OKC exercises group ranged from 1.8 to 4.87 points[1] | The mean usual pain (short-term) in the CKC group was 0.20 higher (0.37 lower to 0.76 higher) | MD 0.20 (-0.37 to 0.76) | 122 (3 studies) | ⊕⊖⊖⊖ very low[3] | |
| **Pain during activity (long-term)**<br>**VAS (0 to 10; higher scores mean worse pain)**<br>**Follow-up: 5 years** | The mean pain in the OKC exercises group was 0.7 points[1] | The mean pain during activity (long-term) in the CKC group was 2.10 higher (1.08 to 3.12 higher) | MD 2.10 (1.08 to 3.12) | 49 (1 study) | ⊕⊖⊖⊖ very low[3] | |

**Summary of findings table for comparison 3c** (continued)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Open kinetic chain (OKC) exercises | Closed kinetic chain (CKC) exercises | | | | |
| **Usual pain (long-term)**<br>**VAS (0 to 10; higher scores mean worse pain)**<br>**Follow-up: 5 years** | The mean pain in the OKC exercises group was 1.0 points[1] | The mean usual pain (long-term) in the CKC group was 0.80 higher (0.07 to 1.53 higher) | MD 0.80 (0.07 to 1.53) | 49 (1 study) | ⊕⊖⊖⊖ very low[3] | |
| **Functional ability (short-term)**<br>**AKPS (0 to 100; higher scores mean better function)**<br>**Follow-up: 6 weeks or 3 months** | The mean AKPS score in the OKC exercises group ranged from 89.1 to 91.7 points[1] | The mean functional ability (short-term) in the CKC group was 3.51 lower (7.84 lower to 0.82 higher) | MD -3.51 (-7.84 to 0.82) | 90 (2 studies) | ⊕⊖⊖⊖ very low[4] | |
| **Functional ability (long-term)**<br>**AKPS (0 to 100; higher scores mean better function)**<br>**Follow-up: 5 years** | The mean AKPS score in the OKC exercises group was 90 points[1] | The mean functional ability (long-term) in the CKC group was 8.30 lower (12.95 to 3.65 lower) | MD -8.30 (-12.95 to -3.65) | 49 (1 study) | ⊕⊖⊖⊖ very low[3] | |
| **Recovery (long-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in any of the 4 studies making this comparison |

*The basis for the assumed risk is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

AKPS: Anterior Knee Pain Score; CKC: closed kinetic chain; CI: confidence interval; MD: mean difference; OKC: open kinetic chain; VAS: visual analogue scale/score

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes
[1]The basis for the assumed risk is the range of the control group risk of the studies.
[2]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding), one level for imprecision (small sample size) and one level for inconsistency (heterogeneity: P value = 0.08; $I^2 = 67\%$).
[3]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding) and two levels for serious imprecision (small sample size).
[4]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding), one level for imprecision (small sample size) and one for inconsistency (heterogeneity: P value = 0.06; $I^2 = 71\%$

**Summary of findings table for comparison 3dI.** Target of exercise: hip + knee versus knee exercises for treating patellofemoral pain syndrome

**Patient or population:** patients with patellofemoral pain syndrome (symptoms > 1 month (3 studies); symptoms > 2 months (1 study); symptoms > 3 months (2 studies); not stated (1 study))
**Settings:** various: orthopaedic clinics, rehabilitation service, physiotherapy practices/clinics
**Intervention**: hip + knee exercises
**Comparison:** knee exercises

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Knee exercises | Hip + knee exercises | | | | |
| **Pain during activity (short-term)**<br>**Scale (0 to 10; higher scores mean worse pain)[1]**<br>**Follow-up range: 4 weeks to 3 months** | The mean pain in the knee exercises group ranged from 2.0 to 5.0 points[2] | The mean pain during activity in the hip + knee exercise group was 2.02 lower (3.80 lower to 0.60 higher) | MD -2.02 (-3.80 to -0.60) | 104 (3 studies) | ⊕⊖⊖⊖ very low[3] | |
| **Usual pain (short-term)**<br>**VAS (0 to 10; higher scores mean worse pain)**<br>**Follow-up: 4 to 6 weeks** | The mean pain in the knee exercises group ranged from 4.0 to 4.8 points[2] | The mean usual pain in the hip + knee exercise group was 1.77 lower (2.78 to 0.76 lower) | MD -1.77 (-2.78 to -0.76) | 46 (2 studies) | ⊕⊖⊖⊖ very low[4] | |
| **Pain during activity (long-term)**<br>**NPRS (0 to 10; higher scores mean worse pain)**<br>**Follow-up: 12 months** | The mean pain in the knee exercises group was 6.4 points[2] | The mean pain during activity in the knee + hip exercise group was 3.90 lower (4.46 to 3.34 lower) | MD -3.90 (-4.46 to -3.34) | 49 (1 study) | ⊕⊖⊖⊖ very low[5] | |
| **Usual pain (long-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in any of the 7 studies making this comparison |

**Summary of findings table for comparison 3dI.** (continued)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Knee exercises | Hip + knee exercises | | | | |
| **Functional ability (short-term) Scale (0 to 100; higher scores mean better function)[6] Follow-up range: 4 weeks to 3 months** | | The mean difference in functional ability (short-term) in the hip + knee exercise group was 0.61 standard deviations higher (0.39 lower to 1.61 higher) | SMD 0.61 (-0.39 to 1.61) | 174 (4 studies) | ⊕⊖⊖⊖ very low[7] | In order to interpret these results in terms of the AKPS, we scaled values to 0 to 100 and multiplied the SMD by the median SD of the AKPS (11.1) The mean functional ability (short-term) in the hip + knee exercises group was an estimated 6.77 higher (4.33 lower to 17.87 higher) |
| **Functional ability (long-term) Scale (0 to 100; higher scores mean better function)[8] Follow-up range: 5 to 12 months** | | The mean difference in functional ability (long-term) in the hip and knee exercise group was 1.49 standard deviations higher (0.17 lower to 3.15 higher) | SMD 1.49 (-0.17 to 3.15) | 78 (2 studies) | ⊕⊖⊖⊖ very low[9] | In order to interpret these results in terms of the AKPS, we scaled values to 0 to 100 and multiplied the SMD by the median SD of the AKPS (11.1) The mean functional ability (short-term) in the hip + knee exercises group was an estimated 16.54 higher (1.89 lower to 34.97 higher) |
| **Recovery long-term Number of patients at least moderately better Follow-up: 5 months** | 688 per 1000[2] | 922 per 1000 (640 to 1000) | RR 1.34 (0.93 to 1.94) | 29 (1 study) | ⊕⊖⊖⊖ very low[10] | These data equate to 234 more (95% CI 48 fewer to 312 more) participants per 1000 who would have recovered in the long term as a result of hip and knee exercise |

*The basis for the assumed risk is provided in the footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

AKPS: Anterior Knee Pain Score; CI: confidence interval; MD: mean difference; NPRS: numerical pain rating score; RR: risk ratio; SMD: standardised mean difference; VAS: visual analogue scale/score

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1]Data were from VAS (0 to 10) and NPRS (0 to 10). We scaled values to 0 to 10 (higher is worse). These measures are comparable and thus we calculated MDs.

[2]The basis for the assumed risk is the range of the control group risk of the studies.

[3]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding), one level for imprecision (wide confidence intervals and small sample size) and one level for serious inconsistency (heterogeneity: P value = 0.004, $I^2$ = 82%).

[4]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding) and two levels for serious imprecision (wide confidence intervals and small sample size).

[5]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding) and two levels for serious imprecision.

[6]Data were from the lower extremity function scale (LEFS) score (0 to 80) in one study, AKPS (0 to 100) in two studies and Lysholm (0 to 100) in one study. We rescaled data from the LEFS to 0 to 100.

[7]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding), one level for imprecision (wide confidence intervals and small sample size) and one level for serious inconsistency (heterogeneity: P value < 0.00001, $I^2$ = 90%).

[8]Data were from the lower extremity function scale (LEFS) score (0 to 80) in one study and AKPS (0 to 100) in the second study. We rescaled data from the LEFS to 0 to 100.

[9]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding), one level for imprecision and one level for serious inconsistency (P value = 0.002, $I^2$ = 90%).

[10]In our assessment of the quality of the evidence for this outcome, we downgraded one level for risk of bias (relating to lack of assessor blinding) and two levels for serious imprecision.

**Summary of findings table for comparison 3dII.** Target of exercise: hip versus knee exercises for treating patellofemoral pain syndrome

**Patient or population:** patients with patellofemoral pain syndrome (symptoms > 1 month (1 study); symptoms > 6 months (1 study))
**Settings:** athletic trainer, physician (not-specified)
**Intervention**: hip exercises
**Comparison:** knee exercises

| | Illustrative comparative risks* (95% CI) | | | | | |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
| **Outcomes** | **Knee exercises** | **Hip exercises** | | | | |
| **Pain during activity (short-term) VAS (0 to 10; higher scores mean worse pain) Follow-up: 8 weeks** | The mean pain in the knee exercises group was 3.27 points[1] | The mean pain in the hip exercises group was 1.16 lower (2.41 lower to 0.09 higher) | MD -1.16 (-2.41 to 0.09) | 36 (1 study) | ⊕⊖⊖⊖ very low[2] | |
| **Usual pain (short-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in either of the 2 studies for this comparison |
| **Pain during activity (long-term) VAS (0 to 10; higher scores mean worse pain) Follow-up: 6 months** | The mean pain in the knee exercises group was 4.0 points[1] | The mean pain in the hip exercises group was 2.00 lower (3.45 to 0.55 lower) | MD -2.00 (-3.45 to -0.55) | 36 (1 study) | ⊕⊖⊖⊖ very low[2] | |
| **Usual pain (long-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in either of the 2 studies for this comparison |
| **Functional ability (short-term) Scale (0 to 100; higher scores mean better function)[3] Follow-up: 8 weeks or 3 months** | | The mean difference in functional ability (short-term) in the hip exercises group was 0.85 standard deviations higher (0.30 to 1.40 higher) | SMD 0.85 (0.30 to 1.40) | 58 (2 studies) | ⊕⊖⊖⊖ very low[2,4] | In order to interpret these results in terms of the AKPS, we scaled values to 0 to 100 and multiplied the SMD by the median SD of AKPS (11.1) The mean functional ability (short-term) in the hip exercises group was an estimated 9.44 higher (3.33 to 15.54 higher) |

**Summary of findings table for comparison 3dII** (continued)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Knee exercises | Hip exercises | | | | |
| **Functional ability (long-term) WOMAC (0 to 96; inverted scores so that higher scores mean better function) Follow-up: 6 months** | The mean WOMAC score in the knee exercises group was 72.84 points[1,5] | The mean functional ability continuous long-term in the intervention groups was 16.22 higher (9.17 to 23.27 higher) | MD 16.22 (9.17 to 23.27) | 36 (1 study) | ⊕⊖⊖⊖ very low[2] | |
| **Recovery (long-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in either of the 2 studies for this comparison |

*The basis for the assumed risk is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
AKPS: Anterior Knee Pain Score; CI: confidence interval; MD: mean difference; SMD: standardised mean difference; VAS: visual analogue scale/score
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes
[1]The basis for the assumed risk is the control group risk of the study.
[2]In our assessment of the quality of the evidence for this comparison, we downgraded two levels for serious risk of bias (relating to lack of allocation concealment and/or lack of assessor blinding) and one or two levels for serious imprecision (wide confidence intervals and small sample size).
[3] Data were from the lower extremity function scale (LEFS) score (0 to 80) in one study and WOMAC Osteoarthritis Index (0 to 96) in the other study. We rescaled data from both scales to 0 to 100; we inverted those from WOMAC first.
[4] We also downgraded the quality of the evidence for this outcome for inconsistency due to heterogeneity (heterogeneity: P value = 0.08; $I^2$ = 68%).
[5]We inverted the data for the WOMAC score (subtracted from 96) so that higher scores = better outcome.

**Summary of findings table for comparison 3f.** High-intensity versus low-intensity exercise programmes for patellofemoral pain syndrome

**Patient or population:** patients with patellofemoral pain syndrome (untreated PFPS of over 2 months in duration)
**Settings:** general practice or orthopaedic clinics
**Intervention:** high-intensity exercise programme
**Comparison:** low-intensity exercise programme

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Low-intensity exercise | High-intensity exercise | | | | |
| **Pain during activity (short-term)** | See comment | See comment | Not estimable | - | See comment | Not measured in the single study testing this comparison |
| **Usual pain (short-term)**<br>**VAS (0 to 10; higher scores mean worse pain)**<br>**Follow-up: 3 months** | The mean pain in the low-intensity exercise group was 2.6 points | The mean pain in the high-intensity exercise group was 1.90 lower (2.85 to 0.95 lower) | MD -1.90 (-2.85 to -0.95) | 40 (1 study) | ⊕⊖⊖⊖ very low[1] | |
| **Pain during activity long-term** | See comment | See comment | Not estimable | - | See comment | Not measured in the single study testing this comparison |
| **Usual pain (long-term)**<br>**VAS (0 to 10; higher scores mean worse pain)**<br>**Follow-up: 12 months** | The mean pain in the low-intensity exercise group was 3.5 points | The mean pain in the high-intensity exercise group was 3.20 lower (4.05 to 2.35 lower) | MD -3.20 (-4.05 to -2.35) | 28 (1 study) | ⊕⊖⊖⊖ very low[1] | |

**Summary of findings table for comparison 3f.** (continued)

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Low-intensity exercise | High-intensity exercise | | | | |
| **Functional ability (short-term) FIQ modified (0 to 16; higher scores mean better function) Follow-up: 3 months** | The mean FIQ score in the low-intensity exercise group was 9.8 points | The mean FIQ score in the high-intensity exercise groups was 3.70 higher (1.59 to 5.81 higher) | MD 3.70 (1.59 to 5.81) | 40 (1 study) | ⊕⊖⊖⊖ very low[1] | |
| **Functional ability (long-term) FIQ modified (0 to 16; higher scores mean better function) Follow-up: 12 months** | The mean FIQ score in the low-intensity exercise group was 10.2 points | The mean functional ability continuous long-term in the intervention groups was 3.90 higher (1.72 to 6.08 higher) | MD 3.90 (1.72 to 6.08) | 28 (1 study) | ⊕⊖⊖⊖ very low[1] | |
| **Recovery (long-term)** | See comment | See comment | Not estimable | - | See comment | |

*The basis for the assumed risk is the control group risk of the study. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: confidence interval; FIQ: Functional Index Questionnaire; MD: mean difference; VAS: visual analogue scale/score
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes
[1]In our assessment of the quality of the evidence for this comparison, we downgraded one level for risk of bias (relating to lack of assessor blinding) and two levels for imprecision (wide confidence intervals and small sample size)

# Chapter 3

## Structural abnormalities on MRI in patients with patellofemoral pain: a cross-sectional case-control study

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## ABSTRACT

### Background

Structural abnormalities of the patellofemoral joint might play a role in the pathogenesis of patellofemoral pain (PFP), a common knee problem among young and physically active individuals. No previous study has investigated if PFP is associated with structural abnormalities of the patellofemoral joint using high-resolution magnetic resonance imaging (MRI).

Purpose: This study aims to investigate the presence of structural abnormalities of the patellofemoral joint on high-resolution MRI in patients with PFP compared to healthy control subjects.

### Study Design

Case-control study.

### Methods

Patients with PFP and healthy control subjects aged between 14 and 40 years underwent high-resolution MRI at 3T. All images were scored using the Magnetic Resonance Imaging Osteoarthritis Knee Score (MOAKS) with the addition of specific patellofemoral features. Associations between PFP and the presence of structural abnormalities were analysed using logistic regression analyses, adjusted for age, BMI, sex and sports participation.

### Results

64 patients and 70 control subjects were included. Mean age was 23.2 (6.4) year, mean BMI 22.9 (3.4) and 56.7% was female. Full thickness cartilage loss was not present. Minor patellar cartilage defects, patellar bone marrow lesions (BMLs) and high signal intensity of Hoffa's fat pad were frequently seen in both patients (23%, 53% and 58% respectively) and control subjects (21%, 51% and 51% respectively). After adjustment for age, BMI, sex and sports participation, none of the structural abnormalities were statistically significantly associated with PFP.

### Conclusions

Many structural abnormalities of the patellofemoral joint were seen on MRI in this relatively young population, but none of them were associated with PFP.

Clinical Relevance: Structural abnormalities of the patellofemoral joint have been hypothesized as a factor in the pathogenesis of PFP, but our findings suggest that structural abnormalities of the patellofemoral joint on MRI are not associated with PFP.

## INTRODUCTION

Patellofemoral pain (PFP) is a common knee condition, defined as retro or peripatellar pain that occurs during knee loading activities, like running, cycling, squatting, stair climbing and during prolonged sitting with the knees bent. PFP is particularly present among young and physically active individuals and may account for up to 40% of all knee problems seen in sports injury clinics.[1-4] PFP can have a debilitating effect, because of the common recurrence of symptoms, tendency to chronicity and its impact on physical activity levels.[5-8] A variety of treatments, such as exercise therapy and orthoses, are applied, but reported effects are moderate and a substantial group of patients with persistent complaints remains.[9-13] In order to develop better-targeted treatment modalities there is a need to elucidate the pathogenesis of PFP. Although there is consensus that the etiology of PFP is multifactorial, precise contributing factors to the pathogenesis of pain are still not well understood.

In the 20th century it was believed that PFP was caused by chondromalacia. However, arthroscopic studies clarified that PFP is not necessarily related to cartilage defects, which was confirmed by the MRI study of Kannus et al.[4,6,14,15] Still, minor cartilage defects, such as signal abnormalities, fraying or fissuring, and hypertrophy, could potentially have been undetected up to now. Nowadays, it is possible to detect even very small cartilage defects with the use of high-resolution magnetic resonance imaging (MRI). In addition, abnormalities of the patellar retinaculum, synovial plicae, Hoffa's fat pad and subchondral bone marrow have been mentioned in literature over the past years as possible source of pain, but have not yet been investigated systematically in a PFP population with high-resolution MRI.[4,16-19] Hypothetically, more abnormalities are expected to be present in patients with PFP.

Therefore, this study will investigate the possible association between PFP and the presence of structural abnormalities of the patellofemoral joint. Based on the degenerative process with aging, as seen in OA, more abnormalities were expected in adult patients. Therefore, differences in number of abnormalities between adolescent and adult patients were also evaluated. This may eventually lead to a better understanding of the pathogenesis of patellofemoral pain.

## MATERIALS AND METHODS

### Study design and participants

A cross-sectional case-control study was conducted between January 2013 and September 2014 including patients with PFP for two months up to two years and healthy control subjects without any type of knee complaints. All subjects were aged between

14 and 40 years. Patients diagnosed with PFP were recruited by general practitioners, sports physicians and physiotherapists and had to fulfil the following criteria: the presence of at least three of the following symptoms: retro or peripatellar pain while walking up or down stairs; while squatting; while running; while cycling; while sitting with knees flexed for a prolonged period of time, or grinding of the patella. Patients were excluded if they had other defined pathological conditions of the affected knee at present such as patellar tendinopathy or osteoarthritis, if the onset of PFP occurred after trauma or if they had previous knee injuries or surgery or previous episodes of PFP more than two years ago. Control subjects were recruited from patients' sports team members, friends or among the university (employees and students). We aimed to match control subjects on age, BMI, sex and activity level. Control subjects were excluded if they were first grade family members of patients or if they had patellofemoral pain at present or in the past, traumatic injury or surgery of both knees. Furthermore, all study participants had to have sufficient knowledge of the Dutch language and no contra-indications for MRI scanning with contrast administration (not used for current study purpose). Written informed consent was obtained from all participants (and parents/wardens in the case of subjects <18 years) and the study was approved by the Institutional Review Board (Medical Ethical Committee of Erasmus MC, protocol MEC-2012- 342).

**Measurements**

After signing informed consent, study participants were asked to fill in an online questionnaire, including questions on demographics (age, sex, BMI), sports participation at the time of inclusion and before onset of pain (yes or no) and knee complaints (duration of complaints, pain at rest and during activity (Numerical Rating Scale (NRS) 0-10) and Anterior Knee Pain (AKP) score 0-100[20]). Subsequently, they were invited for a physical examination (including crepitation during squatting (present or not), palpation of the medial patellar facet (painful or not) and Clarke's compression test[21] (positive or negative)) and MRI scan at our university medical center. In patients, the (most) affected knee was selected for physical examination and MRI, or randomly chosen if both knees were equally painful. For control subjects, a randomly selected knee was used for both physical examination and MRI.

MRI was performed at 3 Tesla(T) (Discovery MR750, GE Healthcare, Milwaukee, WI, USA) with a dedicated eight-channel knee coil (Invivo Inc., Gainesville, USA). The MRI protocol comprised sagittal, axial and coronal fast spin echo proton density weighted sequences with a slice thickness of 3 mm and sagittal, axial T2 weighted sequences with fat suppression with a slice thickness of 3 mm. Furthermore, a 3D high-resolution sagittal fat-saturated spoiled gradient-echo (SPGR) sequence was acquired with a slice thickness of 0.5 mm, a repetition time of 17 milliseconds (ms), an echo time of 5.4ms, a flip angle of 12 degrees, a 288x192 matrix and a 15 cm field of view.

## Assessment of MRI features

All MRI scans were scored primarily by a senior resident in radiology with musculoskeletal subspecialisation, who was blinded for participant status, using the semi-quantitative Magnetic Resonance Imaging Osteoarthritis Knee Score (MOAKS). Subsequently, all findings were discussed with an experienced musculoskeletal radiologist, who was also blinded for participant status and made the final determination. The MOAKS was developed to evaluate articular cartilage loss in conjunction with surrounding bony and soft tissue abnormalities, including bone marrow lesions (BML's), osteophytes, lesions of the menisci, ligaments, and tendons, joint effusion and periarticular features (i.e., iliotibial band abnormalities, ganglion cysts).[22] Since the MOAKS was primarily developed to study osteoarthritis, several additional patellofemoral joint features, possibly more applicable for this young population, were added (See appendix 1).[16] These additional features included minor defects of cartilage (high signal intensity, fraying or fissuring, hypertrophy), medial patellar plica thickness and width, avascular necrosis, stress fractures, thickening of patellar tendon, quadriceps tendon and retinaculum and high signal intensity of retinaculum, quadriceps tendon and fat pads (superolateral part of Hoffa's fat pad, quadriceps fat pad and prefemoral fat pad according to Chhabra et al.[16]). High signal intensity was defined as an abnormally high signal intensity on T2-weighted images of a certain structure. Hypertrophy was seen as a result of cartilage swelling. Fraying, a shredded appearance on MRI, is supposed to be the results of fibrillation of the cartilage surface. Fissuring comprises small cracks in the cartilage surface. Furthermore, in the MOAKS score the complete anterior femur is scored as trochlea.[22] Since we focused on the patellofemoral joint, we subdivided this total anterior femur in a subregion which comprises solely the trochlea and a, medial and lateral condylar subregion. This was done for cartilage loss, and BML's. With regard to the additional scoring of minor cartilage defects, only the trochlear subregion and patella were scored.

Items were clustered and dichotomized to reduce the large number of MRI features. The MOAKS category 'size' was used for dichotomizing cartilage loss and BMLs. If size was 0 the feature was scored negative, if size>1 the feature was scored positive. Osteophytes were scored positive if their size was small to large and effusion if a medium to large amount was present Thickening and high signal intensity were clustered in case of tendons or ligaments. Minor cartilage defects was scored positive if high signal intensity or fraying/fissuring or hypertrophy was present. Plica thickening or widening was scored positive in case of grade 3 for either thickness (≥3mm) or width (being sufficient to reach the midline in a non-distended joint) according to the grading of Boles et al.[23]

## Statistical analysis

Statistical analyses were performed with SPSS for Windows, version 20 (SPSS Inc., Chicago, IL, USA). If normal distribution was present, Chi-square test for dichotomous

variables and independent sample t-test for continuous variables were used to compare differences in characteristics between patients and control subjects, but also between adults and adolescent patients (aged <18 years). Otherwise, a Mann-Whitney U test was applied. Associations between patellofemoral pain and the presence of structural abnormalities were analysed using logistic regression analyses. In addition, logistic regression analyses were applied to test potential differences between adolescent and adult patients in the presence of structural abnormalities. Regression analyses were adjusted for the potential confounders: age, sex, BMI and sports participation. Results are presented as Exp(B) with 95% confidence intervals and adjusted p-values. P -values <0.05 were considered statistically significant.

## RESULTS

### Participants

64 patients (Figure 1) and 70 control subjects were included between January 2013 and September 2014, of which 40, equally distributed between groups, were adolescents.

Mean age was 23.2 (6.4) years, mean BMI was 22.9 (3.4) kg/m2 and 56.7% was female. A significant difference between PFP patients and control subjects was observed in BMI (higher in patient group) and percentage of sports participants (higher in the control group) (Table 1).

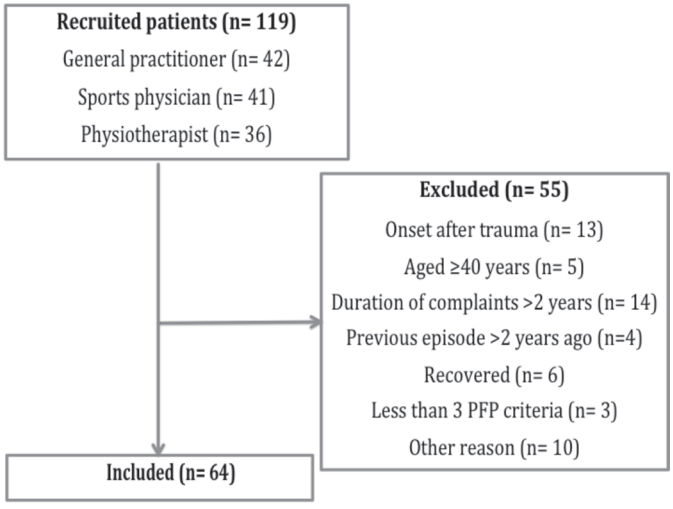


**Figure 1.** Flowchart of recruited patients

**Table 1.** Characteristics of study participants.

| | | Patients *(N=64)* | Controls *(N=70)* | P-value |
|---|---|---|---|---|
| **Female sex** | ***n (%)*** | 35 (54.7) | 41 (58.6) | 0.65 |
| **Age *(years)*** | ***Mean (SD)*** | 23.4 (7.0) | 23.1 (5.9) | 0.88* |
| **BMI *(kg/m$^2$)*** | ***Mean (SD)*** | 23.6 (3.8) | 22.3 (3.0) | 0.04* |
| **Sports participants** | | | | |
| **at study inclusion** | ***n (%)*** | 38 (59.4) | 55 (78.6) | 0.02 |
| **before onset of pain** | ***n (%)*** | 56 (87.5) | n.a. | |
| **Presence of crepitation** | ***n (%)*** | 29 (45.3) | 20 (28.6) | 0.05 |
| **Painful palpation medial patellar facet** | ***n (%)*** | 31 (48.4) | 0 (0) | <0.001 |
| **Positive Clarke compression test** | **n *(%)*** | 14 (21.9) | 2 (2.9) | 0.001 |

N.A.: not applicable; *non-parametric testing

**Table 2.** Characteristics of PFP patient population, subdivided in adults and adolescents

| | | Adolescents *(N=20)* | Adults *(N=44)* | P-value |
|---|---|---|---|---|
| **Female sex** | ***n (%)*** | 14 (70) | 21 (47.7) | 0.10 |
| **Age *(years)*** | ***Mean (SD)*** | 15.9 (1.2) | 26.8 (5.8) | <0.001* |
| **BMI *(kg/m$^2$)*** | ***Mean (SD)*** | 20.7 (2.1) | 24.9 (3.7) | <0.001* |
| **Sport participants** | | | | |
| **during study** | ***n (%)*** | 10 (50.0) | 28 (63.6) | 0.30 |
| **before onset of pain** | ***n (%)*** | 15 (75.0) | 41 (93.2) | 0.04 |
| **Duration of complaints *(months)*** | ***Mean (SD)*** | 14.2 (8.2) | 11.0 (6.4) | 0.14* |
| **Bilateral knee pain** | ***n (%)*** | 14 (70.0) | 19 (43.2) | 0.047 |
| **Pain at rest *(NRS 0-10)*** | ***Mean (SD)*** | 3.75 (2.2) | 4.00 (2.6) | 0.71 |
| **Pain during activity *(NRS 0-10)*** | ***Mean (SD)*** | 7.15 (1.9) | 6.32 (2.3) | 0.17 |
| **Function *(AKP Score 0-100)*** | ***Mean (SD)*** | 60.6 (10.7) | 68.7 (11.7) | 0.17 |
| **Presence of crepitation** | ***n (%)*** | 4 (20.0) | 11 (25.0) | 0.17 |
| **Painful palpation medial patellar facet** | ***n (%)*** | 14 (70.0) | 17 (38.6) | 0.02 |
| **Positive Clarke compression test** | ***n (%)*** | 6 (30.0) | 8 (18.2) | 0.29 |

*non-parametric testing

Compared to adult patients, function (AKP score) was significantly lower in adolescent patients. Bilateral knee pain and painful palpation of the medial patellar facet were significantly more present in adolescents compared to adult patients (Table 2).

## Structural abnormalities on MRI

The results described in Table 3 are the key outcomes from the regression analyses based on adjusted p-values.

**Table 3.** Presence of structural abnormalities of the patellofemoral joint on MRI (n (%))

| | Patients *(N=64)* | Controls *(N=70)* | P-value | Exp (B) (95% CI) | Adjusted P-value |
|---|---|---|---|---|---|
| **Cartilage loss; full thickness** | | | | | |
| **Patella** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **Femur anterior** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **trochlea** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **medial condyle** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **lateral condyle** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **Cartilage loss; partial thickness** | | | | | |
| **Patella** | 6 (9.4) | 1 (1.4) | 0.04 | 0.16 (0.02;1.48) | 0.11 |
| **Femur anterior** | 3 (4.8) | 0 (0) | 0.07 | 0.00 (0.00;n.a.) | 1.00 |
| **trochlea** | 1(1.6) | 0 (0) | 0.29 | 0.00 (0.00;n.a.) | 1.00 |
| **medial condyle** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **lateral condyle** | 2 (3.2) | 0 (0) | 0.14 | 0.00 (0.00;n.a.) | 1.00 |
| **Minor cartilage defects; high signal /hypertrophy/fraying** | | | | | |
| **Patella** | 15 (23.4) | 15 (21.4) | 0.78 | 0.96 (0.39;2.36) | 0.93 |
| **Trochlea** | 2 (3.1) | 0 (0) | 0.14 | 0.00 (0.00;n.a.) | 1.00 |
| **Bone marrow lesions** | | | | | |
| **Patella** | 34 (53.1) | 36 (51.4) | 0.84 | 0.96 (0.46;2.02) | 0.92 |
| **Femur anterior** | 5 (7.8) | 8 (11.4) | 0.48 | 0.95 (0.27;3.30) | 0.94 |
| **trochlea** | 3 (4.7) | 2 (2.9) | 0.63 | 0.39 (0.06;2.62) | 0.33 |
| **medial condyle** | 0 (0) | 3 (4.3) | 0.09 | $2.95*10^{7}$ (0.00;n.a.) | 1.00 |
| **lateral condyle** | 0 (0) | 2 (2.9) | 0.17 | $2.66*10^{7}$ (0.00;n.a.) | 1.00 |
| **Osteophytes; small to large** | | | | | |
| **Patella** | 45 (70.3) | 42 (60.0) | 0.21 | 0.61 (0.28;1.33) | 0.21 |
| **Femur anterior** | 12 (18.8) | 9 (12.9) | 0.35 | 0.64 (0.24;1.72) | 0.37 |
| **Effusion; medium to large** | 4 (6.3) | 11 (15.7) | 0.08 | 2.36 (0.64;8.77) | 0.20 |
| **Meniscus** | | | | | |
| **High signal** | 10 (22.7) | 3 (6.0) | 0.03 | 0.29 (0.07;1.17) | 0.08 |
| **Maceration** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **Tear** | 2 (3.1) | 0 (0) | 0.14 | 0.00 (0.00;n.a.) | 1.00 |
| **Cyst** | 1(1.6) | 0 (0) | 0.29 | 0.00 (0.00;n.a.) | 1.00 |
| **Hypertrohpy** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **Extrusion; >2mm** | 10 (22.7) | 9 (12.9) | 0.65 | 0.74 (0.27;2.05) | 0.57 |
| **Cruciate ligament tear** | | | | | |
| **ACL** | 1(1.6) | 0 (0) | 0.29 | 0.0 (0.00;n.a.) | 0.96 |
| **PCL** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **Tendon thickening or high signal** | | | | | |
| **Patellar** | 24 (37.5) | 21(30.0) | 0.36 | 1.10 *0.49;2.47) | 0.82 |
| **Quadriceps** | 10 (22.7) | 8 (11.4) | 0.48 | 0.52 (0.18;1.56) | 0.24 |
| **Retinaculum thickening or high signal** | | | | | |
| **Medial** | 0 (0) | 1 (1.4) | 0.34 | $1.5*10^{7}$ (0.00;n.a.) | 1.00 |

**Table 3.** Presence of structural abnormalities of the patellofemoral joint on MRI (n (%)) (continued)

| | Patients *(N=64)* | Controls *(N=70)* | P-value | Exp (B) (95% CI) | Adjusted P-value |
|---|---|---|---|---|---|
| **Lateral** | 3 (4.7) | 2 (2.9) | 0.58 | 0.51 (0.06;4.67) | 0.55 |
| **Plica thickening or widening** | 3 (4.7) | 1 (1.4) | 0.27 | 0.16 (0.01;1.79) | 0.14 |
| **Hoffa's fat pad** | | | | | |
| **Edema; moderate to severe** | 3 (4.7) | 6 (8.6) | 0.50 | 1.55 (0.34;7.08) | 0.58 |
| **High signal superolaterally** | 37 (57.8) | 36 (51.4) | 0.46 | 0.80 (0.39;1.66) | 0.55 |
| **Fat pad high signal** | | | | | |
| **Prefemoral** | 45 (70.3) | 46 (65.7) | 0.57 | 0.85 (0.37;1.95) | 0.70 |
| **Quadriceps** | 24 (37.5) | 24 (34.3) | 0.70 | 0.90 (0.42;1.95) | 0.80 |
| **Pes anserinus** | | | | | |
| **Bursitis** | 2 (3.1) | 1(1.4) | 0.80 | n.a. | n.a. |
| **Tendinitis** | 0 (0) | 0 (0) | n.a | n.a. | n.a. |
| **Iliotibial band high signal** | 1(1.6) | 1 (1.4) | 0.95 | 0.27 (0.01;10.89) | 0.49 |
| **Cyst** | | | | | |
| **Ganglion** | 21(32.8) | 24 (34.3) | 0.86 | 1.37 (0.62;3.03) | 0.43 |
| **Popliteal** | 43 (67.2) | 50 (71.4) | 0.60 | 1.05 (0.48;2.32) | 0.90 |
| **Bursa high signal; large** | | | | | |
| **Infrapatellar** | 15 (23.4) | 14 (20.0) | 0.63 | 0.88 (0.36;2.14) | 0.72 |
| **Prepatellar** | 1 (1.6) | 1 (1.4) | 0.95 | 5.00 (0.13;187.94) | 0.39 |
| **Loose bodies** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **Stress fractures** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |
| **Avascular necrosis** | 0 (0) | 0 (0) | n.a. | n.a. | n.a. |

n.a.: not applicable, could not be calculated; CI: confidence interval.

Most frequently found abnormalities in both patients and control subjects were minor cartilage defects of the patella (high signal or hypertrophy or fraying) (23.4% vs. 21.4%), patellar BMLs (53.1% vs. 51.4%), patellar osteophytes (70.3% vs. 60.0%), high signal intensity of Hoffa's fat pad superolaterally (58% vs. 51%), high signal intensity or thickening of the patellar tendon (37.5% vs. 30%), high signal intensity of prefemoral and quadriceps fat pad (70.3% vs. 65.7% and 37.5% vs. 34.3%), ganglion cyst (32.8% vs. 34.3%), popliteal cyst (67.2% vs. 71.4%)(Table 3). Full thickness cartilage loss of the patellofemoral joint was not present in this study population. Partial thickness cartilage loss of the patella occurred in 9% of patients and 1% of control subjects.

Osteophytes of the anterior femur occurred in 18.8% of patients and 12.9% of control subjects. Other structural abnormalities of the anterior femur occurred less frequently. For instance, partial thickness cartilage loss only occurred in three patients and not in control subjects. BMLs were present in five patients and eight control subjects. Minor cartilage defects of the trochlea were only present in two patients.

High signal intensity of the meniscus occurred in 22.7% of patients and 6.0% of control subjects. Meniscal extrusion occurred in 22.7% of patients and 12.9% of control subjects. Medial retinaculum thickening or high signal occurred only in 1 control subject. Plica thickening or widening occurred in three patients and one control subject. After adjustment for age, BMI, sex and sports participation none of the structural abnormalities seen on MRI were statistical significantly associated with the presence of PFP.

Subgroup analyses of a selection of the abnormalities of the patellofemoral joint on MRI in the patient population comparing adult and adolescent patients revealed no significant differences between these patient groups (Table 4). Most frequently found abnormalities in both adult patients and adolescent patients were patellar BMLs (47.8% vs. 65%), patellar osteophytes (79.5% vs. 50%), high signal intensity of Hoffa's fat pad superolaterally (58% vs. 51%) and high signal intensity or thickening of the patellar tendon (38.6% vs. 35%). Partial thickness cartilage loss of the patella occurred in 13.6%

**Table 4.** Presence of structural abnormalities of the patellofemoral joint on MRI (n (%)) in patients, subdivided in an adult and adolescent population

| | Adults *(N=44)* | Adolescents *(N=20)* | P-value | Exp (B) (95% CI) | Adjusted P-value |
|---|---|---|---|---|---|
| **Bone marrow lesions** | | | | | |
| **Patella** | 21 (47.8) | 13 (65.0) | 0.20 | $1.25*10^8$ (0.21;7.94) | 0.79 |
| **Trochlea** | 3 (6.8) | 0 (0) | 0.23 | $1.3*10^8$ (0.00;n.a.) | 1.00 |
| **Cartilage loss; partial thickness** | | | | | |
| **Patella** | 6 (13.6) | 0 (0) | 0.08 | $6.75*10^7$ (0.00;n.a.) | 1.00 |
| **Trochlea** | 1 (2.3) | 0 (0) | 0.50 | $3.0*10^6$ (0.00;n.a.) | 1.00 |
| **Minor cartilage defects; high signal/hypertrophy/ fraying** | | | | | |
| **Patella** | 14 (31.8) | 1 (5.0) | 0.02 | 3.52 (0.23;53.97) | 0.37 |
| **Trochlea** | 2 (4.6) | 0 (0) | 0.33 | $5.11*10^7$ (0.00;n.a.) | 1.00 |
| **Osteophytes; small to large** | | | | | |
| **Patella** | 35 (79.5) | 10 (50.0) | 0.02 | 1.03 (0.15;7.20) | 0.98 |
| **Femur anterior** | 9 (20.5) | 3 (15.0) | 0.60 | 0.20 (0.01;3.04) | 0.25 |
| **Meniscus** | | | | | |
| **High signal** | 9 (20.5) | 1 (5.0) | 0.11 | 5.76 (0.35;96.17) | 0.22 |
| **Extrusion** | 5 (11.4) | 5 (25.0) | 0.16 | 0.34 (0.03;4.38) | 0.41 |
| **Thickening or high signal** | | | | | |
| **Patellar** | 17 (38.6) | 7 (35.0) | 0.78 | 1.16 (0.15;9.02) | 0.89 |
| **Quadriceps** | 7 (15.9) | 3 (15.0) | 0.93 | 1.42 (0.11;17.7) | 0.79 |
| **Hoffa's fat pad** | | | | | |
| **Edema;moderate to severe** | 2 (4.6) | 1 (5.0) | 0.94 | 0.26 (0.00;73.7) | 0.64 |
| **High signal superolaterally** | 29 (65.0) | 8 (40.0) | 0.05 | 2.1 (0.31;14.2) | 0.45 |

n.a.: not applicable, could not be calculated; CI: confidence interval.

of adult patients, but not in adolescents. Minor cartilage defects of the patella (high signal intensity or hypertrophy or fraying) were present in 31.8% of adult patients and 5% of adolescent patients. Trochlear BMLs, partial thickness cartilage loss of the trochlea and minor cartilage defects of the trochlea only occurred in adults.
After adjustment for age, BMI, sex and sports participation no difference in presence of structural abnormalities of the patellofemoral joint on MRI was present between adult and adolescent patients.

## DISCUSSION

The purpose of this study was to investigate if PFP was associated with structural abnormalities of the patellofemoral joint using high-resolution MRI, which enabled us to detect even small lesions. Full thickness cartilage loss of the patellofemoral joint was not present in this study population. Minor patellar cartilage defects, patellar BMLs, patellar osteophytes, high signal intensity of Hoffa's fat pad and high signal intensity or thickening of the patellar tendon were frequently seen in both patients and control subjects. Structural abnormalities of the trochlea occurred less frequently. For partial thickness patellar cartilage loss and meniscal high signal intensity, both only present in small numbers, the difference between patients and control subjects was not statistically significant, but both of them occurred seemingly more in patients. Medial synovial plica and patellar retinaculum abnormalities were rarely seen in this population. Overall, our results indicate that the presence of structural abnormalities of the patellofemoral joint on MRI is not associated with patellofemoral pain.
Subgroup analyses comparing adult and adolescent patients showed consistently more abnormalities in adult patients. However, after adjustment for gender, BMI and sports no statistically significant differences were present between these groups. Additional analyses in the total study population also revealed no differences between adults and adolescents (data not presented).
It could be hypothesized that abnormalities are most likely to occur at the medial part of the patella, since this is the most frequent pain location in patellofemoral pain patients. Furthermore, pain might actually be located in a specific part of a surrounding structure, like the medial meniscus or superior patellar tendon. Therefore, explorative analyses of specific sub-regions of the patella (medial, lateral, superior and inferior), meniscus (medial and lateral) and patellar tendon (superior, middle, inferior) were performed. These analyses also showed no significant differences between patients with PFP and healthy control subjects (see Appendix 2). Differences in the presence of combinations of abnormalities were not tested due to a lack of power.

### Comparison with literature

So far, only one previous study by Kang et al. has investigated MRI findings in patients with PFP.[24] However, they applied MRI at 1.5T, whereas in our study high resolution MRI at 3T was performed. Furthermore, their study consisted of male soldiers with a mean age of 22 years, whereas our study consisted of the general PFP population seeking care in primary care and even included a group of adolescents. Similar to our study, abnormalities of the patellofemoral joint (e.g. cysts, effusion, bone marrow signal change, meniscal lesions) were common in both patients and controls in the study by Kang et al. [24] The prevalence of abnormalities on MRI in asymptomatic knees has been frequently reported in the literature.[25-28] This raises the question if these features really contribute to the pathogenesis of knee pain and, if they do, which other factors need to be present in order to induce pain. Kang et al.[24] did find a higher prevalence of abnormalities of the patellofemoral joint and the extensor mechanism in patients and especially a higher prevalence of thick medial plica in the patient group compared to the control group (9% vs. 0%). In our study plica thickening or widening occurred in two patients and one control subject only. This might be due to a difference in scoring as they scored medial patellar plicae thickening when 2 mm or more contrary to the 3 mm or more in our protocol, which we based on the study of Boles.[23] Furthermore, it is important to notice that their population consisted of soldiers and, consequently, the physical activity level is assumed to be higher compared to our population.

It was apparent that sports participation was not associated with the presence of BMLs, cartilage defects and meniscal lesions, but only with the patellar tendon. For BMLs and cartilage defects these results are in contrast to previous literature stating that subjects with higher physical activity levels have a higher incidence of these abnormalities.[29-34] This might be due to the fact that we have dichotomized physical activity into sports participation or not instead of using a continuous scale for physical activity level.

Retropatellar cartilage damage has been implicated as a possible etiological factor for PFP for many years. In the 20$^{th}$ century, arthroscopic studies clarified that patellofemoral pain was not necessarily related to cartilage defects.[4,14,15] This was confirmed in a MRI study by Kannus et al. who found no correlation between cartilage defects and patellofemoral pain.[6] Similar to these studies, our results indicate that cartilage defects are not associated with PFP. The current high-resolution imaging technique even allowed us to look at minor cartilage defects including high signal intensity, fraying/fissuring and hypertrophy. These were also not associated with the presence of PFP. Therefore, it seems that there is conclusive evidence that major or minor patellofemoral cartilage defects are not associated with PFP.

### Strengths and limitations

This is the first case-control study on structural abnormalities of the patellofemoral joint in PFP including a large group of PFP patients and comprising a group of adolescent patients who are often excluded in literature. To our knowledge, there has been no previous study in PFP using high-resolution MRI, which even enables detection of minimal structural abnormalities.

There are, however, some limitations to our study that need to be addressed. Our intention was to match patients and controls on age, sex, BMI and sports participation. However, some differences were present concerning BMI and percentage of sports participants and therefore all analyses were adjusted for these confounders.

We used the MOAKS, a semi quantitative score primarily developed to study osteoarthritis on MRI. In order to make this score more appropriate for the relatively young population studied, some additional features were added. Therefore, we feel that we covered all potential items.

Finally, a lack of power might be the reason that we did not find an association between certain structural abnormalities and PFP. Although a higher percentage of partial thickness patellar cartilage loss and more frequent meniscal high signal intensity were present in PFP patients compared to control subjects, these differences were not statistically significant. Though, this is one of the largest case-control studies in the patellofemoral pain research field we lacked power due to the small numbers of abnormalities found in the study population. However, since these abnormalities are present in such small numbers, their contribution to the pathogenesis of PFP is unlikely.

## CONCLUSION

A large number of structural abnormalities of the patellofemoral joint on MRI were seen in this relatively young population. Our results indicate that structural abnormalities of the patellofemoral joint on MRI are not associated with patellofemoral pain.

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## APPENDIX

**Appendix 1.** Scoring of additional patellofemoral features on MRI

| MRI feature | Scoring | MRI pulse sequence |
|---|---|---|
| Signal abnormalities of cartilage | Absent/present | Sagittal and axial PD and T2FS sequences |
| Hyperthrophy of cartilage | Absent/present | Sagittal and axial PD and T2FS sequences |
| Fraying/fissuring of cartilage | Absent/present | Sagittal and axial PD and T2FS sequences |
| Thickening patellar tendon | Absent/present | Sagittal and axial PD and T2FS sequences |
| Thickening or high signal quadriceps tendon | Absent/present | Sagittal and axial PD and T2FS sequences |
| Thickening or high signal retinaculum | Absent/present | Axial PD and T2FS sequences |
| Plica thickening | 1: less than 1mm<br>2: less than 3mm<br>3: 3mm or greater | Axial PD and T2FS sequences |
| Plica width | 1: being a small ridge<br>2: being a width large enough to reach the trochlear cartilage of no joint fluid were present<br>3: being sufficient to reach the midline in a non-distended joint | Axial PD and T2FS sequences |
| Signal abnormality fatpad (3x) | Absent/present | Sagittal and axial PD and T2FS sequences |
| Pes anserinus tendinitis | Absent/present | Sagittal and axial PD and T2FS sequences |
| Infrapatellar and prepatellar bursa high signal | Small/medium/large | Sagittal and axial PD and T2FS sequences |
| Stress fracture | Absent/present | Sagittal, coronal and axial PD and T2FS sequences |

PD=proton density, T2FS=T2-weighted with fat suppression.

**Appendix 2.** Presence of structural abnormalities on MRI in subregions (n (%))

| | Patients *(N=64)* | Controls *(N=70)* | P-value | Exp (B) (95%CI) | Adjusted P-value |
|---|---|---|---|---|---|
| **Cartilage loss; partial thickness** | | | | | |
| **Patella** | | | | | |
| **Medial** | 4 (6.3) | 1 (1.4) | 0.14 | 0.25 (0.03;2.50) | 0.24 |
| **Lateral** | 2 (3.1) | 0 (0) | 0.14 | 0.00 (0.00;n.a.) | 1.00 |
| **Superior** | 2 (3.1) | 0 (0) | 0.14 | 0.00 (0.00;n.a.) | 1.00 |
| **Inferior** | 5 (7.8) | 1 (1.4) | 0.07 | 1.78 (0.02;1.67) | 0.13 |
| **Bone marrow lesions** | | | | | |
| **Patella** | | | | | |
| **Medial** | 26 (40.6) | 23 (32.9) | 0.35 | 0.67 (0.31;1.43) | 0.30 |
| **Lateral** | 22 (34.4) | 24 (34.3) | 0.99 | 1.02 (0.48;2.17) | 0.96 |
| **Superior** | 10 (15.6) | 10 (14.3) | 0.83 | 1.03 (0.38;2.82) | 0.95 |
| **Inferior** | 31 (48.4) | 31 (44.3) | 0.63 | 0.76 (0.36;1.59) | 0.47 |
| **Minor cartilage defects; high signal, hypertrophy, fraying** | | | | | |
| **Patella** | | | | | |
| **Medial** | 11 (17.2) | 8 (11.4) | 0.34 | 0.58 (0.19;1.74) | 0.33 |
| **Lateral** | 9 (14.1) | 8 (11.4) | 0.65 | 0.77 (0.26;2.24) | 0.63 |
| **Superior** | 11 (17.2) | 13 (14.3) | 0.84 | 1.29 (0.49;3.41) | 0.61 |
| **Inferior** | 13 (20.3) | 7 (10.0) | 0.07 | 0.35 (0.11;1.05) | 0.06 |
| **Osteophytes; small to large** | | | | | |
| **Patella** | | | | | |
| **Medial** | 23 (35.9) | 25 (35.7) | 0.98 | 1.05 (0.50;2.21) | 0.90 |
| **Lateral** | 19 (29.7) | 19 (27.1) | 0.74 | 0.78 (0.34;1.82) | 0.57 |
| **Superior** | 19 (29.7) | 27 (38.6) | 0.28 | 1.60 (0.73;3.52) | 0.24 |
| **Inferior** | 26 (40.6) | 18 (25.7) | 0.10 | 0.50 (0.23;1.10) | 0.09 |
| **Meniscus** | | | | | |
| **High signal** | | | | | |
| **Medial** | 6 (9.4) | 2 (2.9) | 0.11 | 0.33 (0.06;1.78) | 0.20 |
| **Lateral** | 4 (6.3) | 3 (4.3) | 0.61 | 0.90 (0.17;4.86) | 0.90 |
| **Extrusion** | | | | | |
| **Medial** | 9 (14.1) | 8 (11.4) | 0.65 | 0.70 (0.24;2.02) | 0.51 |
| **Lateral** | 1 (1.6) | 1 (1.4) | 0.95 | 1.34 (0.07;25.7) | 0.85 |
| **Patellar tendon thickening or high signal** | | | | | |
| **Superior** | 6 (9.4) | 5 (7.1) | 0.64 | 1.12 (0.28;4.55) | 0.87 |
| **Middle** | 2 (3.1) | 0 (0) | 0.14 | 0.00 (0.00;n.a.) | 1.00 |
| **Inferior** | 20 (31.3) | 17 (24.3) | 0.37 | 1.06 (0.46;2.44) | 0.90 |

n.a.: not applicable, could not be calculated; CI: confidence interval.

# Chapter 4

## No Difference on Quantitative Magnetic Resonance Imaging in Patellofemoral Cartilage Composition Between Patients With Patellofemoral Pain and Healthy Controls

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## ABSTRACT

### Background

Retropatellar cartilage damage has been suggested as an etiological factor for patellofemoral pain (PFP), a common knee condition among young and physically active individuals. To date, there is no conclusive evidence for an association between cartilage defects and PFP. Nowadays, advanced quantitative magnetic resonance imaging (MRI) techniques enable estimation of cartilage composition.

Purpose: To investigate differences in patellofemoral cartilage composition between patients with PFP and healthy control sub- jects using quantitative magnetic resonance imaging (MRI).

### Study Design

Cross-sectional study; Level of evidence, 3.

### Methods

Patients with PFP and healthy control subjects underwent 3.0-T MRI including delayed gadolinium-enhanced MRI of cartilage and $T1_\rho$ and T2 mapping. Differences in relaxation times of patellofemoral cartilage were compared between groups by linear regression analyses, adjusted for age, body mass index, sex, sports participation, and time of image acquisition.

### Results

This case-control study included 64 patients and 70 controls. The mean (6SD) age was 23.2 6 6.4 years and the mean body mass index was 22.9 6 3.4 kg/m2; 56.7% were female. For delayed gadolinium-enhanced MRI of cartilage, the mean $T1_{GD}$ relaxation times of patellar (657.8 vs 669.4 ms) and femoral cartilage (661.6 vs 659.8 ms) did not significantly differ between pa- tients and controls. In addition, no significant difference was found in mean $T1_\rho$ relaxation times of patellar (46.9 vs 46.0 ms) and femoral cartilage (50.8 vs 50.2 ms) and mean T2 relaxation times of patellar (33.2 vs 32.9 ms) and femoral cartilage (36.7 vs 36.6 ms) between patients and controls. Analysis of prespecified medial and lateral subregions within the patellofemoral cartilage also revealed no significant differences.

### Conclusion

There was no difference in composition of the patellofemoral cartilage, estimated with multiple quantitative MRI techniques, between patients with PFP and healthy control subjects. However, clinically relevant differences could not be ruled out for $T1_\rho$ in the adolescent population. Retropatellar cartilage damage has long been hypothesized as an important factor in the pathogenesis of PFP, but study findings suggest that diminished patellofemoral cartilage composition is not associated with PFP.

## INTRODUCTION

Patellofemoral pain (PFP) is a common knee disorder, especially among young and physically active individuals.[1] PFP is described as retro or peripatellar pain provoked by specific activities, such as kneeling, stair climbing, running, cycling, squatting and prolonged sitting with the knees flexed. On average, the general practitioner encounters 5 to 6 new cases of PFP per 1000 patients per year, whereas the incidence reaches 22 new cases per 1000 persons per year in a highly physically active population.[2,3] In fact, 17% of all patients with a new running injury in sports medicine practices are diagnosed with PFP.[4] Despite a variety of treatment options (eg, exercise therapy, patellar taping/bracing, and foot orthoses), persistent complaints remain for a large group of patients.[5-8] The pathogenesis of PFP must be disentangled to develop better-targeted treatment. The origin of PFP is considered to be multifactorial but is still largely unknown.[9] Retropatellar cartilage damage has long been suggested as a possible etiological factor. However, to date, there has been no conclusive evidence on the presence of morphologic cartilage damage in PFP based on radiography or arthroscopy.[10-13]

PFP has been suggested as a precursor of patellofemoral osteoarthritis (OA).[14,15] Because changes in cartilage composition are known to precede morphologic cartilage damage in OA[16] and because PFP involves a young patient population with typically no morphologic cartilage defects, it could be hypothesized that altered cartilage composition plays a role in the pathogenesis. With recent quantitative magnetic resonance imaging (MRI) techniques such as delayed gadolinium enhanced MRI of cartilage (dGEMRIC), $T1_\rho$ and T2 mapping, it is now possible to estimate cartilage composition.[17]

Thus far, 2 small studies have performed one of these quantitative MRI techniques to investigate possible differences in cartilage composition between specific PFP patient groups and control subjects. Significantly higher $T1_\rho$ relaxation times in patellar cartilage, indicating proteoglycan loss, were found in 20 patients with PFP with patellar maltracking compared to healthy controls.[18] However, in this study and in another study of female patients with PFP, the patellar cartilage of cases and control subjects demonstrated no differences in T2 relaxation time, an estimate of collagen content and network integrity.[18,19] To our knowledge, multiparametric quantitative MRI, including dGEMRIC (considered the best validated method for glycosaminoglycan quantification[17]), has not been applied before in a large PFP patient population without prior selection of subgroups (e.g. maltracking, female sex, professional athletes). Therefore, this study aimed to investigate differences in patellofemoral cartilage composition between patients with PFP and control subjects, estimated with multiple quantitative MRI techniques, which may eventually lead to a better understanding of the pathogenesis of PFP.

## MATERIAL AND METHODS

### Study design and participants

This cross sectional case-control study was conducted between January 2013 and September 2014 and included a healthy control group and patients with PFP with minimum symptom duration of two months to a maximum of two years and. All participants were aged between 14 and 40 years. Patients who visited their general practitioner, physiotherapist or sports physician were included if they were diagnosed with PFP based on the presence of at least 3 of the following symptoms: crepitus or pain while stair climbing, squatting, running, cycling, or sitting for a prolonged period with the knee flexed. Patients were excluded if they currently had a defined pathological knee condition of the affected knee (eg, osteoarthritis or patellar tendinopathy), 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. Control subjects consisted of team members, friends or colleagues of the included patients with PFP. We aimed to match control subjects on age, Body Mass Index (BMI), sex and activity level. Control subjects were excluded if they had current or past PFP, if they previously had a traumatic injury or surgery on both knees or if they were first-grade family members of patients. Other exclusion criteria for all study participants were contraindications for MRI with contrast and insufficient knowledge of the Dutch language. The Medical Ethics Committee of Erasmus MC approved this study (protocol MEC-2012- 342), and informed consent was accordingly obtained from all participants.

### Measurements

All participants completed a questionnaire that included questions on demographics (BMI, age, and sex), sports participation (yes or no) and knee complaints (duration of complaints, pain at rest and during activity using a numerical rating scale of 0-10 and the anterior knee pain scale of 0-100[20]). Participants were subsequently invited to visit our university medical center for MRI and a physical examination, which included an assessment of crepitation during squatting (present or not), palpation of the medial facet (painful or not), and administration of the Clarke compression test[21] (positive or negative). In patients, the more affected knee was selected for physical examination and MRI, or randomly chosen if both knees were equally painful. For control subjects, a randomly selected knee was used for both physical examination and MRI. All participants underwent 3.0-T MRI (Discovery MR750, GE Healthcare) with a dedicated eight-channel knee coil (Invivo Inc.).

The MRI protocol comprised the following 5 sequences: a 3-dimensional (3D) high resolution sagittal spoiled gradient echo (SPGR) sequence, a 3D high resolution sagittal fat-saturated SPGR sequence, a 3D sagittal inversion recovery non-fat-saturated SPGR

sequence for dGEMRIC[22], a 3D sagittal fast spin-echo (FSE) $T1_\rho$ mapping sequence[23] and a 3D sagittal FSE T2 mapping sequence[24] (Table 1).

dGEMRIC was only conducted in adult participants (aged ≥18 years) because it requires the administration of contrast agent. dGEMRIC, expressed as $T1_{GD}$ relaxation time, uses the inverse relation between a negatively charged contrast agent and the amount of glycosaminoglycan in cartilage.[25] This means that in the case of less glycosaminoglycan, more contrast agent is able to penetrate the cartilage, resulting in a lower $T1_{GD}$ relaxation time. $T1_\rho$ mapping, expressed as $T1_\rho$ relaxation time, is proposed to be a noncontrast-enhanced alternative for dGEMRIC, in which higher $T1_\rho$ values indicate less glycosaminoglycan.[17] T2 mapping, expressed as T2 relaxation time, is regarded as the best method to estimate collagen content of cartilage; higher T2 times indicate lower collagen content.[17] After acquisition of the high-resolution SPGR and $T1_\rho$ and T2 mapping sequences, a double dose (0.2 mmol/kg) of gadopentate dimeglumine (Magnevist®, Bayer Schering AG) based on the participants' weight was injected intravenously according to the $T1_{GD}$ mapping protocol.[26] All adult participants were then asked to cycle for 10 minutes on a home trainer to enhance distribution of contrast throughout the knee joint. $T1_{GD}$ was acquired 120 minutes after contrast administration.

**MRI analysis**

For all quantitative MRI techniques, the regions of interest (ROIs) consisted of the cartilage of the whole patella and the trochlear portion of the femoral cartilage. The border between trochlea and weightbearing femoral cartilage was defined by drawing a line tangentially to the anterior aspect of the proximal tibia on the sagittal image until it intersected the femoral surface.[27] An experienced observer, who was blinded for participant status, manually delineated the patellar and femoral cartilage on the high-resolution SPGR scan with Matlab software (R2011a, The MathWorks) (Figure 1).

Previously published in-house developed software (Software for Post-processing and Registration of Cartilage of the Knee [SPARCK]) was used for image postprocessing to calculate relaxation times.[28] SPARCK was applied for postprocessing in studying knee osteoarthritis previously.[29-31] Automated image registration, using open source registration software (Elastix[32], http://elastix.isi.uu.nl), was applied to compensate for subject motion within and between sequences. The $T1_{GD}$, $T1_\rho$ and T2 sequences each consist of 5 images, which are acquired using different inversion times, spin lock times or echo times respectively. These images were co-registered before the relaxation time per voxel was computed. The $T1_{GD}$, $T1_\rho$ and T2 sequences were also registered to the high-resolution SPGR images in which the ROIs were annotated. This had the advantage that ROIs only needed to be annotated once and a comparison between the same ROIs for all MRI

**Table 1.** MRI protocol parameters

| | High resolution SPGR | dGEMRIC | $T1_\rho$ mapping | T2 mapping |
|---|---|---|---|---|
| **Plane** | Sagittal | Sagittal | Sagittal | Sagittal |
| **Imaging mode** | 3D | 3D | 3D | 3D |
| **Sequence** | SPGR | IR SPGR | FSE | FSE |
| **Matrix (frequency)** | 512 | 288 | 288 | 288 |
| **Matrix (phase)** | 512 | 192 | 192 | 192 |
| **Number of slices** | 216 | 36 | 36 | 36 |
| **FOV (mm)** | 150 | 150 | 150 | 150 |
| **Slice thickness/gap (mm/mm)** | 0.5/0.0 | 3.0/0.0 | 3.0/0.0 | 3.0/0.0 |
| **TI (ms)** | n.a. | 2100 / 800 / 400 / 200 / 100 | n.a. | n.a. |
| **TSL (ms)*** | n.a. | n.a. | 1 / 16 / 32 / 64 / 125 | n.a. |
| **TE (ms)** | 5.4 | 1.6 | n.a. | 3 / 13 / 27 / 40 / 68 |
| **Flip angle (˚)** | 12 | 15 | 90 | 90 |
| **Repetition time (ms)** | 17 | 4 | 1261 | 1263 |
| **Number of excitations** | 0.75 | 1 | 0.5 | 1 |
| **Fat saturated** | Yes and No | No | Yes | Yes |
| **Acquisition time (min)** | 05:37 | 14:18 | 05:43 | 9:41 |

3D, 3dimensional; FOV, field of view; FSE, fast spin echo; IRSPGR, inversion recovery spoiled gradient echo; MRI, magnetic resonance imaging; NA, not applicable; SPGR, spoiled gradient echo; TE, echo time; TI, inversion time; TSL, spinlock time. *Spin-lock frequency of 500Hz.

sequences was possible. After registration, the relaxation time per voxel in the ROI was estimated using a maximum likelihood fit and a mean relaxation time per ROI was calculated. Possibly included cortical bone pixels in the ROI were automatically removed by a participant-specific set bone-cartilage threshold. Because voxels at tissue boundaries could influence the mean relaxation time, a weighted mean relaxation time was calculated using the reciprocal of the uncertainty of the fit (ie, voxels for which the estimated relaxation time was more uncertain had less influence on the mean). All slices of each cartilage ROI were averaged. For each participant, 2 averaged weighted mean relaxation times (1 for patellar and 1 for femoral cartilage) were obtained per sequence. In addition, weighted mean relaxation times of prespecified medial and lateral subregions within the patellar and femoral cartilage ROI were calculated. Medial and lateral subregions comprised 3 central slices through the medial and lateral region, respectively. Weighted $T1_{GD}$ relaxation times were corrected for the participant's BMI as proposed by Tiderius et al.[33]

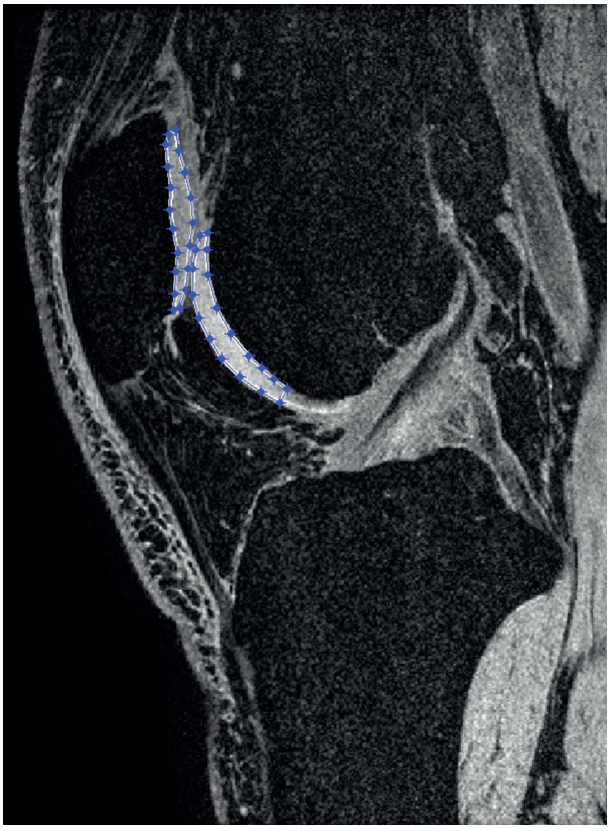

**Figure 1.** Representation of the regions of interest of the patellar and femoral cartilage on a high-resolution image

### Statistical analysis

Differences in characteristics between patients and control subjects, as well as between adult and adolescent patients (aged <18 years), were tested with independent sample t-tests and chi-square tests if normal distribution was present. Otherwise, a Mann-Whitney U test was applied. Differences in patellar and femoral cartilage composition between patients and controls, as well as within adult and adolescent (aged <18 years) subgroups, were analyzed with linear regression analyses adjusted for age, sex, BMI, sports participation and time of image acquisition (morning or afternoon/evening). $P < .05$ was considered statistically significant. All analyses were performed with SPSS 20.0 (SPSS Inc).

## RESULTS

### Participants

Between January 2013 and September 2014, 64 patients and 70 control subjects were included in this study; 40 participants (equally distributed between groups) were adolescents (Figure 2). The mean age was 23.2 ± 6.4 years, mean BMI was 22.9 ± 3.4 kg/m2 and 56.7% of the participants were female.

A significant difference between patients with PFP and control subjects was observed in BMI (higher in patient group) and percentage of sports participants (higher in the control group) (Table 2).

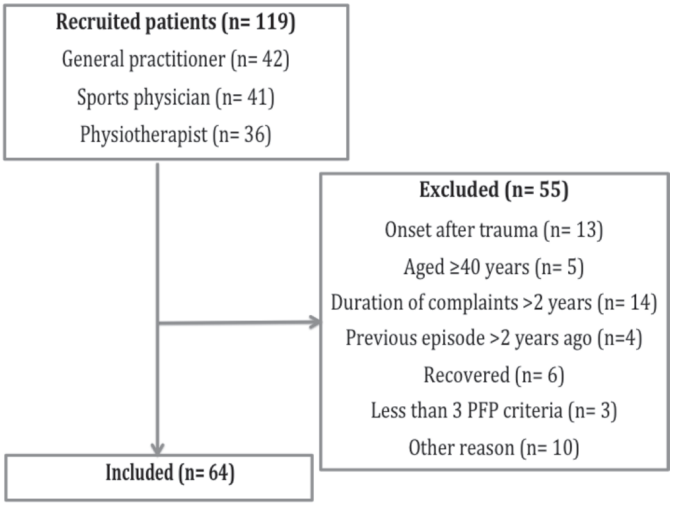


**Figure 2.** Flowchart of recruited patients

**Table 2.** Characteristics of study participants.

| | Patients (N=64) | Controls (N=70) | P Value |
|---|---|---|---|
| **Female sex** | 35 (54.7) | 41 (58.6) | .65 |
| **Age *(years)*** | 23.4 ± 7.0 | 23.1 ±5.9 | .88 |
| **BMI *(kg/m²)*** | 23.6 ±3.8 | 22.3 ± 3.0 | .04 |
| **Sports participants** | | | .02 |
| **During inclusion** | 38 (59.1) | 55 (78.6) | |
| **Before onset of pain** | 56 (87.5) | n.a. | |
| **Presence of crepitation** | 29 (45.3) | 20 (28.6) | .05 |
| **Painful palpation medial facet** | 31 (48.4) | 0 (0) | <.001 |
| **Positive Clarke compression test** | 14 (21.9) | 2 (2.9) | .001 |

Data are reported as n (%) or means ± SD. n.a., not applicable.

Compared with adult patients, bilateral knee pain was more common in adolescents and the mean duration of complaints longer (Table 3). Function (assessed with the anterior knee pain scale) was significantly lower in adolescent patients compared with adult patients. Bilateral complaints and painful palpation of medial facet were significantly more prevalent in adolescents.

**Table 3.** Characteristics of the Adult and Adolescent Patient Populations With PFP.

| | Adolescents (N=20) | Adults (N=44) | P Value |
|---|---|---|---|
| **Female sex** | 14 (70) | 21 (47.7) | .10 |
| **Age *(years)*** | 15.9 ± 1.2 | 26.8 ± 5.8 | <.001 |
| **BMI *(kg/m²)*** | 20.7 ± 2.1 | 24.9 ± 3.7 | <.001 |
| **Sport participants** | | | |
| **During inclusion** | 10 (50.0) | 28 (63.6) | .30 |
| **Before onset of pain** | 15 (75.0) | 41 (93.2) | .04 |
| **Duration of complaints (months)** | 14.2 ± 8.2 | 11.0 ± 6.4 | .14 |
| **Bilateral knee pain** | 14 (70) | 19 (43.2) | .05 |
| **Numerical rating scale score** | | | |
| **Pain at rest** | 3.75 ± 2.2 | 4.00 ± 2.6 | .71 |
| **Pain during activity** | 7.15 ± 1.9 | 6.32 ± 2.3 | .17 |
| **Anterior knee pain scale score (function)** | 60.6 ± 10.7 | 68.7 ± 11.7 | .01 |
| **Presence of crepitation** | 6 (30.0) | 23 (52.3) | .10 |
| **Painful palpation medial facet** | 14 (70.0) | 17 (38.6) | .02 |
| **Positive Clarke compression test** | 6 (30) | 8 (18.2) | .29 |

Data are reported as n (%) or means ± SD.

## Quantitative MR imaging

T1ρ and T2 mapping was conducted in all participants. Acquisition of T2 mapping failed in 1 patient and 1 control subject and acquisition of T1ρ mapping was not conducted in 12 patients and 6 control subjects because this sequence was not yet available at the beginning of the study. dGEMRIC was only conducted in adult participants and failed in 2 patients. Failure was caused by several reasons including technical, logistic and contrast administration issues.

For dGEMRIC, mean $T1_{GD}$ relaxation times of patellar (657.8 vs 669.4 ms) and femoral cartilage (661.6 vs 659.8 ms) did not significantly differ between patients and controls (Table 4). In addition, no significant differences were observed in mean $T1_{\rho}$ relaxation times of patellar (46.9 vs 46.0 ms) and femoral cartilage (50.8 vs 50.2 ms) and mean

**Table 4.** Weighted mean relaxation times of patellar and femoral cartilage

| | Patients | Controls | Mean difference (95% CI) | P Value |
|---|---|---|---|---|
| **dGEMRIC($T1_{GD}$)** | | | | |
| **No. of participants** | *(N=42)* | *(N=50)* | | |
| **patella** | 657.79 ± 83.69 | 669.44 ± 55.06 | -11.65 (-40.58 to 17.28) | .52 |
| **medial** | 670.57 ± 85.94 | 675.36 ± 58.71 | -4.80 (-34.90 to 25.31) | .82 |
| **lateral** | 662.33 ± 95.31 | 683.40 ± 59.02 | -21.07 (-53.37 to 11.24) | .25 |
| **femur** | 661.59 ± 63.80 | 659.81 ± 66.21 | 1.77 (-25.30 to 28.85) | .83 |
| **medial** | 691.32 ± 75.14 | 675.29 ± 73.64 | 16.03 (-14.88 to 46.94) | .30 |
| **lateral** | 655.40 ± 72.05 | 668.97 ± 76.00 | -13.57 (-44.40 to 17.29) | .50 |
| **$T1_{\rho}$** | | | | |
| **No. of participants** | *(N=52)* | *(N=64)* | | |
| **patella** | 46.92 ± 4.00 | 46.00 ± 4.44 | 0.92 (-0.66 to 2.49) | .51 |
| **medial** | 45.25 ± 4.89 | 45.00 ± 4.66 | 0.24 (-1.52 to 2.00) | .87 |
| **lateral** | 47.55 ± 4.86 | 46.07 ± 6.42 | 1.49 (-0.65 to 3.62) | .54 |
| **femur** | 50.75 ± 3.47 | 50.15 ± 3.99 | 0.60 (-0.79 to 2.00) | .46 |
| **medial** | 49.92 ± 4.05 | 49.82 ± 4.48 | 0.10 (-1.19 to 1.69) | .75 |
| **lateral** | 52.78 ± 4.61 | 51.47 ± 5.58 | 1.31 (-0.60 to 3.22) | .44 |
| **T2** | | | | |
| **No. of participants** | *(N=63)* | *(N=69)* | | |
| **patella** | 33.19 ± 2.85 | 32.88 ± 2.54 | 0.31 (-0.62 to 1.24) | .26 |
| **medial** | 32.01 ± 2.84 | 32.01 ± 2.94 | <0.01 (-0.99 to 1.00) | .69 |
| **lateral** | 33.43 ± 4.02 | 32.77 ± 2.94 | 0.66 (-0.54 to 1.87) | .18 |
| **femur** | 36.66 ± 2.50 | 36.64 ± 2.36 | 0.01 (-0.83 to 0.85) | >.99 |
| **medial** | 35.79 ± 2.47 | 35.92 ± 2.66 | -0.13 (-1.02 to 0.75) | .70 |
| **lateral** | 37.79 ± 3.16 | 38.08 ± 2.61 | -0.28 (-1.28 to 0.71) | .77 |

Data are reported as means ± SD unless indicated otherwise. Times are given in milliseconds. CI: confidence interval

T2 relaxation times of patellar (33.2 vs 32.9 ms) and femoral cartilage (36.7 vs 36.6 ms) between patients and control subjects. Analysis of the medial and lateral subregions within the patellar and femoral cartilage also did not reveal significant differences between the study groups.

No significant differences were found in relaxation times of patellar and femoral cartilage between patients and control subjects within the adolescent and adult subgroups (see the Appendix, available online at http://ajsm .sagepub.com/supplemental).

## DISCUSSION

This study aimed to investigate whether there was a difference in patellofemoral cartilage composition, estimated with a multiparametric quantitative MRI protocol, between patients with PFP and healthy control subjects. Our results showed no significant differences in relaxation times between patients and control subjects in all sequences for both patellar and femoral cartilage. Subdividing the study population in adolescents and adults and analyzing prespecified medial and lateral subregions within the patellar and femoral cartilage also revealed no significant differences.

### Comparison with literature

Thus far, only 2 other studies have investigated differences in cartilage composition estimated with quantitative MRI between patients with PFP and controls.[18,19] $T1_\rho$ relaxation times of patellar cartilage in PFP patients in our study were slightly higher compared to values obtained by Thuillier et al. (46.6 vs 44.6 ms).[18] However, T2 relaxation time of patellar cartilage in patients with PFP were comparable between our study and the study of Farrokhi et al. (33.2 vs 32.5 ms), but lower than those of Thuillier et al. (36.9 ms).[18,19] Similar to our results, no significant differences were found in T2 relaxation times between PFP patients and control subjects in both previous studies.[18,19] We were able to confirm these findings, indicating that there is a normal amount of collagen in patellar cartilage of patients with PFP. In OA, loss of glycosaminoglycans precedes loss of collagen.[34] Therefore, dGEMRIC and $T1_\rho$ are proposed to be more sensitive than T2 mapping for detecting very early changes in cartilage composition, which are more likely to be seen in a young PFP population.[35] In contrast with our findings, Thuillier et al.[18] did report higher $T1_\rho$ relaxation times in patients with PFP with patellar maltracking (indicating glycosaminoglycan loss) of the lateral facet of the patella.[18] However, their patient population consisted of an older and very specific group of PFP patients with patellar maltracking, whereas our study included a younger more representative PFP population without prior selection of specific subgroups (ie, maltracking females or athletes only). Furthermore, adjustment for confounders was lacking in the study by Thuillier et al.[18]

However, this seems essential because it has been shown that for instance dGEMRIC is influenced by physical activity and T2 mapping by age and physical activity level.[36-38] Our analyses indeed showed that associations between dGEMRIC, $T1_\rho$ and T2 mapping and specific confounders (age, sex, BMI, sports participation and time of image acquisition) were present in our multivariate adjusted model.
Although no significant differences were found between our study groups, it was apparent that $T1_\rho$ relaxation times were consistently higher in the adolescent patient population compared with the adolescent control subjects. The largest mean difference was seen in the lateral subregion of both the patellar and femoral cartilage. On the basis of the 95%CI intervals of the mean differences we cannot rule out clinically relevant differences, regarded as an effect size of ≥0.5. Therefore, the absence of significant differences might be caused by a lack of power. The relatively higher $T1_\rho$ relaxation times seen in the lateral part of the patella were also reported in a previous study in patients with PFP and maltracking.[18] However, on the basis of our results and because no other literature is available on adolescents, we cannot conclude that the presence of PFP in adolescents is associated with a change in cartilage content.

Retropatellar cartilage damage has long been implicated as a possible etiological factor for PFP and PFP has been suggested as a precursor of patellofemoral OA.[14,15] Because deterioration of cartilage composition is known to precede morphologic cartilage defects in OA, differences in cartilage composition were expected to be found between a young PFP patient population and healthy control subjects. However, no significant differences were found between the study groups. Because clinically relevant differences could not be ruled out for $T1_\rho$ in the adolescent population, future research might focus on conducting $T1_\rho$ in a large cohort of adolescents with PFP.

**Strengths and limitations**

This is the first case-control study on cartilage composition in PFP that includes a large group of patients with PFP comprising adolescents. To our knowledge, there has been no previous study in PFP using multiparametric quantitative MRI, including dGEMRIC., which is considered the best validated quantitative MRI technique to estimate glycosaminoglycan content.[17] Moreover, in contrast with previous studies, we examined both the trochlear and patellar cartilage, which has not been done previously.
There are, however, some limitations of our study that must be addressed. First, we aimed to match patients and controls on age, sex, BMI and sports participation. However, some differences were observed in BMI and percentage of sports participants. Therefore, all analyses were adjusted for these confounders. Second, acquisition of $T1_\rho$ mapping was not conducted in 12 patients and 6 control subjects because this sequence was not yet available at the beginning of the study. We do not expect this to have influenced our

conclusions, because the baseline characteristics of these participants did not differ from the participants in which the $T1_\rho$ acquisition succeeded.
In this study, we primarily focused on the cartilage composition as a possible etiological factor of PFP. Future approaches of our group will focus on the use of MRI to identify other potential relevant etiological factors of PFP, including structural abnormalities (eg, subchondral bone marrow lesions, joint effusion or fat pad abnormalities) and vascular problems (eg, local tissue ischemia or venous outflow obstruction.

## CONCLUSION

Our results indicate that there is no difference in composition of the patellofemoral cartilage, estimated with multiple quantitative MRI techniques, between patients with PFP and healthy control subjects. However, clinically relevant differences could not be ruled out for $T1_\rho$ in the adolescent population.

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## APPENDIX

**Appendix 1.** Weighted mean $T1_\rho$ relaxation times of patellar and femoral cartilage for adolescent and adult population.

| | Patients | Controls | Mean difference (95% CI) | P Value |
|---|---|---|---|---|
| ***Adolescents*** | *(N= 17)* | *(N=19)* | | |
| **patella** | 46.17 ± 3.50 | 43.78 ± 4.50 | 2.39 (-0.36 to 5.15) | .34 |
| **medial** | 44.35 ± 4.96 | 42.46 ± 4.13 | 1.89 (-1.19 to 4.97) | .60 |
| **lateral** | 46.93 ± 5.42 | 43.83 ± 6.85 | 3.10 (-1.12 to 7.32) | .45 |
| **femur** | 50.49 ± 3.33 | 48.80 ± 3.67 | 1.69 (-0.69 to 4.08) | .29 |
| **medial** | 49.82 ± 4.31 | 49.10 ± 4.34 | 0.72 (-2.22 to 3.65) | .63 |
| **lateral** | 52.29 ± 4.16 | 49.46 ± 5.82 | 2.83 (-0.64 to 6.29) | .21 |
| ***Adults*** | *(N=35)* | *(N=45)* | | |
| **patella** | 47.28 ± 4.24 | 46.94 ± 4.12 | 0.34 (-1.53 to 2.21) | .94 |
| **medial** | 45.69 ± 4.85 | 46.08 ± 4.48 | -0.40 (-2.48 to 1.69) | .58 |
| **lateral** | 47.86 ± 4.61 | 47.01 ± 6.06 | 0.85 (-1.61 to 3.30) | .82 |
| **femur** | 50.88 ± 3.57 | 50.72 ± 4.03 | 0.16 (-1.56 to 1.88) | .70 |
| **medial** | 49.97 ± 3.98 | 50.12 ± 4.55 | -0.15 (-2.09 to 1.78) | .75 |
| **lateral** | 53.02 ± 4.86 | 52.32 ± 5.31 | 0.70 (-1.60 to 3.00) | .66 |

Data are reported as means ± SD unless indicated otherwise. Times are given in milliseconds. CI: confidence interval

**Appendix 2.** Weighted mean T2 relaxation times of patellar and femoral cartilage for adolescent and adult population.

| | Patients | Controls | Mean difference (95% CI) | P Value |
|---|---|---|---|---|
| ***Adolescents*** | *(N= 20)* | *(N=20)* | | |
| **patella** | 33.42 ± 2.73 | 33.00 ± 2.33 | 0.42 (-1.20 to 2.04) | .46 |
| **medial** | 32.59 ± 3.15 | 32.19 ± 2.80 | 0.39 (-1.51 to 2.30) | .90 |
| **lateral** | 33.79 ± 3.40 | 33.25 ± 2.72 | 0.54 (-1.43 to 2.51) | .26 |
| **femur** | 37.31 ± 2.55 | 37.13 ± 2.68 | 0.19 (-1.49 to 1.86) | .99 |
| **medial** | 36.65 ± 2.18 | 36.27 ± 3.17 | 0.38 (-1.37 to 2.12) | .86 |
| **lateral** | 38.78 ± 3.30 | 38.80 ± 2.75 | -0.02 (-1.97 to 1.92) | .87 |
| ***Adults*** | *(N=43)* | *(N=49)* | | |
| **patella** | 33.08 ± 2.93 | 32.83 ± 2.64 | 0.25 (-0.90 to 1.41) | .58 |
| **medial** | 31.74 ± 2.68 | 31.93 ± 3.01 | -0.19 (-1.38 to 1.00) | .96 |
| **lateral** | 33.26 ± 4.31 | 32.57 ± 3.03 | 0.69 (-0.84 to 2.22) | .42 |
| **femur** | 36.35 ± 2.45 | 36.45 ± 2.22 | -0.10 (-1.06 to 0.87) | .63 |
| **medial** | 35.39 ± 2.52 | 35.78 ± 2.44 | -0.39 (-1.42 to 0.64) | .31 |
| **lateral** | 37.34 ± 3.02 | 37.78 ± 2.52 | -0.44 (-1.59 to 0.70) | .43 |

Data are reported as means ± SD unless indicated otherwise. Times are given in milliseconds. CI: confidence interval

# Chapter 5

## Dynamic contrast-enhanced MR imaging of the patellar bone: how to quantify perfusion

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*SUBMITTED*

## ABSTRACT

### Purpose

Since no established analysis method for dynamic contrast enhanced (DCE)-MRI in the patella exists, our purpose was to identify the optimal combination of pharmacokinetic model and arterial input function (AIF) for quantitative analysis of blood perfusion in the patellar bone using DCE-MRI.

### Method

This method design study used a random subset of five control subjects from an IRB approved case-control study into patellofemoral pain. We systematically investigated the reproducibility of pharmacokinetic parameters for all combinations of Orton and Parker AIF models with Tofts, Extended Tofts (ETofts), and Brix pharmacokinetic models. We evaluated if the AIF should use literature parameters, be subject specific, or be group specific. Model selection was based on the goodness-of-fit and the coefficient of variation of the pharmacokinetic parameters.

### Results

The vascular component in the ETofts model could not reliably be recovered and the Brix model parameters showed high variability. A subject specific AIF performed worse than a group specific AIF, but better than an AIF with literature parameters. The best reproducibility and goodness-of-fit were obtained by combining Tofts' pharmacokinetic model with the group specific Parker AIF.

### Conclusions

We identified several good combinations of pharmacokinetic model and AIF for quantitative analysis of perfusion in the patellar bone. The recommended combination is Tofts pharmacokinetic model combined with a group specific Parker AIF model.

## INTRODUCTION

Research suggests that altered blood perfusion of the patellar bone may play a role in the pathogenesis of patellofemoral pain (PFP), a common knee complaint[1–8]. Blood perfusion can be visualized and analyzed quantitatively using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)[9]. Despite the well-described use of DCE-MRI for a variety of indications such as tumors and cerebral stroke[10,11], only a limited number of publications address DCE-MRI in bone[12–16], and none specifically in the patella. DCE-MRI in bone has been limited due to the sparse vascularization of bone and the typical low contrast enhancement compared to surrounding tissues[12,16]. The mobility of the patella poses an additional specific challenge.

Signal intensity changes in the DCE-MRI time series are due to the contrast medium entering the tissue through feeding arteries, residing in the extravascular space, and subsequent draining. This process can be studied semi-quantitatively using measures like time-to-peak, or quantitatively by fitting a pharmacokinetic model to the DCE-MRI data to extract truly quantitative measures of perfusion[9]. Quantitative DCE-MRI requires choosing one of multiple proposed arterial input functions (AIFs) and one of the pharmacokinetic models that together are able to describe the dynamic contrast concentration. Selection of appropriate models is especially relevant for low signal intensity regions since a too complex model (too many degrees of freedom)will be influenced stronger by acquisition noise and, hence, is less sensitive to between-group or between-subject differences in perfusion. Moreover, a model that cannot describe the DCE-MRI signal with sufficient accuracy may fail to detect relevant changes in perfusion. Although quantitative DCE-MRI has been performed in several bones[9], no thorough evaluation of the optimal combination of AIF and pharmacokinetic model has been presented.

The aim of this study was to identify the optimal combination of pharmacokinetic model and AIF for quantitative analysis of perfusion in the patellar bone using DCE-MRI. As potentially appropriate AIF models we selected three models by Orton[17] and several parametrizations of Parker's model[18]. As pharmacokinetic models we selected the models of Brix, Tofts, and the extended model of Tofts[19]. The optimal combination of models will be used in studies investigating possible perfusion alterations in PFP[20].

## MATERIALS AND METHODS

### DCE-MRI acquisition

This method design study used a random subset of five control subjects from an IRB approved case-control study into patellofemoral pain[20]. All subjects provided written informed consent. A 3T-MRI scanner (Discovery MR750, GE Healthcare, Milwaukee, USA) with a dedicated 8-channel knee coil (Invivo Inc., Gainesville, USA) was used.

DCE-MRI was acquired by a time-resolved imaging of contrast kinetics (TRICKS) sequence with anterior-posterior (AP) frequency encoding direction to avoid pulsation artifacts of the popliteal artery into the region of interest. MRI parameters were: in-plane pixel resolution 15mm, slice thickness 5mm, field of view 380 × 380 × 70mm, acquisition matrix 256 × 128, 14 sagittal slices, 70% sampling in the phase direction, TE = 1.7MS, TR = 9.3MS, FA = 30º. The DCE-MRI protocol consisted of 35 phases of 10.30s ± 0.07s (constant within subject). Intravenous contrast administration of 0.2mmol/kg gadopentetate dimeglumine (Magnevist, Bayer, Berlin, Germany), at a rate of 2ml/s, was started after the first phase. Additionally, a non-fat-suppressed 3D SPGR sequence with in-plane resolution of 0.3mm × 0.3mm and 5mm slices was acquired before contrast administration for delineation of the patellar bone marrow.

### Motion compensation

Image driven motion compensation was applied, based on a technique developed for $T_1$ mapping in femoral and tibial articular cartilage[21]. A registration mask was drawn around the patella in the 3D SPGR image. Within this mask the DCE-MRI time series were automatically registered to the first DCE-MRI time point using a rigid transformation model. Subsequently, the first phase was registered to the 3D SPGR image and all DCE-MRI scans were transformed to the grid of the high-resolution 3D SPGR. Visual inspection indicated successful alignment of the time series.

### Quantitative DCE-MRI modelling

The dynamic DCE-MRI signal in each voxel $A(t)$ is described by a combination of three models: The arterial input function (*AIF*), the pharmacokinetic response function ($P$), and the function that relates contrast concentration to signal intensity ($S$), combined as:

$$A(t) = S_\xi\left((AIF_X * P_\varphi)(t)\right) \quad [1]$$

where * denotes convolution and $\xi$, $X$, $\varphi$ are model parameters.

For the *AIF* model we evaluated three computationally efficient models of Orton[17] (Orton1, Orton2, Orton3), five variations on Parker's model[18] with increasing degrees of freedom (Parker-L, Parker-A, Parker-S, Parker-E, Parker-T), as well as a 'dummy' triangle shaped AIF function. The *AIF* parameters $X$ were estimated from a manually outlined

arterial region, either from a single subject (*subject specific*) or from the entire group of subjects (g*roup specific*), or obtained from literature (*literature based*).

For the pharmacokinetic model $P$ we evaluate Brix, Tofts, and Extended Tofts (ETofts) models[19,22]. The Brix model has $AH$, $K_{ep}$, and $k_{el}$ as parameters $\varphi$, while Tofts model has $K_{trans}$ and $k_{ep}$ as $\varphi$, and ETofts adds $v_p$ to it; each model additionally includes a delay parameter.

For $S$ we used a standard model suitable for the SPGR based sequence with one free parameter $\xi = S_0$.

Appendices A.1-A.3 provide more details on the models and Appendix A.4 provides details on the maximum likelihood estimation method used to recover $\xi$, $X$, and $\varphi$.

### Technical validation on phantom data

To validate the model fitting method, a simulated dataset from a DCE-MRI anthropomorphic digital reference phantom was used[23]. All AIF models were fitted on selected arterial voxels and evaluated with the R-square value. Subsequently, these AIFs were used to analyze the provided volume-of-interest (VOI) with ETofts; this VOI contained the tumor of which the perfusion was simulated. Accuracy of the pharmacokinetic parameters was measured by the median absolute difference (MAD) between the estimated and ground truth parameters of the ETofts model in the VOI and compared to the median ground truth value.

### Comparative evaluation of AIF models

The AIF models were fitted to the voxels in an ROI drawn in the center of the popliteal artery, approximately at the level of the center of the patella. This artery was the largest artery in the field of view and could easily be identified in all subjects. Fit quality was evaluated by Akaike's information criterion (AIC)[24,25]:

$$AIC = 2\,k + n\,1\mathrm{n}(SSR) \qquad [2]$$

where $k$ is the number of parameters in the model (for all subjects), $n$ is the number of samples to which the model is fitted, and $SSR$ is the sum of squared residuals (measurements minus values predicted by the fitted model). AIC provides an objective way to compare models with different complexities. Since the voxels from which the AIF is estimated are selected from a small region, they have substantial spatial correlation, which reduces the effective number of degrees of freedom. To avoid a biased model selection due to these correlations, we evaluated the AIC on one randomly selected voxel within the arterial ROI of each subject, and we report the mean and standard deviation of the AIC over 1000 random selections.

### Comparative evaluation of pharmacokinetic models

Each combination of AIF and pharmacokinetic model was fitted to the DCE-MRI data. For each pharmacokinetic parameter we computed its weighted mean over a VOI consisting of the patellar bone marrow, drawn by an experienced observer (RH). As weights we used 1/*CRLB* where *CRLB* is the Cramér-Rao lower bound at each voxel, which is a measure of fit uncertainty (see appendix A.4). In this way, we suppress the influence of voxels with an unreliable fit. The mean and coefficient of variation (*CV = standard deviation / |mean|*) across subjects were computed to investigate reproducibility. The residual (=√*SSR*)) was computed to evaluate goodness-of-fit.

## RESULTS

### Technical validation on phantom data

On the phantom data, the Parker-T model fitted best to the arterial signal with an R-square value of 0.9994, whereas Parker-E and Orton3 had R-square of 0.9983 and 0.9870, respectively. Orton3 fitted best among the Orton models. See Table 1 for the MAD of $K_{trans}$, $k_{ep}$, and $v_p$ inside the VOI. Parker-T had the lowest MAD for $K_{trans}$ and $v_p$.

**Table 1.** Median absolute difference (MAD) of ETofts parameters in the VOI of the phantom experiment for the different AIF models. Median ground truth values are given in the bottom row.

| | $K_{trans}$(1/min) | $k_{ep}$(1/min) | $v_p$(fraction) |
|---|---|---|---|
| *Literature based* | | | |
| **Triangle** | 0.1986 | 0.345 | 0.0155 |
| **Orton1** | 0.0696 | 0.459 | 0.0111 |
| **Orton2** | 0.0672 | 0.466 | 0.0059 |
| **Orton3** | 0.0081 | 0.446 | 0.0074 |
| **Parker** | 0.0133 | 0.468 | 0.0079 |
| *Subject specific* | | | |
| **Triangle** | 0.5461 | 0.387 | 0.0379 |
| **Orton1** | 0.0696 | 0.459 | 0.0111 |
| **Orton2** | 0.0695 | 0.032 | 0.0126 |
| **Orton3** | 0.0293 | 0.043 | 0.0107 |
| **Parker-A** | 0.0118 | 0.082 | 0.0092 |
| **Parker-S** | 0.0059 | 0.070 | 0.0047 |
| **Parker-E** | 0.0096 | 0.085 | 0.0058 |
| **Parker-T** | 0.0079 | 0.086 | 0.0011 |
| **Median ground truth** | 0.0701 | 0.418 | 0.0138 |

### Comparative evaluation of AIF models

Figure 1 shows the AIFs that were estimated by the different models. There were substantial differences between AIFs when estimated for each subject individually, especially for the models Orton2, Orton3, and Parker-A. The substantial differences in contrast concentration in the tail of the curve were observed to be correlated to under/over estimation of the baseline signal intensity $\xi$. For subject specific Parker-E and Parker-T, the first-pass contrast concentration differed substantially from the group specific first-pass and the first-pass as provided by the literature based AIFs. The group specific Parker-T was also substantially different from the literature based Parker model.

Table 2 shows the mean and standard deviation of the AIC value of the AIF fits over the 1000 random selections of one voxel per subject. Note that in Equation 2, n=175 (35 time points × 1 randomly selected voxel ×5 subjects) and $k$ varies between 10 (literature based AIF; only estimating delay and $\xi$ per subject) and 60 (subject specific Parker-T).

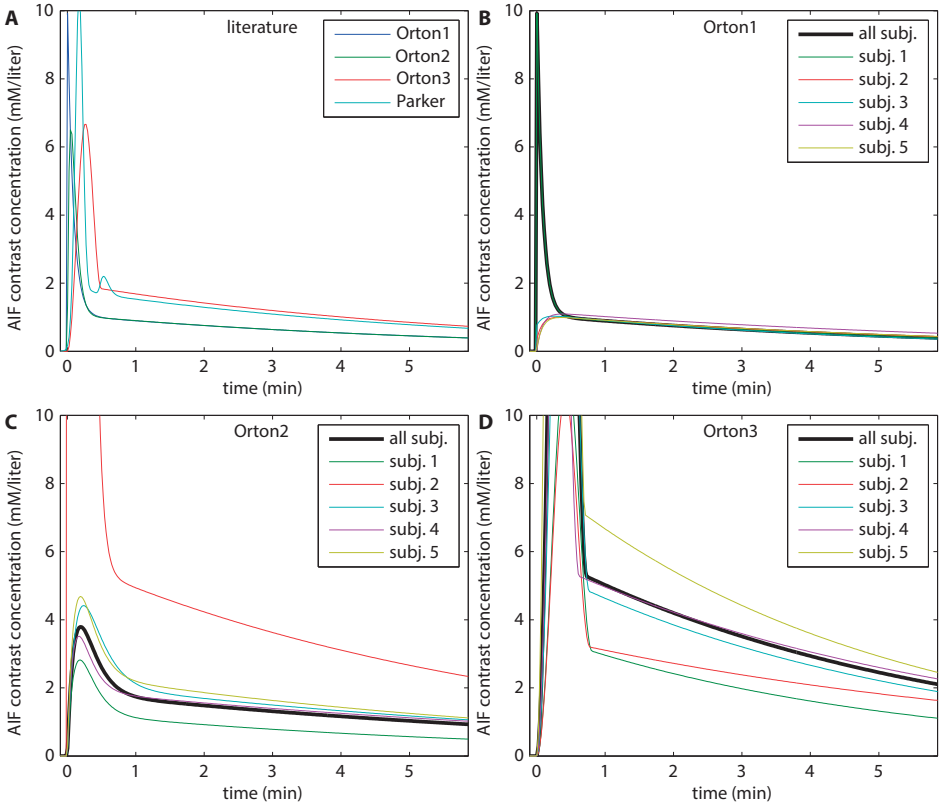


**Figure 1.** Literature based, subject specific, and group specific arterial contrast concentration, from left to right, top to bottom: Literature, Orton1, Orton2, Orton3, Parker-A, Parker-S, Parker-E, Parker-T. In each figure, the group specific estimate is shown by the black bold line

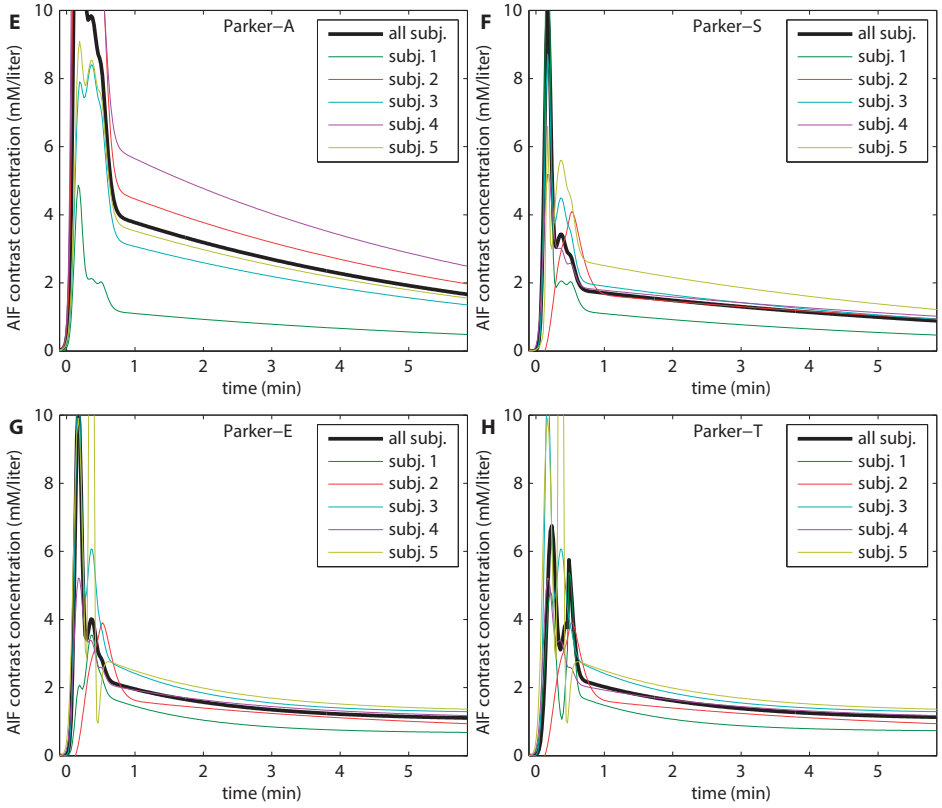


**Figure 1.** (*continued)* Literature based, subject specific, and group specific arterial contrast concentration, from left to right, top to bottom: Literature, Orton1, Orton2, Orton3, Parker-A, Parker-S, Parker-E, Parker-T. In each figure, the group specific estimate is shown by the black bold line

The AIC of Parker-E and Parker-T were much lower than the AIC of the Orton models. All models substantially improved over the triangle AIF.

**Table 2.** The mean (sd) of the AIC of AIF fits. Lower values indicate a better model fit.

| | Literature | | Subject | | Group | |
|---|---|---|---|---|---|---|
| **triangle** | 1180.3 | (14.9) | 846.9 | (15.0) | 843.8 | (14.0) |
| **Orton1** | 776.1 | (25.7) | 581.2 | (23.0) | 777.7 | (23.3) |
| **Orton2** | 613.7 | (26.0) | 141.5 | (17.0) | 236.1 | (38.2) |
| **Orton3** | 512.4 | (14.9) | 202.3 | (14.0) | 268.3 | (32.2) |
| **Parker-L** | 528.0 | (14.6) | | | | |
| **Parker-A** | | | 174.7 | (19.4) | 259.7 | (34.5) |
| **Parker-S** | | | 154.1 | (23.4) | 240.6 | (40.9) |
| **Parker-E** | | | 61.9 | (32.9) | 204.0 | (46.9) |
| **Parker-T** | | | 69.2 | (35.1) | 200.6 | (48.6) |

## Comparative evaluation of pharmacokinetic models

Table 3 and Table 4 show the mean and CV across subjects of the pharmacokinetic parameters, as well as the residual norm, for all combinations of AIF and pharmacokinetic models.

Substantial variations in parameter values for different AIF models were observed (Table 3). The residual of ETofts was not substantially lower than the residual of Tofts, which indicates that, in our patellar VOI, inclusion of the vascular component did not lead to a better fit. For most AIF models, the residual of the Brix model was approximately 10% lower than the residual of Tofts and ETofts. The residual norm did not vary substantially across AIF models, except for the `dummy' Triangle AIF and the literature based AIFs combined with the ETofts model, which resulted in much higher residual norm.

**Table 3.** For each AIF and pharmacokinetic model this table shows the mean over the five subjects of each parameter and the residual. Delay is in *min*; $K_{trans}$, $k_{ep}$, $k_{el}$ in 1/*min*; $v_p$ is a fraction; *AH* is in 1/$min^2$; residual norm is in arbitrary unit but it can be compared across all model combinations.

| | Tofts | | ExtendedTofts | | | Brix | | | Residual | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $K_{trans}$ | $k_{ep}$ | $K_{trans}$ | $k_{ep}$ | $v_p$ | *AH* | $k_{ep}$ | $k_{el}$ | Tofts | ETofts | Brix |
| *Literature based* | | | | | | | | | | | |
| **Triangle** | 0.097 | -0.147 | 0.084 | -0.138 | 0 | 0.132 | 0.022 | 0.441 | 0.113 | 0.382 | 0.070 |
| **Orton1** | 0.035 | 0.138 | 0.028 | 0.140 | -0.004 | 0.060 | 0.262 | 1.367 | 0.079 | 0.147 | 0.069 |
| **Orton2** | 0.037 | 0.155 | 0.029 | 0.153 | -0.005 | 0.064 | 0.281 | 1.377 | 0.077 | 0.135 | 0.069 |
| **Orton3** | 0.021 | 0.166 | 0.016 | 0.162 | -0.001 | 0.036 | 0.213 | 1.342 | 0.076 | 0.077 | 0.069 |
| **Parker** | 0.022 | 0.153 | 0.015 | 0.147 | -0.002 | 0.038 | 0.318 | 0.931 | 0.077 | 0.147 | 0.069 |
| *Subject specific* | | | | | | | | | | | |
| **Triangle** | 0.850 | -0.212 | 0.833 | -0.210 | -0.064 | 0.918 | -0.084 | 0.388 | 0.135 | 0.135 | 0.116 |
| **Orton1** | 0.052 | 0.254 | 0.039 | 0.225 | 0.009 | 0.083 | 0.246 | 1.890 | 0.071 | 0.070 | 0.073 |
| **Orton2** | 0.018 | 0.133 | 0.013 | 0.047 | -0.001 | 0.030 | 0.253 | 1.272 | 0.079 | 0.074 | 0.070 |
| **Orton3** | 0.007 | 0.091 | 0.004 | 0.090 | -0.001 | 0.011 | 0.166 | 1.379 | 0.081 | 0.082 | 0.068 |
| **Parker-A** | 0.011 | 0.130 | 0.008 | 0.098 | -0.001 | 0.018 | 0.286 | 1.090 | 0.079 | 0.080 | 0.069 |
| **Parker-S** | 0.021 | 0.198 | 0.015 | 0.192 | -0.002 | 0.036 | 0.254 | 0.991 | 0.073 | 0.079 | 0.069 |
| **Parker-E** | 0.020 | 0.179 | 0.014 | 0.174 | -0.002 | 0.033 | 0.226 | 1.650 | 0.074 | 0.075 | 0.068 |
| **Parker-T** | 0.019 | 0.174 | 0.014 | 0.171 | -0.002 | 0.032 | 0.399 | 1.358 | 0.074 | 0.075 | 0.068 |
| *Group specific* | | | | | | | | | | | |
| **Triangle** | 0.819 | -0.188 | 0.795 | -0.186 | -0.053 | 0.898 | -0.003 | 0.279 | 0.123 | 0.123 | 0.107 |
| **Orton1** | 0.035 | 0.138 | 0.028 | 0.140 | -0.004 | 0.060 | 0.250 | 1.425 | 0.079 | 0.147 | 0.069 |
| **Orton2** | 0.023 | 0.225 | 0.017 | 0.214 | -0.002 | 0.039 | 0.304 | 1.607 | 0.073 | 0.073 | 0.069 |
| **Orton3** | 0.005 | 0.058 | 0.004 | 0.057 | 0 | 0.007 | 0.151 | 0.812 | 0.084 | 0.085 | 0.068 |
| **Parker-A** | 0.008 | 0.119 | 0.006 | 0.115 | -0.001 | 0.013 | 0.180 | 1.459 | 0.078 | 0.077 | 0.068 |
| **Parker-S** | 0.021 | 0.184 | 0.018 | 0.174 | -0.003 | 0.036 | 0.278 | 1.393 | 0.076 | 0.080 | 0.069 |
| **Parker-E** | 0.019 | 0.171 | 0.016 | 0.164 | -0.003 | 0.031 | 0.227 | 1.149 | 0.075 | 0.077 | 0.069 |
| **Parker-T** | 0.019 | 0.184 | 0.016 | 0.178 | -0.001 | 0.031 | 0.221 | 1.393 | 0.074 | 0.074 | 0.069 |

Table 4 shows that the pharmacokinetic parameters estimated with subject specific AIF models had an increased CV compared to pharmacokinetic parameters estimated with literature based and group specific AIF models. For most combinations there were only small differences in CV of the parameters between literature based and group specific AIF models. The exceptions were $k_{ep}$ of Tofts and ETofts with Orton3, $v_p$ of ETofts with Orton2, and $k_{ep}$ and $k_{el}$ of Brix with Orton2 and Orton3, which were mostly found to have a higher CV for the group specific AIF. When comparing the CV of the different models we noted that the CV for Tofts' model was substantially lower than the CV for the other models. Especially the CV of $K_{trans}$ was substantially larger in ETofts than Tofts. For ETofts, the CV of $v_p$ was very high demonstrating that the vascular component could not be precisely recovered, as was also indicated by the unrealistic (small) negative $v_p$ (Table 3). The CV of the Brix model parameters was, overall, higher than the CV of the Tofts model parameters.

**Table 4.** For each AIF and each parameter of the pharmacokinetic models this table shows the CV (%) over the five subjects. The three right-most columns show the CV of the residual.

| | **Tofts** | | **ExtendedTofts** | | | **Brix** | | | **Residual** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $K_{trans}$ | $k_{ep}$ | $K_{trans}$ | $k_{ep}$ | $v_p$ | *AH* | $k_{ep}$ | $k_{el}$ | **Tofts** | **ETofts** | **Brix** |
| *Literature based* | | | | | | | | | | | |
| **Triangle** | 23.1 | 18.0 | 24.4 | 18.5 | 165.7 | 23.5 | 546.4 | 79.5 | 20.6 | 34.0 | 14.9 |
| **Orton1** | 24.2 | 29.3 | 40.3 | 26.8 | 54.1 | 29.4 | 43.0 | 60.7 | 16.4 | 31.1 | 15.9 |
| **Orton2** | 24.2 | 26.9 | 39.5 | 26.3 | 58.2 | 32.6 | 62.6 | 57.6 | 16.1 | 33.1 | 15.8 |
| **Orton3** | 24.3 | 25.4 | 34.1 | 25.4 | 117.6 | 31.2 | 25.4 | 54.0 | 16.1 | 16.3 | 16.2 |
| **Parker** | 24.2 | 27.2 | 36.0 | 27.8 | 113.5 | 30.0 | 45.2 | 74.6 | 16.0 | 42.6 | 16.1 |
| *Subject specific* | | | | | | | | | | | |
| **Triangle** | 18.2 | 8.4 | 19.9 | 8.0 | 47.2 | 7.7 | 63.7 | 68.4 | 25.4 | 25.3 | 25.5 |
| **Orton1** | 34.3 | 30.9 | 43.6 | 26.7 | 83.7 | 33.8 | 31.3 | 48.1 | 16.0 | 15.7 | 16.6 |
| **Orton2** | 57.0 | 159.5 | 64.9 | 799.2 | 227.1 | 61.3 | 26.7 | 65.7 | 30.7 | 20.4 | 16.1 |
| **Orton3** | 44.6 | 56.4 | 38.4 | 57.1 | 80.8 | 45.5 | 36.0 | 36.1 | 16.4 | 16.5 | 16.7 |
| **Parker-A** | 55.7 | 60.6 | 48.7 | 115.1 | 228.9 | 63.2 | 52.8 | 72.5 | 18.5 | 16.6 | 16.2 |
| **Parker-S** | 24.5 | 37.6 | 40.7 | 40.1 | 102.7 | 30.6 | 47.2 | 70.2 | 17.5 | 19.5 | 15.9 |
| **Parker-E** | 28.0 | 22.6 | 32.2 | 25.0 | 172.2 | 32.4 | 24.3 | 20.9 | 15.9 | 16.2 | 15.8 |
| **Parker-T** | 30.5 | 27.1 | 31.7 | 28.7 | 155.1 | 34.6 | 69.1 | 45.9 | 15.9 | 16.4 | 15.8 |
| *Group specific* | | | | | | | | | | | |
| **Triangle** | 16.9 | 17.6 | 19.6 | 17.3 | 58.1 | 7.9 | 3371.7 | 68.4 | 23.1 | 23.0 | 22.8 |
| **Orton1** | 24.2 | 29.3 | 40.3 | 26.8 | 54.4 | 29.4 | 38.1 | 58.2 | 16.4 | 31.1 | 15.9 |
| **Orton2** | 24.4 | 20.3 | 44.6 | 21.2 | 162.4 | 31.3 | 40.8 | 31.7 | 16.0 | 16.4 | 15.8 |
| **Orton3** | 24.0 | 60.8 | 36.7 | 61.8 | 84.2 | 28.4 | 57.0 | 70.0 | 17.6 | 17.9 | 16.5 |
| **Parker-A** | 24.2 | 32.6 | 36.6 | 35.3 | 96.5 | 29.7 | 34.0 | 33.8 | 16.7 | 17.1 | 16.4 |
| **Parker-S** | 24.2 | 23.5 | 40.2 | 23.9 | 77.0 | 30.1 | 53.9 | 47.1 | 16.3 | 14.6 | 16.1 |
| **Parker-E** | 24.2 | 24.9 | 40.6 | 24.8 | 81.9 | 30.8 | 32.3 | 61.2 | 15.8 | 14.9 | 15.4 |
| **Parker-T** | 24.4 | 23.5 | 36.7 | 24.0 | 140.5 | 31.6 | 24.3 | 53.9 | 15.7 | 16.1 | 15.5 |

## DISCUSSION

This paper presents the first systematic comparative evaluation of AIF and pharmacokinetic models for quantitatively analyzing patellar perfusion with DCE-MRI. Below, we derive several recommendations based on our experimental results, and discuss limitations and impact.

First, the evaluation on digital phantom data shows that the proposed fitting method can accurately recover pharmacokinetic parameters when a correct AIF model is used. Although this phantom dataset simulates tumor perfusion, which is different from patellar perfusion, the comparison with the ground truth confirms the technical validity of the proposed fitting methods.

***Orton or Parker?***

As indicated by the AIC scores (Table 2), Triangle and Orton1 do not model the arterial signal well. For the Parker model, the increase in complexity from Parker-A to Parker-E is supported by the measured imaging data, since Parker-E leads to substantially improved arterial fits, reflected by lower AIC. This indicates that our addition of a persisting contrast concentration to the Parker-E model was justified. Overall, in terms of AIC, most competitive models are Orton2, Parker-E and Parker-T.

***Subject specific, group specific, or literature based?***

The AIC score shows substantially improved arterial fits of the subject and group specific AIFs compared to the literature based AIF (Table 2). Moreover, the literature based AIFs lead to high residuals when used in combination with the ETofts pharmacokinetic model (Table 3). Based on these results, we recommend against using a literature based AIF.

Since the large intersubject variability in the shape of the first-pass contrast concentration for subject specific AIF modelling with Parker-E and Parker-T, and to a lesser extent with Orton2 and Orton3, cannot be explained biologically, the group specific AIF is preferred for these models, despite the higher AIC value that was seen in Table 2. This is additionally supported by the fact that the CV of the pharmacokinetic parameters (Table 4) is lower for the group specific AIF than for the subject specific AIF, which also suggests that intersubject variation in true AIF is small compared to the variance of the single subject estimate. Hence, we recommend to use a group specific AIF, as it leads to highest reproducibility of the pharmacokinetic parameters.

***Tofts, ETofts, or Brix?***

Comparing pharmacokinetic models, the CV typically is lowest for Tofts (Table 4). This is probably due to the larger number of parameters in ETofts and Brix. The larger number of parameters in Brix probably also explains the lower residual compared to Tofts. As all three pharmacokinetic models explain a similar fraction of the DCE-MRI signal, we expect that group differences, e.g. between cases and controls, in perfusion cause similar relative changes in parameter values. This implies that the model with the smallest CV (Tofts) will likely be more sensitive to detect group differences than the other models (ETofts, Brix).

## Limitations and impact

We chose to aggregate the voxelwise pharmacokinetic measures by computing a weighted mean over the patella VOI. Any spatial heterogeneity within the patella is thus averaged out. Hence, it should be noted that using these measures to study group differences implicitly assumes non-localized physiological changes in the patella.

As no *in-vivo* ground truth values for pharmacokinetic parameters are available, we could not base model selection on closeness to ground truth and this implies that reliable absolute quantification of perfusion values currently cannot be claimed. As in Schmid et al.[26], we used a statistical analysis method to trade off model complexity against goodness-of-fit, in order to guide model selection. Note that, compared to Schmid et al., we evaluated a wider range of models, both for AIF and for pharmacokinetic model, and applied it to patellar DCE-MRI data.

The substantial differences in pharmacokinetic parameters obtained with different AIFs emphasize the relevance of choosing a good AIF model. Severe bias in parameters could occur with a suboptimal AIF. The small differences observed among the best candidates indicate that potentially other combinations can be best for acquisitions with different settings and/or in different body parts; even for other bones. Hence, our proposed framework for evaluating perfusion is an important contribution in itself. It allowed identification of a few combinations of AIF models and pharmacokinetic models that performed well on all aspects: AIC score and biological credibility of the AIF, CV of pharmacokinetic parameters, and goodness-of-fit in the patella VOI.

## Overall recommendation

Although Orton2 combined with Tofts' model seems to slightly improve reproducibility and goodness-of-fit in this dataset, we consider the lower AIC score of Parker-T as well as the improved biological credibility of that AIF to be more important. Together with the accuracy of this combination on phantom data, this gives good confidence that group

specific Parker-T combined with Tofts' model is suitable to identify patellar perfusion abnormalities.

The observed values of the CV indicate that with a consistently used combination of models, reproducibility is sufficient to allow identification of group differences in perfusion with reasonably sized groups; e.g. approx. 40 subjects per group allow identification of group differences of 10% in $K_{trans}$ or $k_{ep}$ at a significance level of $p < 0.05$ with 75% power.

## CONCLUSION

We conclude that the most suitable choice of models for the analyzed patellar DCE-MRI data is Parker's arterial input model where all parameters of Parker's model are estimated from arterial voxels of the full group of subjects, combined with Tofts' pharmacokinetic model. This combination will be used in a large study on patellar perfusion in patients with PFP[20].

## APPENDIX

### A.1 DCE-MRI models – Arterial input function

In the next subsections the different AIF models used in the evaluations are described.

***Triangle***

To investigate if the arterial input needs to be modelled at all, we investigate the performance of a triangle function as dummy reference AIF:

$$AIF_X(t) = a/w \begin{cases} 1 - |t|/w & |t| \le w \\ 0 & |t| > w \end{cases}$$

with $X = [a, w]$ and using $a = 1$ and $w = TR$ as `literature' value.

***Orton***

We investigated the three AIF models of Orton[17]. These AIF models can be convolved analytically for often used pharmacokinetic models. When this analytical convolution is used, the computational performance might be better than for other models where a numerical approximation of the convolution should be employed. Even though the Orton models can be convolved analytically, our implementation relied, for all models, on numerical convolutions to ease testing and implementation in this investigative research.

Specifically, the Orton model 1 (Orton1) is given by:

$$AIF_X(t) = \begin{cases} A_B \exp(-t\mu_B) + A_G \exp(-t\mu_G) & t > 0 \\ 0 & t \le 0 \end{cases}$$

with $X = [A_B, \mu_B, A_G, \mu_G]$ and as literature values[17]: $A_B = 9.32$ mM, $A_G = 1.06$ mM, $\mu_B = 12.0$ min$^{-1}$, $\mu_G = 0.169^{-1}$.

The Orton model 2 (Orton2) is given by:

$$AIF_X(t) = \begin{cases} t\, A_B \exp(-t\, \mu_B) + A_G(\exp(-t\, \mu_G) - \exp(-t\, \mu_B)) & t > 0 \\ 0 & t \le 0 \end{cases}$$

with $X = [A_B, \mu_B, A_G, \mu_G]$ and as literature values[17]: $A_B = 323$ mM min$^{-1}$, $A_G = 1.07$ mM, $\mu_B = 20.2$ min$^{-1}$, $\mu_G = 0.172^{-1}$.

Orton model 3 (Orton3) is given by:

$$AIF_X(t) = \begin{cases} a_B\,(1 - \cos(-t\,\mu_B) + a_B a_G f(t, \mu_G) & 0 < t \le t_B \\ a_B a_G f(t_B, \mu_G)\exp(-(t - t_B)\mu_G) & t > t_B \\ 0 & t \le 0 \end{cases}$$

with

$$t_B = 2\Pi/\mu_B,\ f(t, \mu_G) = \frac{1}{\mu_G(1-\exp(-t\mu_G))} - 1/(\mu_G^2+\mu_B^2)(\mu_G \cos(t\,\mu_B) + \mu_B \sin(t\,\mu_B) - \mu_G \exp(-t\mu_G)),$$

$X = [a_B, \mu_B, a_G, \mu_G]$ and as literature values[17]: $\mu_B = 22.8$ min$^{-1}$, $\mu_G = 0.171$ min$^{-1}$, $a_B = 2.84$ mM, $a_G = 1.36$ min$^{-1}$.

***Parker***

The AIF model of Parker et al.[18] is a general function for describing the arterial impulse response. It models the first pass and second pass of the bolus separately, followed by an exponential decay. As will be motivated below, we slightly extended this model to:

$$AIF_X(t) = \frac{\sum_{n=1}^{2} \frac{A_n}{\sigma_n \sqrt{2\pi}} \exp\left(\frac{-(t-T_n)^2}{2\sigma_n^2}\right) + \frac{\alpha \exp(-\beta t) + \gamma}{1 + \exp(-s(t-\tau))}}{1 - Hct}$$

where $A_n$, $T_n$, and $\sigma_n$ are scaling constants, centers, and widths of two Gaussians; $\alpha$, $\beta$, and $\gamma$ are the amplitude, decay constant, and asymptote of the exponential tail; and $s$ and $\tau$ are the width and center of the sigmoid that is used as soft step function for the exponential tail, respectively. Our extension is the introduction of $\gamma$ as we observed that a mono-exponential decay did not accurately describe the decay. The literature values that we used are[18]: $A_1 = 0.809$ mM min, $A_2 = 0.330$ mM min, $T_1 = 0.17046$ min, $T_2 = 0.365$ min, $\sigma_1 = 0.0563$ min, $\sigma_2 = 0.132$ min, $\alpha = 1.050$ mM, $\beta = 0.1685$ min$^{-1}$, $\gamma = 0$ mM, $s = 38.078$ min$^{-1}$, $\tau = 0.483$ min, $Hct = 0.42$.

Since this model contains many parameters, some of which are hard to identify due to the relatively low temporal resolution in our dataset, we also tested restricting some parameters to the literature values[18]. In this work, the following restricted models were used, where all parameters not in $X$ are taken from the literature with values given above.

Parker-L : All values from **L**iterature.
Parker-A : $X = [A_1, A_2, \alpha]$ ; Estimate only the **A**mplitude parameters.
Parker-S : $X = [A_1, A_2, \sigma_1, \sigma_2, \alpha, \beta]$; In addition to Parker-A also estimate the **S**cale parameters.
Parker-E : $X = [A_1, A_2, \sigma_1, \sigma_2, \alpha, \beta, \gamma]$; **E**xtend Parker-S by including $\gamma$.
Parker-T : $X = [A_1, A_2, T_1, T_2, \sigma_1, \sigma_2, \alpha, \beta, \gamma, s]$; In addition to Parker-E add **T**iming $T_n$ and $s$ to estimate all parameters except $\tau$. Note that including $\tau$ would lead to a degenerate model as we estimate a delay per subject (see A.4) and also estimate all other timing parameters ($T_n$).

The optimization of $X$ of the Parker AIF models was nested, such that the result of each of the listed restricted Parker models was used as initialization for the next.

### A.2 DCE-MRI models - Pharmacokinetics

Three different pharmacokinetic models were compared: Tofts, Extended Tofts, and Brix[19,22]. The extension in the Extended Tofts model is the inclusion of a vascular compo-

nent. While obviously in actual tissues there is a vascular component, the addition of an extra parameter may make the fitting less robust. Especially, since only in a few frames around the first pass there is a substantial difference between the Tofts and Extended Tofts model. The pharmacokinetic impulse of the Extended Tofts model is given by

$$P_\varphi(t) = v_p\delta_{t,0} + \frac{K_{trans}\exp(-t\,k_{ep})}{1+\exp(-\frac{t}{\Delta t})}$$

where $\varphi = [K_{trans}, k_{ep}, v_p]$. The vascular volume fraction $v_p$ is defined as zero in the Tofts model. Thus, for the Tofts model $\varphi = [K_{trans}, k_{ep}]$.

The pharmacokinetic impulse response model of Brix[19,22] is given by:

$$P_\varphi(t) = \begin{cases} -AH\,\dfrac{\exp(-t\,k_{ep}) - \exp(-t\,k_{el})}{k_{ep} - k_{el}} & t > 0 \\ 0 & t \le 0 \end{cases}$$

with $\varphi = [AH, k_{ep}, k_{el}]$.

### A.3 DCE-MRI models - Contrast concentration to signal

The gadolinium-based contrast medium gadopentetate dimeglumine (Magnevist; Bayer, Berlin, Germany) that we used predominantly shortens the $T_1$ (spin-lattice) relaxation time. Hence, as commonly done, we used a $T_1$ sensitive SPGR based TRICKS sequence[18,19] which can be modelled with the symbols defined below as (modification of [27])

$$S_\xi(c) = S_0\,\frac{1-\mathrm{E}_{10}\cos\alpha}{1-E_{10}}\,\frac{1-E_1(c)}{1-E_1(c)\cos\alpha}$$

with $\xi = [S_0]$, $E_{10} = \exp(-TR\,R_1)$, $E_1(c) = \exp(-TR\,(R_1 + c\,R_{contrast}))$. This model has $S_0$, the signal intensity without contrast agent present, as parameter to ease estimation and interpretation. According to Tofts et al.[19], the relaxivities of tissue and contrast medium can be assumed to be additive. To infer the contrast concentration, the $T_1 = 1/R_1$ value of the tissues of interest without contrast agent should be known. Our protocol did not include a non-contrast-enhanced quantitative $T_1$ scan due to acquisition time considerations. However, the native $T_1$ value was expected to be constant across subjects, and at least to not be strongly correlated with PFP as $T_1$ itself is not known to be a biomarker for PFP. Hence, using a fixed $T_1$ value for all subjects was considered appropriate. For blood we used $T_1$ = 1664 ms, which is given as best estimate at normal hematocrit values in Lu et al.[28]. For bone and patella we used $T_1$ = 288 ms as given in Han et al.[29]. Based on Rohrer et al.[30] we used $R_{contrast}$ = 4.3 liter/(mM sec) as relaxivity of the contrast agent.

### A.4 DCE-MRI model fitting

Using the models defined in the appendices above, the signal intensity predicting model $A(t)$ (Equation 1) was fitted with a Maximum Likelihood estimation procedure to the magnitude MR images $I$:

$$\hat{\xi}, \hat{\varphi}, \hat{\sigma} = \arg\max_{\xi, \varphi, \sigma} \Sigma_t \ln p(I(t), A(t), \sigma) \quad [3]$$

where $p$ is the likelihood function of the Rice distributed measurements $I(t)$, which are assumed to be independent. Note that the voxel location $X$ is not shown for convenience of notation. The optimization uses MRI fitting tools[31] and was performed in two stages. In the first stage a Halton sequence based 'grid' search was performed with 1000 points. In the second stage, the six best matches of the first stage were refined by a local nonlinear optimization with lower and upper bound constraints on the individual parameters (fmincon in MATLAB 2011b, MathWorks with the active-set algorithm). The final result was the best match after optimization. The range for the initial grid and the constraints applied during nonlinear optimization are given in Table 5. The constraints applied during optimization were chosen based on the range that was assumed to be identifiable by the acquisition that was performed, while the ranges used for initialization were determined by encompassing the observed range of values. The fitting tools used are provided online on the website fitmri.bigr.nl.

The parameters of the AIF, $X$, were estimated from, in each subject, a manually drawn (small) ROI in a part of an artery that by visual inspection did not contain imaging artifacts. The estimation procedure, which was similar to equation 3, recovered the subject specific as well as the group specific $X$ by using a delay per subject as pharmacokinetic model and summing the log likelihood over all voxels in the arterial ROIs. As the arterial SNR was sufficiently high in all cases, the likelihood function $p$ was replaced with a Gaussian distribution in this estimation. For the subject specific AIF the fit was performed for each subject individually, while for the group specific AIF the selected arterial voxels in all subjects were combined into a single fit.

Maximum Likelihood estimation additionally allows evaluating the Cramér-Rao lower bound (CRLB)[32]. This is a lower bound for the variance of the parameters $\hat{\theta}$ due to the noise in the acquisition ($\sigma$) for any unbiased estimation procedure. Even though it is a lower bound, the Maximum Likelihood estimator was observed to almost reach this bound in simulation experiments. Hence, the CRLB was used in the evaluation of the weighted mean of the pharmacokinetic parameters over the patellar bone marrow VOI.

**Table 5.** Parameters, units and constraints applied during estimation.

| | **all** | **Tofts and ETofts** | | | **Brix** | | |
|---|---|---|---|---|---|---|---|
| **parameter** | delay | Ktrans | kep | vp | AH | kep | kel |
| **unit** | min | $(min)^{-1}$ | $(min)^{-1}$ | (fraction) | $min^{-2}$ | $(min)^{-1}$ | $(min)^{-1}$ |
| **lower bound optimization** | 0 | -0.1 | -1 | -0.1 | -0.2 | -1 | 0 |
| **lower bound initialization** | 0.17 | -0.01 | -0.2 | -0.001 | -0.05 | -0.2 | 0.2 |
| **upper bound initialization** | 2.50 | 0.5 | 0.5 | 0.001 | 0.25 | 0.8 | 4 |
| **upper bound optimization** | 5 | 1 | 3 | 0.2 | 1 | 3 | 10 |

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# Chapter 6

## Blood perfusion of patellar bone measured by dynamic contrast-enhanced MRI in patients with patellofemoral pain: a case-control study.

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*SUBMITTED*

## ABSTRACT

### Background/Aim

Patellofemoral pain (PFP) is a common knee complaint with unknown pathophysiology. Vascular problems, like bone ischemia or increased intraosseous hydrostatic pressure due to venous outflow obstruction, might play a role in PFP. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) enables quantitative measurement of patellar bone blood perfusion. This case-control study aims to investigate differences in DCE-MRI perfusion parameters between patients with PFP and healthy control subjects.

### Methods

Patients diagnosed with PFP and healthy controls underwent MRI at 3T including DCE-MRI. Quantitative MR perfusion parameters (i.e. $k_{ep}$, $k_{trans}$) of manually segmented patellar bone were derived from motion-compensated DCE MRI-data by fitting Tofts' model to the measured data in each voxel. Differences in perfusion parameters of patellar bone were compared between groups by linear regression analyses, adjusted for age, body mass index (BMI), gender, and sports participation.

### Results

35 adult patients and 44 adult controls were included. Mean age was 26.1 (SD 5.0), mean BMI was 24.1(SD 3.4)kg/m2 and 49% was female. Mean $k_{ep}$ was 0.189(SD 0.147)$min^{-1}$ for patients and 0.154(SD 0.114)$min^{-1}$ for controls(Table 2). Mean $k_{trans}$ was 0.019(SD 0.015) $min^{-1}$ for patients and 0.014(SD 0.009)$min^{-1}$ for controls. Both perfusion parameters were not significantly different between groups. However, a significant difference in variance between populations was observed for $k_{trans}$.

### Conclusions

In contrast to expected, higher values of patellar bone perfusion parameters were found in patients with PFP compared to healthy control subjects, but these differences were not statistically significant. This result, and the observed significant difference in $k_{trans}$ variance warrant further research.

## INTRODUCTION

Patellofemoral pain (PFP) is a common knee complaint, which occurs especially in young physically active individuals.[1] PFP is characterized by retro or peripatellar pain during kneeling, stair climbing, running, cycling, squatting and prolonged sitting with the knees flexed. A substantial percentage of patients experiences persistent symptoms, despite a variety of treatments.[2-6] The pathophysiology of PFP is largely unknown. An increasing body of research suggests that vascular problems might play a role in patellofemoral pain.[7-13] In 1978, Lemperg and Arnoldi reported an elevated intraosseous hydrostatic pressure in the femur and tibia of patients with aching rest pain of the knee without osteoarthritis.[12] They were the first to describe the intraosseous engorgement-pain syndrome, characterized by reduced venous outflow from bone marrow, elevated intraosseous hydrostatic pressure and rest pain. More recently, Ho et al. demonstrated an elevated patellar water content, suggestive of venous engorgement on MRI in recreational runners with PFP.[11] Increased intraosseous hydrostatic pressure is proposed to induce pain by activating nociceptors in the subchondral bone.[14] Another proposed vascular source of pain is local bone tissue ischemia, which could be induced by increased intraosseous pressure due to impaired venous outflow, or by impaired arterial blood inflow. Local bone tissue ischemia might be particularly important in PFP patients with pain during prolonged sitting, since Naslund et al. showed a reduced pulsatile patellar blood flow on photoplethysmography in flexed knees.[10]

Visualization and quantitative analysis of blood perfusion is possible with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).[15] DCE-MRI is routinely applied in clinical practice for a variety of indications such as tumor and cerebral stroke imaging.[16,17] However, there have only been a limited number of studies on the application of DCE-MRI for bone using a quantitative approach, due to the relatively poor vascularization of bone and the typical low contrast enhancement compared to surrounding tissues.[18-22] To our knowledge, DCE-MRI has neither been applied in the patellar bone nor in patients with PFP before.

Therefore, the purpose of this study was to investigate differences in blood perfusion of the patellar bone, measured with quantitative DCE-MRI, between patients with PFP and control subjects. This may lead to a better understanding of the pathophysiology of PFP. Lower values of patellar bone perfusion parameters, suggestive for local tissue ischemia or venous outflow obstruction, are expected to be found in patients with PFP compared to healthy control subjects.

## MATERIAL AND METHODS

### Study design and participants

For the current study purpose, patients aged 18-40 years with PFP and healthy control subjects were included between January 2013 and September 2014. Patients with PFP for two months to two years diagnosed by their general practitioner, physiotherapist or sports physician, based on the presence of at least three of the following symptoms: crepitus or, retro or peripatellar pain during stair climbing, squatting, running, cycling, or sitting for a prolonged period with flexed knees were included. Exclusion criteria were: previous PFP episodes more than two years ago, onset after trauma, defined pathological condition of the affected knee at present, or previous surgery or injury of the affected knee. Healthy controls were recruited from patients' sports team members, friends, or colleagues. We aimed to match patient and controls on age, gender, body mass index (BMI), and activity level. Exclusion criteria for controls were: present or past PFP, surgery or traumatic injury of both knees, or first degree relatedness with patients. Other exclusion criteria were: contra-indications for contrast-enhanced MRI and insufficient knowledge of the Dutch language. Written informed consent was obtained and this study was approved by our Institutional Review Board.

### Measurements

Participants completed a questionnaire on demographics, sports participation (yes/no) and knee complaints (duration, bilateral pain, Anterior Knee Pain Scale (AKP) 0-100[23]) and underwent 3 Tesla MRI (Discovery MR750, GE Healthcare) using a dedicated 8-channel knee coil (Invivo Inc., Gainesville, USA) at our institution. The (most) symptomatic knee of PFP patients was selected, or randomly chosen if both knees were equally painful or if both were asymptomatic (controls). The MRI protocol consisted of routine clinical proton density and T2-weighted fat-saturated sequences in three orthogonal planes, and a 3D spoiled gradient-echo (SPGR) sequence with in-plane resolution of 0.29 mm. In adult subjects, DCE-MRI was acquired, consisting of a sagittal, anterior-posterior frequency-encoded, fat suppressed 3D SPGR sequence, 35 phases of 10 seconds with intravenous contrast administration (0.2 mmol/kg Magnevist (Bayer)) at 2 ml/s starting after the first phase. Other parameters were: field of view 38x38cm, acquisition matrix of 256x128, zero filled to 256x256, in-plane resolution 1.5 mm, slice thickness 5 mm without interslice gap.

### Image analysis

DCE-MRI measures the amount of contrast enhancement, based on signal intensity, over time in a specific volume of interest (VOI) as a measure of blood perfusion[15]. This can be visualized by a time-intensity curve, enabling qualitative analysis on an individual basis.

By voxelwise fitting of a pharmacokinetic model, which takes into account the differences in time required for the contrast agent to reach each voxel, quantitative perfusion parameters, $k_{trans}$ and $k_{ep}$, can be calculated. Quantitative analysis enables comparison on group level.[15] Tofts' model[24] combined with a group-wise arterial input function (AIF) was applied, since this combination best fitted our data in a pilot study.[25] Over the entire dataset, the residual was close to the acquisition noise level. This model uses the AIF from the popliteal artery and assumes one tissue compartment and one vascular compartment (Figure 1).[24]

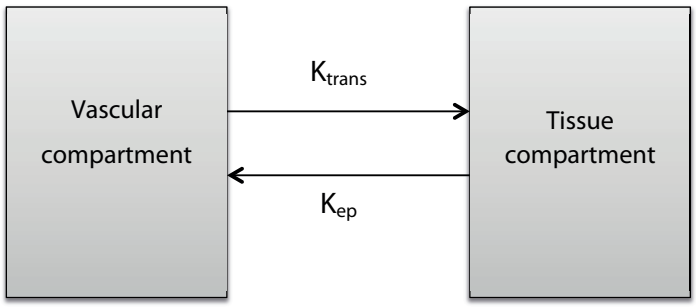


**Figure 1.** Schematic representation of Tofts' pharmacokinetic model

$K_{trans}$ reflects the volume transfer constant into the tissue compartment while $k_{ep}$ describes the rate constant back to the vascular component. Low $k_{trans}$ values might indicate local tissue ischemia, while low $k_{ep}$ values are suggestive for venous outflow obstruction. The VOI, consisting of the patellar bone marrow (Figure 2), was manually delineated on the 3D SPGR non-fat saturated MR images with Matlab (R2011a, The MathWorks) by an experienced blinded observer.

In-house developed software was used to correct for patient motion during MRI acquisition.[26-29] Perfusion parameters were calculated voxel-wise and weighted by the reciprocal Cramér-Rao-Lower-Bound (indicating fit uncertainty) obtained by using a Maximum-Likelihood (ML) estimator during fitting.[30] Weighted mean and median $k_{ep}$ and $k_{trans}$ were calculated for all participants.

## Statistical analysis

Independent sample t-tests and chi-square tests, or Mann-Whitney U test if distribution was not normal, were applied to investigate differences in baseline characteristics between groups. Differences in perfusion parameters ($k_{ep}$ and $k_{trans}$) were compared between groups by linear regression analyses, adjusted for age, gender, BMI, and sports participation. Logarithmic transformations of weighted mean and median $k_{trans}$ were performed to acquire normal distributions. Due to the presence of negative values, median $k_{ep}$ was not transformed logarithmically, but tested non-parametrically with

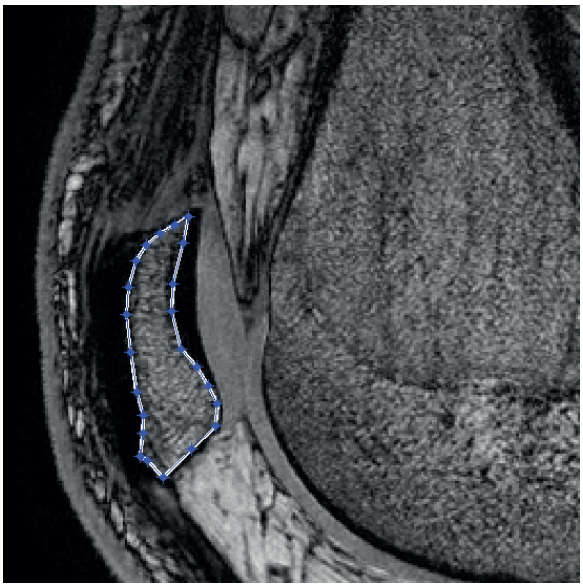

**Figure 2.** Single slice of the VOI of the patellar bone marrow

a Mann-Whitney U test. Differences in variance of perfusion parameters were tested with Levene's test. Explorative analyses were conducted to investigate differences in perfusion parameters between participants with and without sitting pain. Item 8 of the AKP score was used to define sitting pain. Two categories were formed from five possible responses: (i) no sitting pain ("no difficulty" or "pain after exercise"); and (ii) sitting pain ("constant pain", "pain forces to extend the knees temporarily", or "unable"). We calculated mean, standard deviation (SD), and mean differences with 95% confidence intervals. P-values < 0.05 were considered to be statistically significant. All analyses were performed with SPSS 20.0 (SPSS Inc).

## RESULTS

### Participants

35 adults PFP patients and 44 adult control subjects were included in this analysis, since DCE-MRI data were only acquired in adult participants. Mean age was 26.1 (range 18-40, SD 5.0) years, mean BMI was 24.1 (SD 3.4) kg/m2 and 49% was female. The BMI was significantly higher in the patient group (Table 1). Patients reported a mean duration of complaints of 11.2 months and 45.7% reported bilateral pain. Mean AKP score of patients was 68.6 and 77.1% of the patients, reported the presence of sitting pain.

**Table 1.** Characteristics of study participants

| | | Patients (N=35) | Controls (N=44) | P-value |
|---|---|---|---|---|
| **Female gender** | ***n (%)*** | 18 (51.4) | 21 (47.7) | 0.74 |
| **Age *(years)*** | ***Mean (SD)*** | 26.4 (5.6) | 25.9 (4.6) | 0.53 |
| **BMI *(kg/m²)*** | ***Mean (SD)*** | 25.1 (3.8) | 23.3 (2.8) | 0.01 |
| **Sports participants** | | | | 0.39 |
| **during inclusion** | ***n (%)*** | 24 (68.6) | 34 (77.3) | |
| **before onset of pain** | ***n (%)*** | 32 (91.4) | n.a. | |
| **Duration of complaints** | ***Mean (SD)*** | 11.2 (6.3) | n.a. | n.a. |
| **Bilateral pain** | ***n (%)*** | 16 (45.7) | n.a. | n.a. |
| **AKP score** | ***Mean (SD)*** | 68.6 (11.0) | n.a. | n.a. |
| **Sitting pain** | ***n (%)*** | 27 (77.1) | 0 (0) | n.a. |

n.a.: not applicable

## DCE-MR imaging

Figure 3 shows the normalized mean time-intensity curves for patients and controls. To facilitate comparison, time-intensity curves were synchronized in order to compensate for differences in contrast arrival time. Per subject, the mean of the synchronized time-intensity curve was computed over the VOI. Subsequently, these were normalized and the group mean and confidence interval were computed. The curve of the patient group appeared to have a slightly larger amplitude compared to controls. The rest of the shape of the curve was not noticeably different between groups. Confidence intervals of the curves showed an overlap over the entire trajectory.

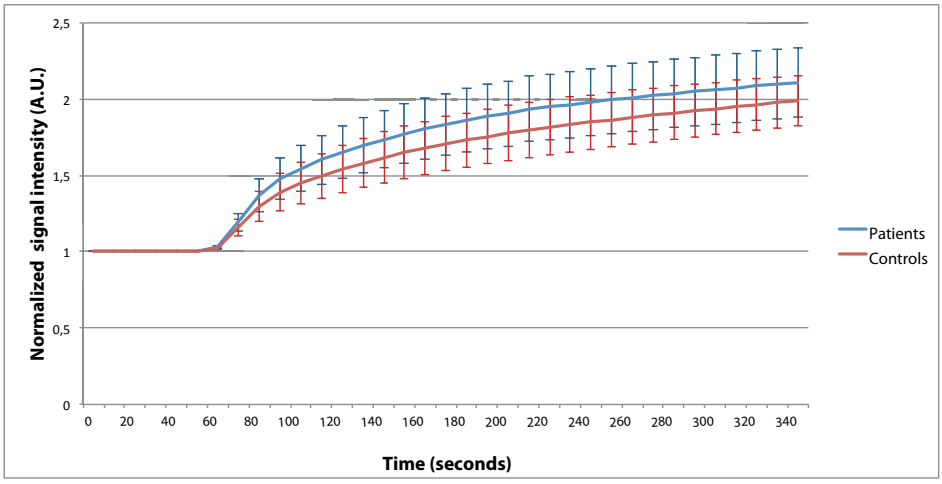


**Figure 3.** Normalized mean synchronized time intensity curves and corresponding confidence intervals for patients and controls

Quantitative analysis demonstrated a group mean of weighted mean $k_{trans}$ of 0.017 (SD 0.014)$min^{-1}$ for patients and 0.013 (SD 0.008)$min^{-1}$ for control subjects. The group mean of the weighted mean $k_{ep}$ was 0.19 (SD 0.16)$min^{-1}$ for patients and 0.14 (SD 0.14)$min^{-1}$ for control subjects (Table 2). Mean and median of both quantitative perfusion parameters were not statistically significantly different between patients and control subjects (Table 2) A significant difference in variance of weighted mean $k_{tran}$ was observed between populations (p=0.007) (Figure 4).

Explorative analyses with respect to sitting pain showed no significant differences between patients with and without pain during sitting (data not presented).

**Table 2.** Group mean and standard deviation of weighted mean over VOI for $k_{ep}$ and $k_{trans}$ ($min^{-1}$) and group mean and standard deviation of median over VOI $k_{ep}$ and $k_{trans}$ of patellar bone in patients and controls.

| | Patients *(N=35)* | Controls *(N=44)* | Mean difference (95% CI) | Adjusted p-value |
|---|---|---|---|---|
| **$K_{trans}$ *($min^{-1}$)*** | | | | |
| **Mean** | 0.017 (0.014) | 0.013 (0.008) | 0.0039 (-0.0013 ; 0.0091) | 0.32 |
| **Median** | 0.029 (0.028) | 0.023 (0.030) | 0.0052 (-0.0078 ; 0.018) | 0.47 |
| **$K_{ep}$ *($min^{-1}$)*** | | | | |
| **Mean** | 0.19 (0.16) | 0.14 (0.14) | 0.046 (-0.021 ; 0.11) | 0.24 |
| **Median** | 0.19 (0.23) | 0.11 (0.16) | 0.069 (-0.017 ; 0.15) | 0.15* |

CI: confidence interval; *non-parametric testing

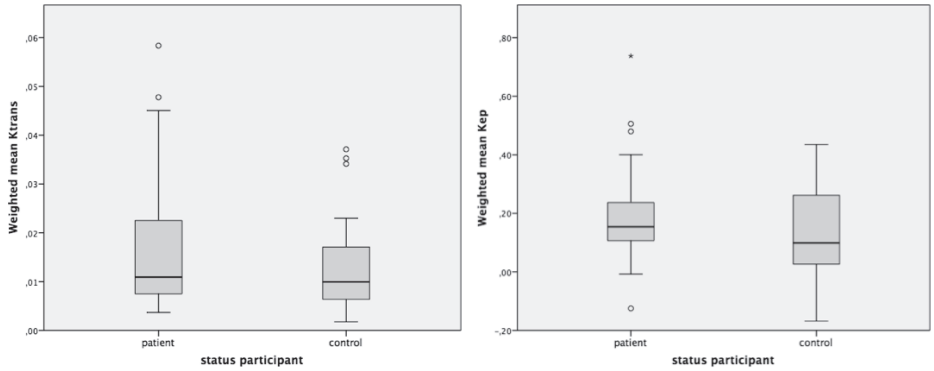


**Figure 4.** Distribution of weighted mean $k_{trans}$ (left plot) and $k_{ep}$ (right plot) ($min^{-1}$) subdivided in patients and controls

## DISCUSSION

This case-control study showed higher values of quantitative MRI derived perfusion parameters in patellar bone in PFP patients compared to healthy control subjects, but

these differences were not statistically significant. The observed trend toward higher blood flow in PFP patients is contrary to what was expected, since lower values, suggestive for local tissue ischemia or venous outflow obstruction, were presumed to be found. Interestingly, a larger variance of $k_{trans}$, comprising higher $k_{trans}$ values, was observed in patients compared to controls. The reason behind this needs to be elucidated, but it may suggest that a subgroup with higher $k_{trans.}$ values is present in the patient population.

To our knowledge, only one previous study has evaluated blood perfusion of bone of the knee joint using a quantitative DCE-MRI approach. Seah et al. applied quantitative DCE-MRI in knee osteoarthritis patients and found no association between perfusion of tibial bone marrow lesions and pain.[18] Their results, however, cannot be directly compared to ours, since a different pharmacokinetic model was used. Although the application of an appropriate pharmacokinetic model is crucial for the accurate calculation of quantitative DCE-MRI parameters, there is no consensus in literature regarding the recommended model in bone. In a pilot study comparing Brix' [31], Tofts' [24], and extended Tofts' models, Tofts' model was identified as best model to fit DCE data of patellar bone.[25] To our knowledge, two other studies used Tofts' model in an osseous structure of the lower extremity. Breault et al. showed femoral $k_{ep}$ values ranging between 3.48-3.85 $min^{-1}$ [21], whereas Budzik et al. showed a $k_{trans}$ of 0.06 $min^{-1}$ and a $k_{ep}$ of 0.8 $min^{-1}$ for femoral red bone marrow.[22] The discrepancy between these values and ours is likely explained by the fact that femur and patella have different blood perfusion. Values obtained in our study are relatively closer to those reported by Budzik et al. than to those of Breault et al., which may indicate that use of an AIF measured from the data, as was done in our study and by Budzik et al., is more accurate than an a priori assumed model as applied by Breault et al.

Explorative analyses of one hypothetic subgroup revealed no significant differences in blood perfusion of the patellar bone between patients with and without sitting pain. In order to study the phenomenon of sitting pain further, an interesting prospect would be to acquire DCE-MRI in an open MRI scanner with the knee flexed, particularly since some PFP patients especially experience pain during knee flexion and Naslund et al. reported a decreased pulsatile patellar blood flow in patients with flexed knees.[10]

Strengths of our study are that were able to include a large number of patients with PFP and evaluate them with quantitative DCE-MRI, which had not been done previously for the patella and in the context of PFP. Furthermore, in contrast to previous studies in other pathologies or bones, we first conducted a pilot study to determine the pharmacokinetic model best suited for our DCE-MRI data.[25] There are also some limitations that need to be addressed. First, although we aimed to match patients and controls on

age, gender, BMI, and sports participation, differences were observed in BMI. Therefore, all analyses were adjusted for these confounders. Second, median $k_{ep}$ was tested non-parametrically and thus adjustment for confounders was not possible. However, as all confounders in the regression analysis of median $k_{ep}$ were not statistically significant and had low regression coefficients, we believe that the Mann-Whitney U test was used appropriately. Third, analyses showed a high spatial heterogeneity of patellar blood perfusion. Since the fit of the pharmacokinetic model, and therefore the uncertainty derived weight, is dependent on the degree of blood perfusion (better perfused areas have a better fit), we decided to additionally calculate the medians of both perfusion parameters to avoid underweighting of less-perfused areas. Finally, the large inter-subject variability, possibly caused by measurement variability or normal tissue heterogeneity, makes it difficult to detect significant differences. It is important to notice that DCE-MRI of bone is still an emerging field of research and poses important challenges due to the relatively poor vascularization of bone compared to other tissues. Unfortunately, reproducibility of quantitative DCE-MRI parameters could not be studied due to the nature of our method, which involves the burden of contrast administration. Consequently, we were not able to disentangle measurement variability and normal tissue heterogeneity.

In conclusion, in contrast to expected, higher values of patellar bone perfusion parameters, measured with quantitative DCE-MRI, were found in PFP patients compared to healthy control subjects, but these differences were not statistically significant. This result, and the observed significant difference in $k_{trans}$ variance warrant further research.

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# Chapter 7

## Strength and pain threshold handheld dynamometry test reliability in patellofemoral pain

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## ABSTRACT

Patellofemoral pain syndrome (PFPS), characterized by peri- and retropatellar pain, is a common disorder in young, active people. The etiology is unclear; however, quadriceps strength seems to be a contributing factor, and sensitization might play a role. The study purpose is determining the inter-rater reliability of handheld dynamometry to test both quadriceps strength and pressure pain threshold (PPT), a measure for sensitization, in patients with PFPS. This cross-sectional case-control study comprises 3 quadriceps strength and one PPT measurements performed by 2 independent investigators in 22 PFPS patients and 16 matched controls. Inter-rater reliability was analyzed using intraclass correlation coefficients (ICC) and Bland-Altman plots. Inter-rater reliability of quadriceps strength testing was fair to good in PFPS patients (ICC= 0.72) and controls (ICC=0.63). Bland-Altman plots showed an increased difference between assessors when average quadriceps strength values exceeded 250N. Inter-rater reliability of PPT was excellent in patients (ICC=0.79) and fair to good in controls (ICC=0.52). Handheld dynamometry seems to be a reliable method to test both quadriceps strength and PPT in PFPS patients. Inter-rater reliability was higher in PFPS patients compared to control subjects. With regard to quadriceps testing, a higher variance between assessors occurs when quadriceps strength increases.

## INTRODUCTION

Patellofemoral pain syndrome (PFPS) is a common diagnosis, especially in young and physically active people.[1-3] PFPS is characterized by diffuse peri and retropatellar pain provoked by climbing or descending stairs, squatting, running and prolonged sitting with the knees flexed. Other symptoms are crepitus and a feeling of giving way.[3-5] Despite adequate treatment PFPS often becomes a recurring or chronic problem.[6,7] The etiology of PFPS is still unknown.[4,8] Quadriceps strength seems to play an important role. Less knee extension strength is associated with PFPS[9] and lower knee extension peak torque is a possible risk factor for PFPS.[10] Furthermore, new insights indicate that pain in chronic sports injuries like PFPS might be neuropathic.[11,12] The profiles of sensory dysfunction show that central sensitization may play a role in PFPS.[13,14] If so, treatment options focusing on peripheral and/or central sensitization should be considered. To measure quadriceps strength and possible sensitization in patients with PFPS, reliable measurement methods are needed. Especially for clinical practice, it would be very practical to use one device for both tests.

A handheld dynamometer (HHD) is often used to assess muscle strength, because it is a convenient and relatively inexpensive method.[15] The inter-rater reliability of quadriceps strength testing with HDD shows conflicting results and has not yet been tested in patients with PFPS.[16-20] To test sensitization, the pressure pain threshold (PPT) test can be used. The use of a handheld dynamometer with algometry tip for the PPT test has proven to have good inter-rater reliability in various populations, but also has not yet been tested in patients with PFPS.[21-25]

The aim of this study is therefore to investigate the inter-rater reliability of handheld dynamometry for quadriceps strength and PPT testing in patients with PFPS.

## MATERIALS AND METHODS

### Study design

This reliability study was conducted within a cross-sectional case-control study on the aetiology of PFPS, and was executed according to the medical ethical regulations of the University Medical Center Rotterdam (MEC-2012-342) and ethical standards in sports and exercise science research.[26] Patients, aged between 14 and 40 years, consulting their sport physician, general practitioner or physiotherapist were eligible to participate. Inclusion criteria comprised present PFPS for two months until two years, based on the presence of at least three of the following symptoms: pain during climbing or descending stairs, squatting, running and prolonged sitting with the knees flexed of time or

grinding of the patella. Patients were excluded if they had defined pathological knee conditions, onset after trauma, previous knee injuries or surgery.
Control subjects were recruited from patients' sports teams, family or friends and matched by age, gender, BMI and sports participation. They were excluded if they had a history of knee injury or were first grade family members of patients. All participants were informed about the study and signed an informed consent. In case of minors, parents or guardians additionally signed an informed consent.

### Test protocol

All subjects filled in a questionnaire including demographics (age, gender, height, weight), sports participation, duration of complaints, bilateral complaints, pain intensity during rest and activity (0 to 10 numeric rating scale). 2 independent investigators assessed quadriceps strength and the PPT in a clinical examination room at the Erasmus MC with approximately 30 minutes in between both assessments. Assessors were blinded for each other's results. A randomization list, using a random number generator in blocks of 4 without stratification, was used to determine the assessor order. Assessor 1 was a medical student (height 158cm, weight 45kg); assessor 2 was a medical doctor (height 175cm, weight 78kg). To make sure both assessors conducted testing in the same manner, the protocol was practiced with the HHD on multiple healthy subjects under supervision of an experienced tester.

### Quadriceps strength

Quadriceps strength was measured using a HHD (Biometrics MicroFET 2, Almere, The Netherlands). The subject was seated on the edge of the examination table with the knees in 90 degrees flexion and hands in the lap (Fig. 1a). The dynamometer was placed above the malleoli on the ventral side of the leg. In order to familiarize the subject with the desired movement, the subject was asked to apply force by extending the knee actively, while the assessor fixated the leg. Thereafter, the test was done with the same procedure, but this time the subject was asked to apply maximum force. The isometric maximum voluntary contraction (MVC) lasted approximately 5 seconds. Maximum force was read from the display of the dynamometer and noted in Newtons (N), the International System of Units derived unit of force. One Newton is the force needed to accelerate 1 kilogram of mass at the rate of 1 meter per second squared. If the subject was able to break through the assessor' strength, the measurement was labelled inadequate. Quadriceps strength testing was conducted 3 times. The mean of the highest 2 values was used for analysis.[27]

## Pressure pain threshold

To determine the PPT the same HHD was used after attaching a metal tip of 1cm$^2$. The PPT was measured with the subject supine on the examination table. In order to place the algometry tip, subjects with PFPS were asked to point out the most painful location on the knee. When this was behind the patella the algometer was placed on the center of the patella. In control subjects, the algometer was placed on the medial patellar facet, since this is often regarded as the most painful location in PFPS patients (Fig. 1b). The assessor slowly increased pressure until the subject indicated that it became painful. Maximum applied force was read from the display of the dynamometer in N/cm$^2$. Assessors placed the algometer on the same location.

To prevent tissue damage a cut-off value of 70N/cm$^2$ was defined. N/cm$^2$ is the amount of force per square centimeter, which is the surface of our algometry tip. A recent study used a cut-off value of 45N/cm$^2$ for patellar tendon[21] Since a tendon is more vulnerable, we increased the cut-off value to 70N/cm$^2$ (also based on a small test trial among students). The measurements of both assessors were excluded from the analyses when either one of the assessors reached the cut-off value of 70N/cm2 in a subject. For both the strength and algometry measurements, both legs were tested and analyzed in control subjects while in patients only the (most) affected leg was included.

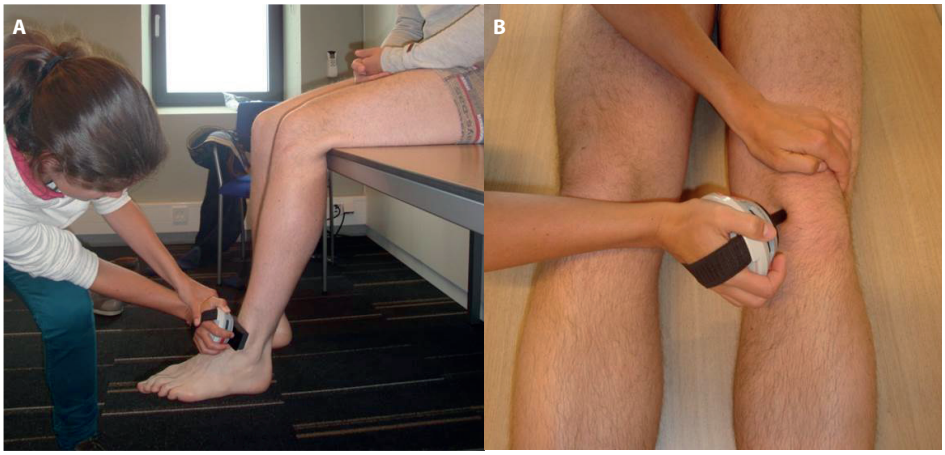


**Figure 1.** Measuring methods a) Quadriceps strength b) Pressure pain threshold

## Statistical analysis

Statistical analyses were performed with SPSS for Windows, version 20. To compare subject characteristics, a non-parametric chi squared test for dichotomous variables and Mann Whitney U test for continuous variables were used. To determine the inter-rater reliability, a 2 way mixed model of the intraclass correlation coefficient (ICC) was used on absolute agreement between assessors 1 and 2. The measurements of both

assessors were excluded from the analyses when either one of the assessors reported an inadequate measurement. For both tests, ICCs in patients were calculated using the values of the (most) affected knee. Reliability was considered excellent for ICCs higher than 0.75, fair to good for values from 0.40-0.75 and poor for values less than 0.40.[28] Bland-Altman plots were made to visualize the limits of agreement.

## RESULTS

All eligible patients and control subjects seen between February 1 and May 17, 2013 were included for the present study, resulting in a total study sample of 38 subjects: 22 PFPS patients and 16 control subjects. The mean age of the study population was 22.2(6.0) years, BMI 23.6(4.5) and 68% was female. On average, patients had knee pain for 12 months and 55% had bilateral complaints. Patients and control subjects were only significantly different in percentage of sports participants (Table 1).

**Table 1.** Characteristics of the study population (n=38)

| | | Patients *(N=22)* | Control subjects *(N=16)* | P-value |
|---|---|---|---|---|
| **Age in years** | ***mean (SD)*** | 22.0 (5.8) | 22.5 (6.5) | 0.97 |
| **Female gender** | ***n (%)*** | 16 (72.7) | 10 (62.5) | 0.50 |
| **BMI** | ***mean (SD)*** | 23.9 (4.8) | 23.3 (4.2) | 0.83 |
| **Sport participants** | ***n (%)*** | 12 (54.5) | 13 (81.3) | 0.09 |
| **Duration of knee pain in months** | ***mean (SD)*** | 12.0 (6.5) | n.a | n.a |
| **Bilateral knee pain** | ***n (%)*** | 12. (54.5) | n.a. | n.a. |
| **Pain score in rest *(NRS 0-10)*** | ***mean (SD)*** | 4.7 (2.3) | n.a | n.a |
| **Pain score during activity *(NRS 0-10)*** | ***mean (SD)*** | 7.1 (1.9) | n.a. | n.a. |
| **Recruiting physician** | | | | |
| **Sport physician** | ***n (%)*** | 10 (45.5%) | n.a. | n.a. |
| **General practitioner** | ***n (%)*** | 10 (45.5%) | n.a. | n.a. |
| **Physiotherapist** | ***n (%)*** | 2 (9.1%) | n.a. | n.a. |

BMI= body mass index; SD= standard deviation; NRS= numeric rating scale; n.a.= not applicable

### Quadriceps strength

Strength measurements of 2 patient knees and 14 control knees were inadequate for assessor 1, compared to 1 patient knee for assessor 2. Therefore, 20 patient knees and 18 control knees were analyzed. Mean quadriceps strength of patients measured by assessor 1 was 198(39)N, compared to 206(52)N for assessor 2 (Table 2). The ICC of the strength measurements in patients shows fair to good agreement (ICC 0.72). Mean quadriceps strength in control subjects was 239(32)N in assessor 1, compared to 270.9(54.9)N in

**Table 2.** Descriptive statistics and ICC's of HHD quadriceps strength measurements in Newtons

| | Assessor 1 | | Assessor 2 | | |
|---|---|---|---|---|---|
| **Group** | **Mean (SD)** | **Range** | **Mean (SD)** | **Range** | **ICC (95% CI)** |
| **Patients (20 knees)** | 198.4 (39.7) | 91.4 – 267.6 | 206.3 (52.1) | 101.9 – 301.4 | 0.72 (0.43 – 0.88) |
| **Control subjects (18 knees)** | 239.0 (32.2) | 161.9 – 271.2 | 270.9 (54.9) | 166.2 – 367.2 | 0.63 (-0.01 – 0.87) |

SD= standard deviation; ICC= intraclass correlation coëfficient; CI= confidence interval

assessor 2. The ICC of strength measurements in control subjects shows fair to good agreement (ICC 0.63).

The Bland-Altman plot shows on average lower assessed values for assessor 1 compared to assessor 2 (MD 7.9N (95% CI 59.9; -75.7) and 31.9N (95% CI 27.1 to -90.9N), in PFPS patients and in control subjects, respectively. (Fig. 2). Furthermore, the Bland-Altman plot shows an increased difference between assessors when average quadriceps strength values exceed 250N.

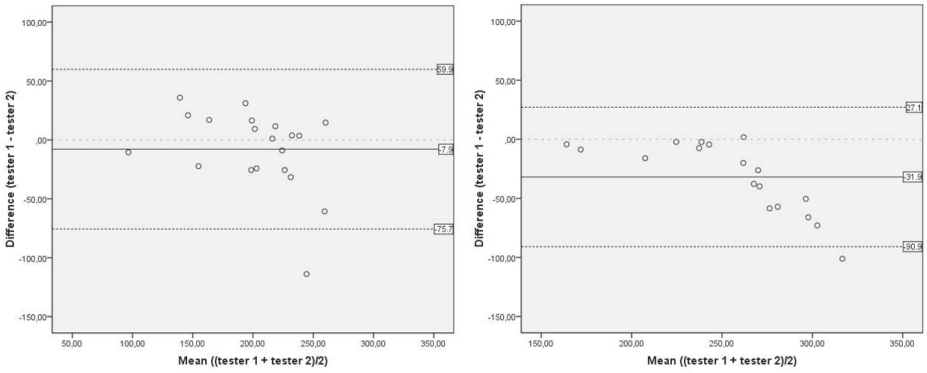


**Figure 2.** Bland-Altman plots of dynamometry in patients (left plot) and control subjects (right plot). The solid black line shows the mean difference between assessor 1 and assessor 2. The black dotted lines show the 95% CI = mean difference ± 1.96 x SD. All values are in Newtons

## Pressure pain threshold

For analysis, 1 PFPS patient was excluded, because the most painful place differed between assessors. In 12 knees of control subjects, the cut-off value of 70N/cm$^2$ was reached; in 9 of these knees, the cut-off value was reached by both assessors. Therefore a total of 21 knees of PFPS patients and 20 knees of control subjects were eligible for analysis.

Mean PPT of patients assessed by assessor 1 was 32.6(12.4)N/cm$^2$, compared to 35.4(11.1)N/cm$^2$ in assessor 2 (Table 3). The ICC of the PPT shows excellent agreement

(0.79) in PFPS patients. In control subjects, the mean PPT was 34.2(10.1) N/cm$^2$ in assessor 1, compared to 40.2(9.7)N/cm$^2$ in assessor 2. The ICC shows a fair to good agreement (0.52) in this group. The Bland-Altman plot of the PPT shows that on average assessor 1 measured lower values compared to assessor 2 in PFPS patients (MD 2.8N/cm$^2$ (95%CI 11.5 to -17.2N/cm$^2$) and in control subjects (5.9N/cm2 (95% CI 11.3 to -23.2N/cm2)). (Fig. 3)

**Table 3.** Descriptive statistics and ICC's of HHD pressure pain threshold measurements in Newton/cm$^2$

| | Assessor 1 | | Assessor 2 | | |
|---|---|---|---|---|---|
| **Group** | **Mean (SD)** | **Range** | **Mean (SD)** | **Range** | **ICC (95% CI)** |
| **Patients (21 knees)** | 32.6 (12.4) | 14.2 – 61.3 | 35.4 (11.1) | 20.9 – 61.3 | 0.79 (0.53 – 0.91) |
| **Control subjects (20 knees)** | 34.2 (10.1) | 19.1 – 60.0 | 40.2 (9.7) | 25.8 – 60.5 | 0.52 (0.09 – 0.78) |

SD= standard deviation; ICC= intraclass correlation coëfficient; CI= confidence interval

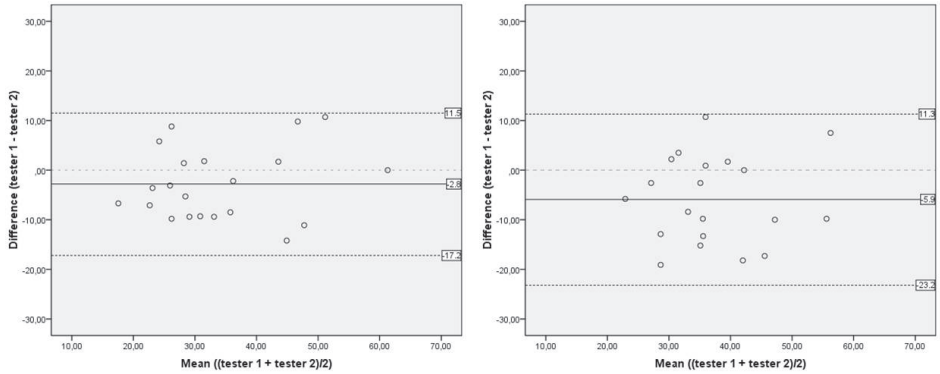


**Figure 3.** Bland-Altman plots of PPT testing in patients (left plot) and control subjects (right plot). The solid black line shows the mean difference between assessor 1 and assessor 2. The black dotted lines show the 95% CI = mean difference ± 1.96 x SD. All values are in Newtons/cm

## DISCUSSION

The use of a HHD to test quadriceps strength has a fair to good inter-rater reliability in patients with PFPS (ICC 0.72) and control subjects (ICC 0.63). The use of a HHD to test the PPT has an excellent inter-rater reliability in patients with PFPS (ICC 0.79). In control subjects the inter-rater reliability of the PPT test is fair to good (ICC 0.52).

Inter-rater reliability of quadriceps strength testing was lower compared to other studies with the same test protocol (ICCs 0.80 to 0.85).[16,18] However, samples in these studies

consisted of patients with advanced cancer or elderly and consequently maximum strength assessed in these groups was considerably lower; 200 and 218N respectively, compared to the current study.[16,18] Higher values of quadriceps strength cause larger variability in measurements (Fig. 2a and Fig. 2b), which seem to result in lower ICCs and wider 95% confidence intervals. When the mean quadriceps strength was higher than 250N the difference between both assessors increased rapidly, with assessor 2 achieving much higher values. In total, there were 2 PFPS patients and 7 control subjects (14 knees), in which assessor 1 was not able to retain quadriceps strength; for assessor 2, this involved only 1 PFPS patient (2 knees). Since assessor 1 had a lower weight and height, it can be assumed that assessor 2 was weaker compared to assessor 1. This might imply that tester physics plays a role in the inter-rater reliability of HHD use to test quadriceps strength in stronger individuals. The influence of the tester' physics on the inter-rater reliability of HHD use in quadriceps strength has also been reported by other authors.[16,17] To avoid the influence of tester physics, other authors used a fixed HHD, especially in a healthy athletic population, yielding perfect inter-rater reliability of quadriceps strength testing with an ICC of 0.96.[29] However, to use the fixed HDD additional equipment is necessary, which compromises the feasibility of the HHD in clinical practice. Furthermore, it is questionable whether it has any clinical implication for PFPS patients, because in patient knees most quadriceps strength measurements were adequate and did not exceed 250N, as could be seen in the Bland Altman plot (Fig. 2a).

The inter-rater reliability of the PPT test in PFPS patients is comparable with the inter-rater reliability of biceps brachii testing in healthy volunteers (ICC 0.74-0.78)[25] and is slightly lower compared to the PPT of myofacial trigger points (ICC 0.82-0.86).[24] However, the reliability found in this study is markedly lower compared to the reliability of the PPT in patients with patella tendinopathy (ICC 0.93)[21] This might be explained by the fact that the assessors in the tendinopathy study were more experienced or by the low mean PPT value since higher pressure is harder to apply and might account for more variability between assessors. Furthermore, it is not clear whether they have used ICC's on consistency or on absolute agreement. ICC's on consistency tend to be higher than those on absolute agreement.[30]

**Strengths and limitations**

The most important strength is that the study sample represents the population of PFPS patients. Furthermore, the lack of external fixture and use of straps makes these results more generalizable to clinical practice in which use of extra equipment is not feasible.
A limitation might be the use of one trial for the PPT. Previous studies have shown that the inter-rater reliability is higher when the mean of multiple trials or the value of a second or third trial is used for analysis.[24,25] We chose not to perform multiple trials on

the painful location, as it would be an extra burden for the participants. Therefore the ICC found in this study for the PPT test could have been slightly underestimated.
Furthermore, studies suggest standardizing the rate of pressure increase per second. However, when higher pressure needs to be applied, it is harder to gradually increase the pressure using a standardized rate.[23,24] This might in part account for bigger variability in the differences of measurements between both assessors.

## Conclusions

Handheld dynamometry seems to be a reliable method to test both quadriceps strength and the PPT in PFPS patients. Compared to controls, the inter-rater reliability for both tests was higher in PFPS patients. Further research on the inter-rater reliability of HHD used to test quadriceps strength and the PPT is needed.

## Practical implications

The HHD is a small, portable and relatively inexpensive device. It offers a fast, reliable and easy-to-use method for testing quadriceps strength and the PPT in clinical practice in PFPS patients.

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# Chapter 8

## Pain pressure thresholds especially lower in female patellofemoral pain patients: a cross-sectional case-control study

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*SUBMITTED*

## ABSTRACT

### Study Design

Case-control study

### Objectives

To investigate differences in pressure pain threshold (PPT) between patients with patellofemoral pain (PFP) and healthy control subjects and study associations between PPT and patients characteristics.

### Background

PFP is a common knee complaint among active adolescents with unknown pathogenesis. It has been suggested that repeated overload might sensitize nociceptors causing local hyperalgesia. This might also lead to an altered central pain processing. The PPT can be measured to identify pressure hyperalgesia,

### Methods

Patients with PFP (n=64) and healthy controls (n=70) were included. Demographics, pain (numerical rating score) and function (anterior knee pain score) were obtained by questionnaire. The PPT was measured with a handheld dynamometer with algometry tip at the most painful spot of the affected knee (medial facet in controls), same spot contralateral knee and at the contralateral forearm. Differences between groups were tested with linear regression analyses adjusted for age, gender, BMI and sports participation.

### Results

Patients had significantly lower PPTs compared to controls at all locations (β affected knee -13.98(-18.62;-9.33); β contralateral knee -6.91(-11.84;-1.97); β arm -7.57(-12.07;-3.07)). A significant interaction effect was found between participant status and female for the PPT at the contralateral arm (β -9.95, 95%CI -18.74;-1.16). Female gender was significantly associated with a lower PPT in the patient population.

### Conclusion

Local, distal and generalized pressure hyperalgesia, suggesting alterations in both peripheral and central pain mechanisms, were present in patients with PFP. Females with PFP were most likely to suffer from generalized hyperalgesia.

## INTRODUCTION

Patellofemoral pain (PFP) is a common knee complaint among active adolescents and young adults.[1] It is characterized by peri-patellar and retro-patellar pain, mainly during activities as prolonged sitting, kneeling, squating, walking up and down the stairs or repetitive activities as running and biking.

The exact origin of PFP is still unknown.[2] The current theory is that PFP originates from excessive patellofemoral contact stress due to high loading and/or maltracking of the patella. Dye et al. suggested in 2005 that this may result in a symptomatic loss of tissue homeostasis.[3] Next to this structural approach, he suggested the presence of an altered pain mechanism, by stating that once loss of tissue homeostasis was initiated, it may persist indefinitely.[3] Previous studies by Jensen et al. indicated that aberrations of the nervous system leading to altered pain perception might play a role in chronic PFP.[4,5] More recently two studies demonstrated the presence of pressure hyperalgesia, an increased response to a pain provoking mechanical stimulus, in PFP using the pain pressure threshold (PPT).[6,7] Rathleff et al. were the first to demonstrate lower local and distal PPTs in female adolescent PFP patients compared to controls.[6] In a small group of female adult patients Noehren et al. demonstrated that an increase in both localized and centralized pain sensitivity in PFP is related to movement mechanics.[7] These lowered PPTs found in females PFP patients may have implications for treatment strategies. This is further strengthened by the fact that female adolescents with PFP deeming themselves to be recovered showed a greater improvement in PPT compared to adolescents who had not recovered following treatment. This indicates that it is possible to change PPTs as a consequence of treatment.[8]

So it appears that female PFP patients seem to have pressure hyperalgesia. Though it is up to now unclear whether this is also present in the general PFP population, including both male and female patients. Additionally, there is emerging evidence that pain processes are age dependent[9] and a difference between adult and adolescent patients with PFP is suggested.[10] Furthermore, more knowledge on associations between patient characteristics and PPT is essential in order to develop better-targeted treatment strategies.

Therefore, the aim of the present study was investigate differences in PPTs between PFP patients and matched control subjects, to analyze potential differences between adult PFP and adolescent PFP patients and to explore patient characteristics associated with altered PPTs.

## METHODS

### Study design and participants

This cross-sectional case-control study was performed between January 2013 and September 2014. Patients aged between 14 and 40 years, with PFP for at least two months and for a maximum of two years were compared to a healthy control group without knee complaints.

Patients diagnosed with PFP were included by their general practitioner, physiotherapist or sports physician during consultation. All patients diagnosed with PFP had to fulfill the following criteria: the presence of at least three of the following symptoms: pain complaints while stair climbing; while squatting; while running; while cycling; while sitting for a prolonged period with the knee flexed, or crepitus. Exclusion criteria included a defined pathological knee condition at the affected knee, such as osteoarthritis or patellar tendinopathy, previous surgery or injury of the affected knee, previous episodes of PFP more than two years ago or onset of PFP after trauma. Control subjects were recruited by sports team members, friends or colleagues of the patients. We aimed to match the control subjects to the patient group on age, BMI, gender and activity level. Subjects suffering knee pain or a history of PFP, subjects with traumatic injury or knee surgery and first grade family members were excluded as control subjects. All subjects with contra-indications for MR scanning with contrast administration (for other study purposes) or insufficient knowledge of the Dutch language were excluded. Approval for the study was given by the Institutional Review Board (Medical Ethical Committee of Erasmus MC, protocol no. MEC-2012-342) and, accordingly, informed consent was obtained from all participants and if participants were aged < 18 years, their parents additionally gave informed consent.

### Measurements

After signing informed consent, all subjects were asked to fill in a questionnaire and were additionally invited for a physical examination at the Erasmus MC in Rotterdam.

The questionnaire included questions on demographics (gender, age, weight and height to calculate BMI), sports participation (yes/no) and type of complaints (bilateral (yes/no), duration of complaints in months, more pain in cold environment (yes/no), function (AKP scale)[11] and pain intensity on a numeric rating scale (NRS) from 0 to 10 at rest and during activity).[19] During physical examination the presence of neuropathic pain was assessed with the DN4[12], widespread pain was assessed according to the tenderpoints index and according to the Manchester definition of chronic widespread pain with a mannequin.[13] Subsequently, crepitation during squatting (present or not), palpation of the medial patellar facet (painful or not) and the Clarke compression test (positive or negative) were assessed.

### Pain pressure threshold

The PPT was determined by a handheld dynamometer (HHD) with a special algometry tip of 1cm$^2$ (Biometrics MicroFET 2, Almere, The Netherlands). We showed earlier that this is a reliable method to test PPT in PFP patients.[14] The PPT measurement was performed by one assessor (RvdH). Subjects were lying supine on the examination table and the algometry tip was placed at the most painful location on the knee in the patients with PFP. If this place was located behind the patella (i.e. retropatellar pain), the algometer was placed on the center of the patella. PPT testing in patients was performed on the same site of the contra-lateral knee and dorsolateral mid-shaft of the contralateral forearm. In control subjects PPT testing was done on the medial facet of both knees, since the medial patellar facet is often regarded as the most painful location in PFP, and dorsolateral mid-shaft of the contralateral forearm. Once the algometry tip was placed, pressure was slowly increased until the subjects indicated that it became painful. Maximum applied force was read from the display of the dynamometer in N/cm2 and consequently pain severity was assessed using the 0-10 NRS. We applied a cut-off of 70N/cm$^2$ to prevent possible tissue damage.

### Statistical analysis

Differences in characteristics between patients and control subjects and between adult and adolescent patients (aged < 18 years) were tested with independent sample t-test (continuous variables) and chi-square (categorical variables) tests if normal distribution was present. Otherwise the Wilcoxon test was applied.

Differences in PPT and experienced pain at threshold between patients and control subjects, and in predefined subgroups divided by age status (adult vs. adolescent) and gender were analyzed using a linear regression model with adjustment for age, gender (not in gender subgroup analyses), BMI and sport participation. If differences were present in these subgroup analyses, effect modification was tested by adding the relevant interaction term to the primary comparison of patients and control subjects. The association between patient characteristics and the PPT in a subgroup of patients was assessed using a multivariable linear regression model, entering all variables at once. Results are presented in mean differences and Betas (β) with accompanying 95% confidence intervals (95%CI). P-values <0.05 were considered statistically significant.

## RESULTS

### Participants

The study population consisted of 64 patients with PFP and 70 healthy control subjects (Figure 1). Both groups comprised 20 adolescents. The mean age of the patient group

**Table 1.** Baseline characteristics of the study population

| | | Patients *(N=64)* | Controls *(N=70)* | P-value |
|---|---|---|---|---|
| **Female gender** | **n(%)** | 35 (54.7) | 41 (58.6) | 0.65 |
| **Age *(years)*** | ***Mean (SD)*** | 23.4 (7.0) | 23.1 (5.9) | 0.88* |
| **BMI *(m/kg2)*** | ***Mean (SD)*** | 23.6 (3.8) | 22.3 (3.0) | 0.04* |
| **Sport participants** | | | | |
| **-during inclusion** | **n(%)** | 38 (59.1) | 55 (78.6) | 0.02 |
| **-before onset of pain** | **n(%)** | 56 (87.5) | n.a. | |
| **Function *(AKP score 0-100)*** | ***Mean (SD)*** | 66.3 (11.6) | 99.5 (1.7) | <0.001 |

*non-parametric testing

**Table 2.** Characteristics of the patient population, subdivided by age status and gender status

| | | Adults *(N=44)* | Adolescents *(N=20)* | P-value | Females *(N=35)* | Males *(N=29)* | P-value |
|---|---|---|---|---|---|---|---|
| **Female gender** | ***n(%)*** | 21 (47.7) | 14 (70) | 0.10 | 35 (100) | 0 (0) | n.a. |
| **Age *(years)*** | ***Mean (SD)*** | 26.8 (5.8) | 15.9 (1.2) | <0.001* | 20.2 (4.5) | 27.2 (7.6) | <0.001* |
| **BMI *(m/kg2)*** | ***Mean (SD)*** | 24.9 (3.7) | 20.7 (2.1) | <0.001* | 23.0 (4.0) | 24.2 (3.5) | 0.06* |
| **Sport participants** | | | | | | | |
| **-during inclusion** | ***n(%)*** | 28 (63.6) | 10 (50.0) | 0.30 | 21 (60.0) | 17 (58.6) | 0.91 |
| **-before onset of pain** | ***n(%)*** | 41 (93.2) | 15 (75.0) | 0.04 | 29 (82.3) | 27 (93.1) | 0.22 |
| **Duration of complaints *(months)*** | ***Mean (SD)*** | 11.0 (6.4) | 14.2 (8.1) | 0.14* | 13.7 (6.8) | 9.9 (7.1) | 0.02* |
| **Bilateral knee pain** | ***n(%)*** | 19 (43.2) | 14 (70) | <0.05 | 25 (71.4) | 8 (27.6) | <0.001 |
| **Pain at rest *(NRS 0 -10)*** | ***Mean (SD)*** | 4.0 (2.6) | 3.8 (2.2) | 0.71 | 4.6 (2.4) | 3.1 (2.4) | 0.59 |
| **Pain during activity *(NRS 0-10)*** | ***Mean (SD)*** | 6.3 (2.3) | 7.2 (1.9) | 0.17 | 7.1 (2.1) | 5.9 (2.3) | 0.54 |
| **Function *(AKP score 0-100)*** | ***Mean (SD)*** | 68.7 (11.7) | 60.6 (10.7) | 0.01 | 61.7 (10.2) | 71.9 (10.9) | <0.001 |
| **Presence of crepitation** | ***n (%)*** | 23 (52.3) | 6 (30.0) | 0.10 | 13 (37.1) | 16 (55.2) | 0.15 |
| **Painful palpation medial facet** | ***n (%)*** | 17 (38.6) | 14 (70.0) | 0.02 | 20 (57.1) | 11 (37.9) | 0.13 |
| **Positive Clarke compression test** | ***n (%)*** | 8 (18.2) | 6 (30) | 0.29 | 10 (28.6) | 4 (13.8) | 0.16 |

*non-parametric testing; n.a. not applicable

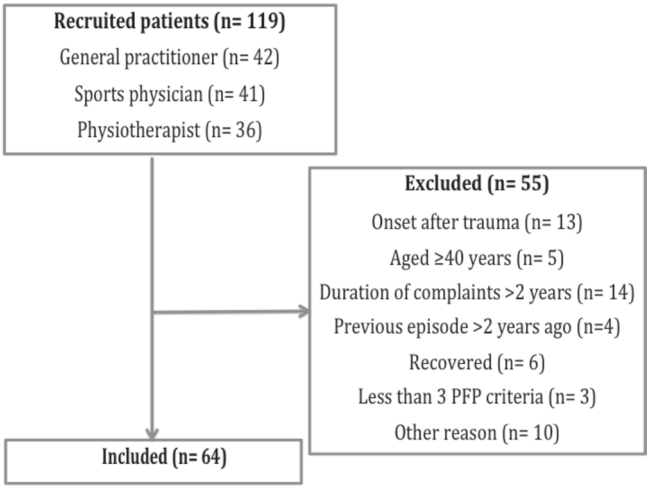


**Figure 1.** Flow diagram of patients.

was 23.4 (SD 7.0), mean BMI was 23.6 (SD 3.8)kg/m$^2$ and 54.7% of the participants were female. Patients had a significantly higher BMI, participated less frequently in sport and had a lower AKP function score compared to healthy control subjects (Table 1).
Compared to adolescent PFP patients, the adult PFP patients had a significantly higher BMI and less frequently reported bilateral complaints (Table 2). Compared to male patients, female patients were significantly younger, had a longer duration of complaints and reported bilateral complaints more frequently.

## Pain measures

Significantly lower PPTs were observed in patients compared to healthy control subjects (P<0.001) at all three locations (Table 3). Beta's were -13.98(-18.62;-9.33) in the affected knee, -6.91(-11.84;-1.97)) in the contralateral knee and -7.57(-12.07;-3.07) in the contralateral arm. In addition, reported pain intensity scores at threshold were significantly higher in PFP patients compared to healthy controls indicating that patients experienced significantly more pain when pain was felt.
Subgroup analyses by age status demonstrated a significant lower PPT at the affected knee in both adolescent and adult patients compared to their control groups (Table 4). Concerning the contralateral knee and contralateral arm, a significant difference between patients and controls was present only in adults, in which adult patients had lower PPTs compared to adult control subjects.
Subgroup analyses by gender showed significantly lower PPTs at the affected knee were present in male and female patients compared to their control groups (Table 4). Concerning the contralateral knee and contralateral arm, a significant difference between patients and controls was present only in females, in which female patients had lower PPTs compared to male control subjects. Further analysis showed a significant interaction

effect between participant status and female with respect to the PPT at the contralateral arm (β -9.95, 95%CI -18.74;-1.16). Generalized widespread pain according to either the Manchester coding or the tenderpoints index was not present in the study population. Neuropathic pain according to the DN4, was present in 12.5% (n=8) of patients.

The multivariable linear regression model demonstrated a significant association between female gender and lower PPTs at the affected knee (β -8.20, 95%CI -16.36;-0.04), contralateral knee (β-11.10, 95%CI -20.40;-1.79) and the contralateral arm (β -18.94, 95%CI -25.85;-12.02) (Table 5). Furthermore, sports participation was significantly associated with lower PPTs in the contralateral arm (β-7.62, 95%CI -13.75;-1.48).

**Table 3.** Pain pressure thresholds (algometry) for patients and control subjects

| | Patients *N=64* | Controls *N=70* | Mean difference (95%CI) | B (95%CI)* | Adjusted p-value* |
|---|---|---|---|---|---|
| **Affected knee *(N/cm²)*** | 38.5 (15.3) | 50.7 (14.6) | -12.2 (-17.33;-7.14) | -13.98 (-18.62;-9.33) | <0.001 |
| **Pain *(NRS 0-10)*** | 4.7 (2.0) | 2.9 (2.1) | 1.80 (1.10;2.50) | 1.88 (1.15;2.61) | <0.001 |
| **Contralateral knee *(N/cm²)*** | 44.9 (16.2) | 49.6 (14.7) | -4.7 (-10.05;0.52) | -6.91 (-11.84;-1.97) | 0.006 |
| **Pain *(NRS 0-10)*** | 4.0 (2.4) | 2.9 (2.2) | 1.01 (0.23;1.79) | 1.22 (0.42;2.02) | 0.003 |
| **Contralateral arm *(N/cm²)*** | 49.6 (13.9) | 55.2 (14.6) | -5.65 (-10.53;-0.78) | -7.57 (-12.07;-3.07) | 0.001 |
| **Pain *(NRS 0-10)*** | 3.7 (2.4) | 2.3 (2.1) | 1.34 (0.56;2.12) | 1.60 (0.81;2.38) | <0.001 |

* adjusted for age, gender, BMI and, sport participation; CI: confidence interval

**Table 4.** Pain pressure thresholds (algometry) for patients and control subjects subdivided based on age and based on gender.

| | Patients | Controls | Mean difference (95%CI) | B (95%CI)* | Adjusted p-value* |
|---|---|---|---|---|---|
| **Adolescents** | *N=20* | *N=20* | | | |
| **Affected knee *(N/cm²)*** | 30.2 (10.1) | 46.1 (13.9) | -15.86 (-23.64;-8.08) | -15.22 (-23.89;-6.64) | <0.01 |
| **Contralateral knee *(N/cm²)*** | 40.7 (16.9) | 45.1 (13.7) | -4.38 (-14.21;5.45) | -5.85 (-15.68;3.98) | 0.24 |
| **Contralateral arm *(N/cm²)*** | 46.6 (14.8) | 52.3 (15.3) | -5.75 (-15.38;3.89) | -6.72 (-14.96;1.52) | 0.11 |
| **Adults** | *N=44* | *N=50* | | | |
| **Affected knee *(N/cm²)*** | 42.3 (15.8) | 52.6 (14.5) | -10.34 (-16.56;-4.13) | -13.08 (-18.85;-7.30) | <0.001 |
| **Contralateral knee *(N/cm²)*** | 46.7 (15.7) | 51.4 (14.8) | -4.69 (-10.96;1.57) | -7.73 (-13.63;-1.82) | 0.01 |
| **Contralateral arm *(N/cm²)*** | 51.0 (13.4) | 56.4 (14.3) | -5.45 (-11.14;0.24) | -7.62 (-13.09;-2.14) | <0.01 |
| **Male** | *N=29* | *N=29* | | | |
| **Affected knee *(N/cm²)*** | 47.1 (16.7) | 55.3 (14.7) | -8.19 (-16.46;0.088) | -11.28 (-19.41;-3.14) | <0.01 |
| **Contralateral knee *(N/cm²)*** | 54.0 (14.3) | 54.3 (14.3) | -0.30 (-7.84;7.24) | -2.85 (-10.62;4.91) | 0.47 |
| **Contralateral arm *(N/cm²)*** | 59.5 (11.4) | 59.9 (13.4) | -0.49 (-7.04;6.06) | -2.07 (-8.81;4.68) | 0.54 |
| **Female** | *N=35* | *N=41* | | | |
| **Affected knee *(N/cm²)*** | 31.4 (9.3) | 47.5 (13.7) | -16.15 (-21.45;10.85) | -16.77 (-22.57;-10.99) | <0.001 |
| **Contralateral knee *(N/cm²)*** | 37.2 (13.7) | 46.3 (14.2) | -9.04 (-15.44;-2.64) | -9.32 (-16.16;-2.49) | <0.01 |
| **Contralateral arm *(N/cm²)*** | 41.4 (9.9) | 51.9 (14.6) | -10.50 (-16.15;-4.85) | -10.36 (-16.60;-4.11) | <0.01 |

*adjusted for age, gender, BMI and sport participation (no adjustment for gender in the second part of the table); CI: confidence interval

**Table 5.** Association between pain pressure threshold (algometry) and PFP patient characteristics (n=64).

| | Pain pressure threshold Affected knee | | | Pain pressure threshold Contralateral knee | | | Pain pressure threshold Contralateral arm | | |
|---|---|---|---|---|---|---|---|---|---|
| | B (95%CI) | B (95%CI)^ | p-value^ | B (95%CI) | B (95%CI)^ | p-value^ | B (95%CI) | B (95%CI)^ | p-value^ |
| **Age *(years)*** | 1.17 (0.71;1.64)** | 0.34 (-0.32;1.00) | 0.301 | 0.98 (0.45;1.51)** | 0.12 (-0.64;0.87) | 0.760 | 0.69 (0.21;1.16)* | -0.02 (-0.57;0.54) | 0.952 |
| **Gender *(female)*** | -15.74 (-22.34;-9.13)** | -8.20 (-16.36;-0.04) | 0.049 | -16.78 (-23.79;-9.77)** | -11.10 (-20.40;-1.79) | 0.020 | -18.03 (-23.37;-12.69)** | -18.94 (-25.85;-12.02) | <0.001 |
| **BMI *(kg/m2)*** | 1.44 (0.48;2.39)* | 0.85 (-0.19;1.89) | 0.106 | 1.03 (-0.03;2.08) | 0.57 (-0.62;1.75) | 0.340 | 0.91 0.01;1.81)* | 0.45 (-0.43;1.33) | 0.311 |
| **Duration of complaints *(months)*** | -0.48 (-1.01;0.05) | -0.23 (-0.75;0.30) | 0.394 | -0.64 (-1.19;-0.09)* | -0.36 (-0.96;0.24) | 0.239 | -0.13 (-0.63;0.36) | 0.13 (-0.31;0.58) | 0.551 |
| **Bi-laterality** | -10.18 -17.43;-2.95)* | 0.27 (-7.54;8.08) | 0.944 | -10.42 (-18.15;-2.69)** | -1.04 (-9.94;7.87) | 0.816 | -6.23 (-13.06;0.59) | 2.06 (-4.57;8.68) | 0.536 |
| **Sport participation** | -1.07 (-8.89;6.74) | -2.42 (-9.66;4.81) | 0.504 | -5.70 (-13.88;2.49) | -6.55 (-14.80;1.70) | 0.117 | -8.15 (-14.97;-1.33)* | -7.62 (-13.75;-1.48) | 0.016 |
| **NRS rest *(0-10)*** | 0.25 (-2.46;0.66) | 0.50 (-1.28;2.28) | 0.575 | -0.94 (-2.60;-0.72)* | -0.49 (-2.52;1.54) | 0.630 | -0.62 (-2.05;0.81) | -0.33 (-1.84;1.18) | 0.662 |
| **NRS activity *(0-10)*** | -2.09 (-3.75;-0.42)* | -0.89 (-2.86;1.09) | 0.373 | -0.99 (-2.83;0.85)* | 0.51 (-1.75;2.76) | 0.654 | -0.48 -2.07;1.10) | 0.40 (-1.28;2.07) | 0.636 |
| **AKP score *(0-100)*** | 0.59 (0.30;0.89)** | 0.30 (-0.11;0.71) | 0.153 | 0.33 (-0.02;0.68)* | 0.19 (-0.27;0.66) | 0.408 | 0.21 (-0.09;0.51) | -0.11 (-0.36;0.34) | 0.951 |
| **More pain in cold environment** | -3.53 (-11.89;4.83) | -3.86 (-11.15;3.43) | 0.293 | 5.43 (-3.40;14.26) | 4.75 (-3.57;13.06) | 0.257 | 3.65 (-3.96;11.25) | 2.51 (-3.67;8.69) | 0.418 |
| **PPT location *(bone)*** | -1.32 (-5.91;3.27) | -1.13 (-5.06;2.81) | 0.568 | -3.08 (-7.91;1.75) | -1.60 (-6.09;2.89) | 0.477 | -0.34 (-4.53;3.86) | -0.01 (-3.34;3.33) | 0.996 |

^= multivariate analyses

*= p<0.05; **= p<0.001 (for univariate analyses)

CI: confidence interval

## DISCUSSION

The purpose of this study was to investigate whether there is a difference in PPT between patients with PFP and healthy control subjects. Our results showed that PFP patients had significant lower PPT's compared to healthy controls on all three locations, suggesting the presence of local, distal and generalized pressure hyperalgesia. Subgroup analyses for both age and gender status revealed that PPTs at the contralateral knee and arm were only significantly lower in adult patients and female patients. Female gender was identified as effect modifier with respect to the PPT at the contralateral arm. Multivariable analyses of patient characteristics showed a significant association of female gender with a lower PPT.

Our finding that PFP patients had significant lower PPTs compared to healthy controls is in line with recent studies.[6,7] Rathleff et al. demonstrates lower local and distal pressure hyperalgesia in female adolescent PFP patients compared to controls.[6] Noehren et al. showed an increase in both localized and centralized pain sensitivity in a small group of female adult patients with PFP compared to controls.[7] Both studies focused on women only, probably because the incidence of PFP is seemingly higher in females.[15] In the present case-control study also male PFP patients were included. Significant lower PPTs at the affected knee were present in both male and female patients. However, PPTs at the contralateral knee and contralateral arm were only significantly lower in female patients and adult patients. It would be expected that a difference in prevalence of bilateral complaints among subgroups would influence the difference in PPT of the contralateral knee, but not the contralateral arm. Therefore, the presence of bilateral complaints was added to the model for the contralateral knee and indeed differences between subgroups for the contralateral knee were no longer significantly different.

The fact that no significant differences between patients and control subjects in PPTs at the contralateral knee and arm were found in the adolescent subgroup is presumably due to a lack of power. PPTs at the contralateral knee and arm were consistently lower in adolescent patients compared to adolescent controls, and based on the 95%CI intervals of the mean differences clinically relevant differences, regarded as an effect size of ≥0.5, cannot be ruled out.

Female gender was identified as effect modifier for the contralateral arm and was significantly associated with lower PPTs in the patient population. This indicates that generalized hyperalgesia, indicative for an altered central pain perception, is predominantly present in female patients. In a recent study, Rathleff et al. also indicated that PFP might have a central component.[16] Other symptoms indicative for a central component, such

as generalized widespread pain and neuropathic pain, were not explicitly present in our study. Noehren et al did find hypoesthesia, depicted as an elevated threshold to detect light touch over the center of their patella. Furthermore, a recent study by Rathleff et al. showed an impaired conditioned pain modulation, indicative for a central component, in female adolescents with chronic PFP.[7,16] Moreover, the profile of the sensory dysfunctions in the study of Jensen et al. also indicates an involvement of the central nervous system.[4] Differences in findings between our study and the other two could be due to the use of different measures. Since a central component could be targeted with pain modifying drugs, more research focusing on the presence of a central component in PFP would be worthwhile.[17] Further research is also warranted, considering the dose-response and the effect of additional patient-education, because, Rathleff et al. showed the ability of exercise therapy to alter PPTs and demonstrated that recovered female patients with PFP have larger reduction in localized pressure hyperalgesia compared to non-recovered females.[8]

### Strengths and limitations

To our knowledge, this is the first case-control study focusing on the presence of altered pain processing in both adults and adolescents, and males and females. Furthermore, associations between PPT and patient characteristics have also not been studied previously. In order to develop better-targeted treatment strategies, more knowledge on association between patient characteristics and PPT is essential.

Since we placed the dynamometer on the most painful spot on the knee in patients it was not feasible to blind the assessor. Though a previous study showed a good reliability for PPT testing between the current assessor and an independent assessor in a subgroup of the study population.[14]

We intended to match the patients and their controls on age, gender, BMI and sports participation. However, some differences were present concerning BMI and percentage of sports participants and therefore all analyses were adjusted for these confounders.

It is off course not possible to test the PPT at the most painful spot, when no pain is experienced. Therefore, the medial patellar facet was chosen. This seems justified, since most patients indeed pointed the medial facet to be the most painful location. In order to be sure that placement of the algometer on different surfaces (patellar bone or peripatellar soft tissue) would not have influenced our results, PPT location was added to the multivariate analyses. However, no association between PPT and algometry at the patellar bone location was present.

## CONCLUSION

In conclusion, our results show that patients with PFP have local, distal and generalized pressure hyperalgesia. Females with PFP were most likely to suffer from generalized hyperalgesia.

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# Chapter 9

## General discussion

## DISCUSSION

Patellofemoral pain (PFP) is a common knee complaint, especially among physically active young individuals.[1] Unfortunately, PFP is no trivial self-limiting disorder.[2-8] A large percentage of patients have persistent symptoms, despite a variety of treatment modalities.[9-13] The pathogenesis and treatment modalities of PFP are widely debated, but no consensus on treatment modalities has been reached and the pathogenesis is still largely unknown.[14] This thesis includes a systematic review on one of these treatment modalities and a cross-sectional case-control study that aimed to contribute to a better understanding of the pathogenesis of PFP.

### Exercise therapy

Most patients with PFP are treated conservatively with exercise therapy. In order to assess the effectiveness of exercise therapy in patients with PFP **chapter II** comprises a systematic literature review including multiple comparisons of exercise therapy, like exercise therapy versus a control strategy (no treatment, placebo or waiting list controls), a combination of knee and hip exercises versus quadriceps exercises alone and closed kinetic chain exercises versus open kinetic chain exercises. This review found very low quality but consistent evidence that exercise therapy for PFP may result in a clinically important reduction of pain and improvement of function, as well as enhancing long-term recovery. In addition, there is very low quality evidence that a combination of knee and hip exercises may be more effective in reducing pain than knee exercises alone. The latter corresponds with a recent review of Lack et al. that demonstrates the effectiveness of proximal muscle rehabilitation in PFP.[15] However, the best form of exercise therapy, and whether it would be effective in all patients with PFP is still unknown. Comprehensive studies to identify subgroups of patients who would benefit more from a specific approach are therefore necessary. Some previous studies did focus on certain hypothetic subgroups, like females, sedentary patients or patients with maltracking.[16-19] Fukuda et al. only included sedentary females, in which sedentary was defined as not having practiced physical activity (aerobic and strengthening exercises) any day of the week for at least 6 months previously.[16] Their study showed both an effect in pain reduction at short and long term and improvement of function at long term in favor of hip and knee exercises compared to knee exercises alone.[16] The effect on pain during activity at short term was notably larger compared to effects on pain or function in other studies of the same comparison that included people who did not engage regular in sports activity[20], a general PFP population[21,22], or recreational athletes.[23] This implies that a larger improvement in pain during activity at short term seems to be achieved in less active patients by applying a combination of exercises for hip and knee muscles. The reason behind this might lay in an overall less developed musculature and core-stability in sedentary

patients in comparison to the general population or to recreational athletes. Another possible explanation for such a big improvement might be the presence of a systemic effect. This systemic effect could be anti-inflammatory as demonstrated for exercise interventions in knee osteoarthritis.[24] Supposedly, the systemic effect would be larger when more or larger muscle groups are targeted with exercise therapy and would also be larger in patients that are not used to physical exposure at all. However, this has not yet been studied in PFP. In sedentary females, a systemic effect could also be based on pain modulation of processing, since altered central pain processing is predominantly present in female patients with PFP (chapter VIII) and exercise therapy seems to be able to diminish pressure hyperalgesia.[25] Therefore, further research into this hypothetic working mechanism is needed.

Another study in a subgroup of patients with untreated PFP of over two months in duration provides evidence that a high-intensity medical exercise therapy program (MET) is more effective than a low intensity exercise program in reducing usual pain and improving functional ability.[18,19] Even at long-term, an effect of MET appears to be present.[18] MET is a concept in physiotherapy where the exercises are constructed according to both open and closed kinetic chain, with variable loads and ranges of motion to enable the patients to perform highly repetitive (≥30 repetitions) exercises without increasing pain.[19] It is suggested that such a graded activity program may modulate fear-avoidance beliefs, and improve coping and self-efficacy.[19] The question, however, is if this fairly large effect would also apply to the general PFP population. It is important to notice that the study population has not engaged in treatment despite a long mean duration of symptoms of 3.6 years in the intervention group and 2.9 years in the control group. Therefore, it might be a specific subgroup especially struggling with fear-avoidance beliefs or with an altered pain perception. Nevertheless, MET seems to be effective, but this is just a single study and therefore further research is warranted.

Recently, Barton et al. proposed a best practice guideline for effective PFP management after combining the findings from six high quality systematic reviews with expert opinions.[26] A tailored multimodal intervention program, complemented with patient education and activity modification would be the key.[26] To achieve individual tailored treatment, the first aim would be to classify clinical subgroups. In 2005, Witvrouw et al. proposed a clinical classification system based on consensus reached by the European Rehabilitation Panel and clinical experience. Their aim was to develop a specific non-operative treatment protocol for each individual with PFP, by guiding the clinician through clinical examination.[27] Recently, Selfe et al. used a series of low cost simple clinical tests to identify possible subgroups and showed that three subgroups of patients with PFP may exist.[28] The 'strong' subgroup had the highest mean hip abductor strength, highest mean quadriceps strength and greatest rectus femoris length. Most patients in this

group were male and had a lower body mass index, a higher level of physical activity, lower pain scores and better function. The 'weak and tighter' group had low mean hip abductor and quadriceps strength and less flexibility. This subgroup had a higher BMI, worse function and a trend towards low physical activity and longer symptom duration was present. The 'weak and pronated foot' subgroup was based on the results of the foot posture index and had greater patellar mobility. This group was younger and had the shortest symptom duration. The findings of Selfe et al. do seem to coincide with the findings of the studies that included specific subgroups, as stated above.[16,18,19] In these studies, the effect of exercise therapy in inactive patients or patients with a longer duration of symptoms, which would fall in the 'weak and tighter' group, was larger compared to the effect in studies with active patients or athletes. This makes sense, since the 'weak and tighter' group has low mean hip abductor and quadriceps strength, and would therefore benefit more from exercise therapy. Contrary to this, active patients would fit in the 'strong' subgroup, which already has high mean strength scores. Therefore, it is highly unlikely that strength based exercise training would improve pain and functional outcome measures in the 'strong' subgroup. Still, the question remains whether an improvement in strength would lead to an improvement in pain and function. The next phase would be to study if targeted interventions for these subgroups do improve pain and functional outcomes.

## Pathogenesis

Up till now, the pathogenesis of PFP is still unknown. The current hypothesis is that high loading conditions of the patellofemoral joint induce PFP by disturbing tissue homeostasis.[14,29] Loss of tissue homeostasis may, once initiated, persist indefinitely.[29] Multiple pathophysiologic mechanisms of knee pain that might also apply to PFP have been proposed in literature.[30-48] This thesis **(chapter III to VIII)** focused on three of these mechanisms, which will be discussed in more detail in the next paragraphs, using a broad range of advanced MRI techniques.

### *Structural joint tissue abnormalities*

Although multiple arthroscopic studies and a MRI study showed that PFP is not necessarily related to cartilage defects, the term 'retropatellar chondropathy' is still used to characterize PFP.[3,30,49,50] Furthermore, abnormalities of patellar retinaculum, synovial plicae, Hoffa's fat pad and subchondral bone marrow had long been mentioned in literature as possible origin of pain, but had not yet been investigated systematically in a PFP population.[30-33,51] Therefore, **Chapter III** of this thesis investigated the association between structural abnormalities of patellofemoral joint tissues on MRI and PFP using 3 Tesla high-field MRI with high spatial resolution (Figure 1).

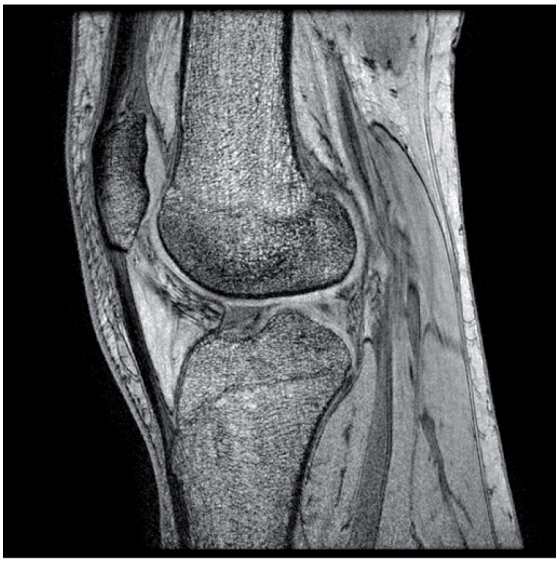

**Figure 1.** 3D high-resolution sagittal fat-saturated spoiled gradient-echo of a control subjects' knee.

Our studies showed that neither full or partial thickness cartilage defects nor minor cartilage defects were associated with PFP. Together with the previous studies[3,30,49,50], there seems to be conclusive evidence to state that patellofemoral cartilage damage is not associated with PFP. Therefore, 'retropatellar chondropathy' and 'chondromalacia patellae' are incorrect synonyms for PFP and from now on should not be used anymore. Furthermore, our study showed that structural abnormalities on MRI of patellar retinaculum and plica, such as increased thickness or high signal intensity, were not associated with PFP. These abnormalities were, in fact, rarely seen in this population.

Other abnormalities, such as minor patellar cartilage defects, patellar bone marrow lesions (BMLs), and a high signal intensity of fat pads, were frequently seen in both patients with PFP and healthy control subjects. This might indicate that other factors need to be present to induce pain in patients. It could be hypothesized that the location of the abnormality might distinguish between patient and controls. However, additional analyses of sub-regions (medial or lateral patella, medial or lateral meniscus, superior or inferior part of patellar tendon) also revealed no significant differences between patients with PFP and healthy control subjects. Another theory might be that certain combinations of abnormalities need to be present to induce PFP. A logical combination, that of both trochlear and patellar abnormalities, could not be tested, because trochlear abnormalities were only present in very small numbers. Nevertheless, this does imply that the contribution of this combination to the pathophysiology of PFP is unlikely.

There are currently no other anticipated combinations based on literature and we lacked power to study all possible combinations.

Apparently, a large percentage of healthy control subjects had abnormalities of the patellofemoral joint on MRI. A high prevalence of abnormalities in asymptomatic knees of adults has also been shown by other studies.[52-58] Even more remarkable was the presence of patellar BMLs in 65% of adolescent control subjects and the presence of patellar osteophytes in 45%, and a high signal intensity in Hoffa's fat pad in 50% of these healthy adolescents. This stirs the question whether certain MRI findings are physiological instead of pathological. With respect to osteophytes, this phenomenon has already been discussed in osteoarthritis research and a Delphi process has been undertaken.[59] However, the definition of a 'definite osteophyte' was not yet delineated and requires further validation. Thus, the question remains whether small osteophytes as seen in our case-control study are actually osteophytes as seen in osteoarthritis or just normal bone-cartilage transitions. In this thesis, the MOAKS MRI score was used, which distinguishes between medium size osteophytes (grade 2) and small osteophytes (grade 1).[60] A large percentage of our study population had osteophytes, however only few participants had medium size osteophytes. The presence of small osteophytes in healthy control subjects, and even in the healthy adolescent population, suggests that this may be a physiologic finding. Hart et al. investigated the natural history of a K&L grade 1 osteophyte.[61] The radiographic Kellgren and Lawrence (K&L) score distinguishes between definite osteophytes, classified as grade 2, and possible osteophytic lipping, classified as grade 1.[62] Hart et al. found that 'doubtful' osteophytes are significantly related to later life radiographic knee OA, and concluded that K&L grade 1 osteophyte cannot be ignored or classified as normal.[61] Whether this also applies to small osteophytes on MRI is unknown up to know.

Another interesting finding was the high percentage of patellar BMLs in both patients and control subjects, even in the adolescent population. Over the past decade, BMLs have received more attention in the field of OA research, because it has been suggested that bone rather than cartilage may be the initiating site of pathophysiological events in OA and that BMLs are related to pain.[63-66] But, if BMLs are related to pain, how come that such a large percentage of healthy control subjects have BMLs? The answer might be that other factors need to be present to induce pain or that BMLs in healthy control subjects are a different type of BML than the ones in patients experiencing pain. The importance of identifying different entities of subchondral BMLs has previously been emphasized by Roemer et al.[67] It would be interesting to investigate if a specific type, volume, location of BMLs, or concurrent abnormality is associated with PFP. In the current study, the distribution of BMLs is comparable between patients and control subjects, with a 5 times higher percentage of BMLs in the patella compared to the anterior femur

in both groups. With respect to BML' size, additional analyses to the studies presented in this thesis showed that only 3 patients had a larger sized patellar BML according to the MOAKS classification and none of the control subjects. One specific type of BML that might exist is an activity related BML. The association between physical activity and BMLs is controversial. A review by Lim et al. found limited evidence for an association between physical activity and BMLs.[68] More recently, Antony et al. studied this association in young adults and found no association overall.[58] However, when dividing physical activity into moderate and vigorous, a protective association was found in their study for moderate activity and a deleterious association for vigorous.[58] In our study, activity was not associated with the presence of BMLs, however activity was dichotomized and level of activity was not taken into consideration.
It has been shown that BMLs with different content exists in osteoarthritic knees.[69] Furthermore, Lee et al. demonstrated more blood going and a failure to "wash out" in BMLs compared to normal bone, which can be interpreted as stasis or outflow obstruction.[70] Both stasis and an altered content might hypothetically lead to a higher intraosseous pressure, another hypothetic pathophysiologic mechanism for PFP. With advanced imaging techniques, like DCE-MRI and ultrashort echo time (UTE) MRI it should be possible to study these features in the future. Failure to "wash out" can be measured with DCE-MRI. In the current study DCE-MRI was not yet specifically to BMLs, but only applied to the patellar bone marrow. UTE-MRI can characterize BML content by imaging the structure of trabecular bone.[71] Additionally, UTE can image the osteochondral junction[72,73]. This osteochondral junction has received increasing attention over the years as possible factor in OA pathophysiology.[74,75]

The current case-control study demonstrated that cartilage defects on MRI are not associated with PFP. However, in OA compositional alterations are known to precede morphological alterations of cartilage [76] and PFP has been suggested as a precursor for osteoarthritis.[77,78] Nowadays, it is possible to study cartilage composition with advanced MRI techniques. These quantitative MRI techniques for cartilage, such as delayed gadolinium enhanced MRI of cartilage (dGEMRIC), $T1_{\rho}$ and T2 mapping, quantitatively measure cartilage composition by measuring its structural components, like glycosaminoglycan and collagen.[79] Therefore, **chapter IV** of this thesis focused on the association between PFP and patellofemoral cartilage composition. Previously published in-house developed software (Software for Post-processing and Registration of Cartilage of the Knee: SPARCK) was optimized for the patellofemoral joint and used to calculate cartilage composition (Figure 2).[80-83]

One of the strengths of SPARCK is automated image registration, which compensates for subject motion within and between sequences. Thereby, facilitating the use of the same

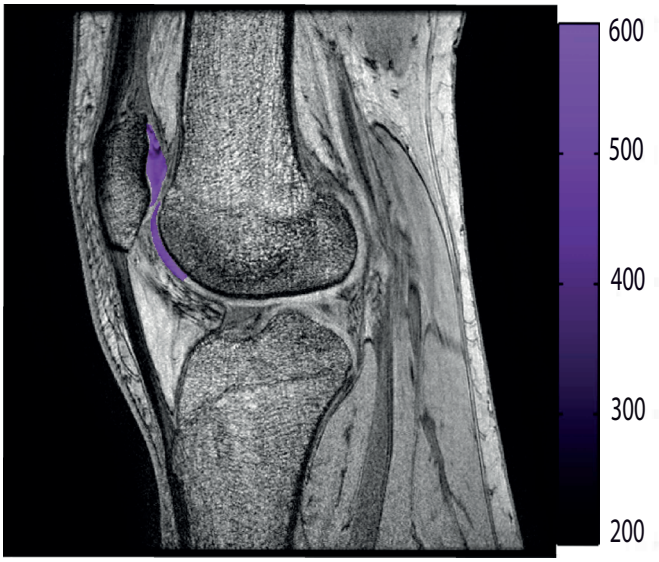


**Figure 2.** Color overlays of a T1-map of the patellofemoral joint of a control subject. Lower $T1_{GD}$ relaxation times in milliseconds, shown in black, depict less GAG content.

region of interest (ROI) for all sequences. Another strength is the automatic removal of possible included cortical bone pixels in the ROI based on a participant-specific bone-cartilage threshold. Furthermore, a weighted mean relaxation was calculated using the reciprocal of the uncertainty of the fit. This is of importance as more uncertain voxels, for instance at tissue boundaries, could influence the mean relaxation time. By calculating a weighted mean, voxels for which the estimated relaxation time was more uncertain had less influence on the mean.

The study population comprised a relatively young population of patients with PFP and therefore early changes in cartilage composition were expected more frequently than morphologic defects. However, no significant differences were found in patellofemoral cartilage composition between patients and control subjects for all applied MRI sequences. Since, based on finite elements analysis studies[43,84], the highest patellofemoral joint stresses are observed on the lateral side of the patellofemoral joint, it could be hypothesized that differences are specifically present in the lateral part of the cartilage. On the other hand, less pressure on the medial side of the joint, theoretically, could also lead to deterioration of cartilage due to insufficient loading. Therefore, additional analyses of pre-specified medial and lateral subregions within the patellar and femoral cartilage were done, but also revealed no significant differences between groups.

Based on the degenerative process with aging, as seen in OA, a diminished cartilage composition would rather be expected in adult patients than in adolescent patients. Therefore, additional analysis focused on differences between patients and controls subdivided in an adult and adolescent age group. This was only done for $T1_{\rho}$ mapping and T2 mapping, because $T1_{GD}$ mapping was not acquired in minors due to contrast

administration restrictions. A recent in-vivo validation study demonstrated that $T1_\rho$-mapping is no substitute for dGEMRIC, thus we lack a GAG measure for the adolescent population. [85] Nevertheless, this study also indicated that $T1_\rho$-mapping is still suitable for measuring early compositional changes of cartilage by measuring water content or a combination of composites of the cartilage extracellular matrix instead.[85] Analyses within age groups showed no significant differences, but clinically relevant differences could not be ruled out for $T1_\rho$-mapping in the adolescent population. Based on the degenerative process with aging, mentioned earlier, it is illogical that differences would occur in the adolescent age group and not in the adult age group. The absence of a possible clinical relevant difference between patients and controls at the adult age implies that the possible clinical relevant differences at the adolescent age are transient. Furthermore, $T1_\rho$-mapping values of adolescent patients are actually quite comparable to $T1_\rho$-mapping values of adult patients and controls. Therefore, it is highly unlikely that these possible clinically relevant differences in cartilage composition at the adolescent age contribute to the pathogenesis of PFP.

This does not alter the fact that the difference at the adolescent age is interesting and presumes there needs to be another factor that influences cartilage composition in a different degree in adolescent patients and controls. In the current study we have adjusted our analyses for BMI, age, sex, sports participation and time of image acquisition, but more confounders may exist. Moreover, the influence of certain confounders may be more profound in specific age groups. For instance, the influence of activity level might be more profound. Sports participation was significantly associated with multiple variables of cartilage composition. Although analyses were adjusted for sports participation, they were not adjusted for the actual level of activity. Anther confounder, closely related to activity level, would be muscle strength. Kumar et al. recently demonstrated a relation between cartilage relaxation times and muscle mass anatomical cross-sectional area, which is strongly correlated to strength measures.[86] To date, there is still much unknown with respect to factors influencing cartilage composition and in what degree, especially in adolescents. Therefore, future research should focus on factors influencing cartilage composition instead of conducting $T1_\rho$-mapping in a larger cohort of adolescent patients.

Based on the absence of morphologic cartilage defects on MRI and the absence of a diminished cartilage composition in PFP, it is unlikely that PFP is a precursor to patellofemoral OA. It is however important to notice that the cross-sectional design of this study only facilitates investigation of associations and not of cause and effect.

***Patellar bone ischemia***

Local bone tissue ischemia, induced by impaired arterial blood inflow or by increased intraosseous pressure due to impaired venous outflow, is suggested to be a pathophysiologic mechanism of PFP.[34-38] Blood perfusion can be measured with dynamic contrast-enhanced MRI (DCE-MRI). DCE-MRI measures the amount of contrast, equivalent to the amount of blood, getting into and out of a preselected region over a time period. The most innovative, but also the most challenging, part of this thesis was applying quantitative DCE-MRI in patellar bone. To our knowledge, this has not been done before and rendered serious acquisition and post-processing challenges due to the sparse vascularization of bone and the typical low contrast enhancement compared to surrounding tissues. Since, there is no consensus on the optimal acquisition and pharmacokinetic models for the patellar bone, **chapter V** of this thesis focused on the development of a method to apply DCE-MRI in patellar bone. For DCE-MRI, native T1 values are needed to convert signal intensity to contrast concentration. However, due to acquisition time restrictions when conducting dGEMRIC and DCE-MRI in one session, acquiring a native T1 map was not feasible. Nevertheless, native T1 values among subjects were expected to be similar or at least not strongly correlated with PFP, because T1 itself is not known to be a biomarker for PFP. Therefore, native T1 values were based on literature. SPARCK, previously used to study patellofemoral cartilage composition, was optimized for patellar bone blood perfusion.[80-83] Because the optimal combination of arterial input function (AIF) model and pharmacokinetic model for the patellar bone is unknown, all possible combinations of pharmacokinetic models and AIF models were tested. A surprising finding was that Tofts' model was likely to be more sensitive to detect group differences than Brix' model[87], since Brix' model has been applied in previous studies in bones of the lower extremity (femur, tibia).[70,88,89] With respect to the other two pharmacokinetic models that were tested, there were hardly any obvious differences between Tofts'[90] and extended Tofts' model. Tofts' model appeared to perform consistently better and best fitted our data combined with a population average AIF based on the model of Parker[91]. Over the entire dataset, the residual was close to the acquisition noise level. Therefore, this combination was implemented in our method and used to study differences in patellar bone blood perfusion in our study population in **chapter VI** (Figure 3).

Low $k_{trans}$ and low $k_{ep}$ values were expected to be found in patients with PFP, suggestive for local tissue ischemia and venous outflow obstruction, respectively. However, higher but non-significant, values of $k_{trans}$ and $k_{ep}$ were found in patients with PFP compared to healthy control subjects. Furthermore, a statistically significant larger variance of $k_{trans}$ was observed in patients compared to controls. These results suggest that a subgroup with higher $k_{trans.}$ values in the patient population might be present. Higher values correspond with hyperperfusion; more blood going into the patellar bone marrow. Hyper-

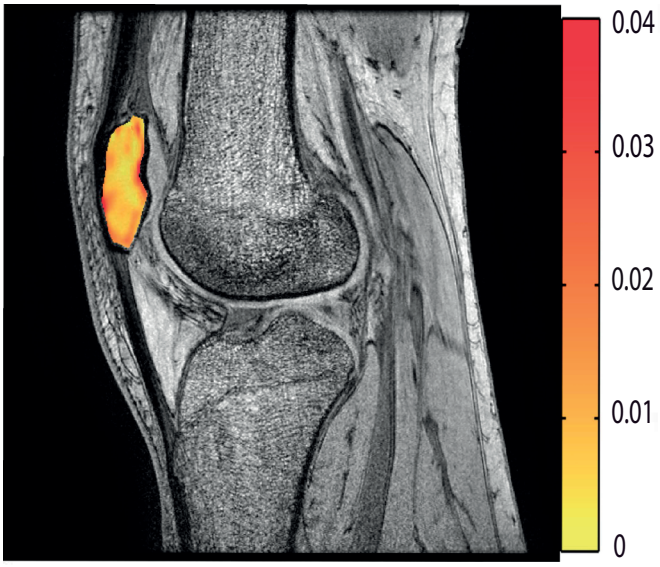


**Figure 3.** Color overlays of a $k_{trans}$ map of the patellar bone marrow of a control subject. Higher $k_{trans}$ values ($min^{-1}$), shown in red, depict more blood going into the patellar bone marrow.

vascularization could be a possible explanation for hyperperfusion. It is hypothesized by Sanchis-alfonso et al. that episodes of ischemia, possibly due to vascular torsion during sitting, could trigger hypervascularization of the patellar retinaculum in patients with patellofemoral pain due to malalignment as a result of increased vascular endothelial growth factor release.[92] The same could apply to the subchondral bone of patients with sitting pain and therefore higher perfusion values would be expected in this subgroup. However, explorative analyses in our study revealed no significant differences in blood perfusion of the patellar bone between patients with and without sitting pain. Nevertheless, possible differences could be undetected due to a lack of discriminating power, because 77% of patients in our study population reported sitting pain. More recently we showed in an international dataset that 50% of patients with PFP had sitting pain (unpublished data) and it would thus be possible to discriminate between patients with and without sitting pain. Therefore, future research might focus on a bigger cohort of PFP patients. Furthermore, a future prospect might be acquiring DCE-MRI in an open MRI scanner in patients with sitting pain with their knee in different degrees of knee flexion. Particularly since Naslund et al. reported a decreased pulsatile patellar blood flow in patients with PFP during knee flexion.[93] Although, this might give insight in the pathophysiologic mechanism of sitting pain, it would not clarify why patients experience pain during activities without knee flexion. If the same underlying mechanism would account for pain with and without flexed knees, than this mechanism can be investigated without the knees flexed, as was done in our study. Another perspective on ischemia-induced changes proposed by Sanchis-alfonso et al. is perivascular hyperinnervation

as a result of increased neural growth factor production.[94] It would be logical that this perivascular hyperinnervation would lead to hyperalgesia, a finding predominantly present in females (chapter VIII). Therefore, it could be hypothesized that perfusion parameters are higher in female patients compared to male patients. However, additional analyses to those presented in this thesis revealed no significant differences in perfusion parameters between female and male patients.

A more suitable explanation for hyperperfusion would be the presence of BMLs. As mentioned before, Lee et al. demonstrated more blood going in and a failure to "wash out", which can be interpreted as stasis or outflow obstruction, in BMLs compared to normal bone in adult patients with OA or avascular necrosis with painful bone marrow edema.[70] Analyses, additional to this thesis, indicate that patients with patellar BMLs have higher values of both perfusion parameters. Moreover, patients with a larger sized patellar BML seemed to have higher perfusion values than patients with smaller sized BMLs. However, these larger sized BMLs were only present in three patients. Accumulation of fluid in a BML may lead to an increased intraosseous pressure, which might induce pain. Increased intraosseous pressure is one of the hypothetic pathophysiologic mechanisms for PFP that was not further studied in the current thesis. More recently, Ho et al. showed elevated patellar water content, indicative for an increased intraosseous pressure, resulting from repetitive patellofemoral joint overloading in recreational runners with PFP compared to control subjects.[37] Thus, more research regarding the possibility of an increased intraosseous pressure in PFP is warranted using advanced MRI techniques, such as DCE-MRI and the recently developed chemical-shift-encoded water-fat protocol.[37]

During the development of the DCE-MRI method that was applied in the case-control study new challenges arose. Spatial heterogeneity of patellar blood perfusion appeared to be high. To avoid underweighting of less-perfused areas in the region of interest, unweighted medians of both perfusion parameters were calculated additionally. Furthermore, a large inter-subject variability was present. A large inter-subject variability makes it difficult to detect significant differences. We were not able to distinguish between two possible causes of this large inter-subject variability, i.e. measurement variability or normal tissue heterogeneity, since no reproducibility study was done due to the contrast burden. Reproducibility, as well as clinical relevant differences of patellar bone perfusion parameters need further investigation to be sure no clinical relevant differences will be missed in future research. Overall, enhancing temporal resolution would also be preferable, but the dynamic nature of the DCE experiment limits simultaneous improvement of temporal and spatial resolution. For now, we can conclude that we are the first who have applied a tailored DCE-MRI acquisition protocol and post-processing tool to the patellar bone of patients with PFP and healthy control subjects that success-

fully extracted the dynamic contrast enhancement from the MRI data, and thus can be used to study patellar bone blood perfusion.

***Altered pain perception***

Next to this structural approach, an altered pain mechanism might also contribute to PFP. One of the symptoms of an altered pain perception is hyperalgesia, an increased sensitivity to pain. The current hypothesis is that repeated overload sensitizes local nociceptors, which causes local hyperalgesia. The presence of pressure hyperalgesia can be assessed with the pressure pain threshold (PPT). **Chapter VII** showed that handheld dynamometry with algometry tip is a reliable method to assess the PPT in both patients with PFP and control subjects, wherein the inter-rater reliability was higher in patients. Subsequently, differences in PPT between patients with PFP and healthy control subjects were tested in **chapter VIII**. PPTs were significantly lower in patients with PFP compared to controls at the affected knee, the contralateral knee and the contralateral arm, indicative for local, distal and generalized pressure hyperalgesia, respectively. Subgroup analyses for both age and gender status demonstrated significantly lower PPTs at the contralateral knee and arm in adult patients and female patients only. Considering age status, PPTs at the contralateral knee and arm were consistently lower in adolescent patients compared to adolescent controls, and based on the 95%CI intervals of the mean differences clinically relevant differences, regarded as an effect size of ≥0.5, cannot be ruled out. Though, no significant interaction effects were found between participant status and age status. Considering female gender, a significant interaction effect between participant status and female with respect to the PPT at the contralateral arm (β -9.95, 95%CI -18.74;-1.16) was identified and multivariable analyses of patient characteristics showed a significant association of female gender with a lower PPT. Thus, an altered central pain perception, based on the presence of generalized pressure hyperalgesia, is predominantly present in female patients. Recent studies also showed results indicative for a central component in females with PFP.[95-97] Because a central component could be targeted with specific exercise therapy or even pain modifying drugs, more research focusing on the presence of a central component in PFP would be worthwhile.[98] To our knowledge, it is unknown why central pain processing is only altered in females. A logical explanation would be hormones, though female patients in the present study indicated that pain was not associated with their hormonal cycle.

Furthermore, it has been demonstrated that exercise therapy is able to alter PPTs, but more research is needed considering the dose-response and the effect of additional patient-education.[25] Moreover, insight needs to be gained with regard to patient characteristics associated with altered pain perception and with regard to the working mechanism(s) and the time it takes to alter pain perception. If this would be known,

therapy could be targeted and patients could be properly educated in an early stage to prevent an altered pain perception.

### Methodological strengths and challenges

To our knowledge this is the largest case-control study using innovative quantitative MRI sequences to study the pathophysiology of PFP.

A representative sample of the population comprising both adults and adolescents patients with PFP and control subjects was included. Patients with PFP were referred for inclusion by their general practitioner, physiotherapist or sports physician. The diagnosis PFP had to be based on the presence of at least three of the following symptoms: crepitus, and/or retro or peripatellar pain during stair climbing, squatting, running, cycling, or during sitting for a prolonged period with the knees flexed. These inclusion criteria were based on standards from international literature. Exclusion criteria comprised: a current knee pathology of the affected knee (e.g. osteoarthritis or patellar tendinopathy), or previous surgery or injury of the affected knee, or previous episodes of PFP more than two years ago, or onset of PFP after trauma. Because the diagnosis of PFP might be challenging, all caregivers were thoroughly informed, and the necessity to exclude other pathology, especially patellar tendinopathy, was emphasized. No pre-determined set of physical sets was applied during patients' inclusion, since sensitivity and specificity of physical tests, such as the Clarke compression test, are disputable.[99,100] The strength of this study is that we included a representative group of patients with PFP without prior selection of hypothetic subgroups of patients (e.g. maltracking, female gender, professional athletes). It is highly anticipated that different subgroups in PFP exist. However, to date, clear subgroups have not been identified in a systematic manner and due to our sample size it was not possible to test all hypothetic subgroups. Therefore, we decided only to perform additional analysis in patients with sitting pain with regard to blood perfusion and to investigate the effect of gender with respect to pain perception. Furthermore, additional analyses were done for different patient age groups: adults and adolescents. The inclusion of adolescents, 20 patients with PFP and 20 control subjects, aged 14-18 years, is a big strength, because many studies excluded this group. There is a lack of information in adolescents, for instance considering the presence of structural abnormalities. This is striking, because PFP is especially prevalent in young individuals.[8] Moreover, it has recently been suggested that adolescent patients with PFP might differ from adult patients with PFP based on a different success-rate despite providing similar exercise treatment and having similar exercise compliance.[101]

Symptom duration of the current study patient population was 2 months to 2 years. It could be hypothesized that patients with longer symptom duration have a different pathophysiology compared to patients with shorter symptom duration. However,

univariate analyses, additional to this thesis, showed that symptom duration was not significantly associated with cartilage relaxation times, perfusion parameters, or pain pressure thresholds. Of all recruited patients, 15% were excluded because their symptom duration was more than 2 years or they have had previous episodes of PFP more than 2 years ago. Thus, overall, the majority of referred patients was included, and for now there is no evidence to suggest that patients with longer symptom duration have a different pathophysiology compared to patients with shorter symptom duration. Nevertheless, a follow-up study is currently conducted in order to investigate if clinical and imaging baseline characteristics of recovered and chronic patients differ.

There is still a missing link between the presence of pathology and biomechanical/kinematic factors that might predispose to PFP. The current hypothesis on PFP pathogenesis is that high loading conditions of the patellofemoral joint lead to a disturbed tissue homeostasis.[14,29] Therefore, conducting both advanced imaging techniques to study tissue homeostasis together with methods to assess biomechanics/kinematics need to be aspired. It was not feasible to additionally assess biomechanics and/or kinematics for the current study, because advanced imaging techniques are rather time-consuming. This should be a future prospect when advanced imaging protocols are less time-consuming or when pathophysiology of PFP has already been clarified and thus a subset of imaging techniques could be chosen. It is important, though, to keep in mind that in cross-sectional studies it would still be unknown if the biomechanical and/or kinematic values were the same before onset of PFP and/or if these values would actually induce pathophysiology. Thus, longitudinal studies will be needed in the future. For now, emphasis should first be placed on identifying possible origins of pain and, from a radiology prospect, on improving imaging methods to do so, as was done in this thesis. If possible origins of pain are identified in the future, it would be of high value if these could be linked to certain predisposing biomechanics and/or kinematics that could be targeted in clinical practice.

### Clinical implications

Exercise therapy is more effective compared to a control strategy. It is still unknown which type of exercise therapy is the most effective and whether this effect is present in all patients with PFP. However, hip and knee exercises seem to be more effective than knee exercises alone. This implies that exercise therapy, including hip and knee exercises should be prescribed to patients with PFP. Furthermore, the possibility of an altered pain perception should be kept in mind when treating patients with PFP, especially female patients. The PPT, an indication for an altered pain perception, could easily be assessed in clinical practice with handheld dynamometry. However, to our knowledge reference values and cut-off points are unknown and would need to be established first.

Furthermore, treatment options in case of an altered pain perception still need further investigation, but at this stage it may be worthwhile to give the patient more insight into his/her condition. For now, a graded activity program, such as high intensity, pain free exercises, could be given if alterations in pain perception seem to be present, because it is known that this may modulate fear-avoidance beliefs, and improve coping and self-efficacy.[19]

For now, the pathophysiology of PFP is still a black box. Nevertheless, according to the results of this thesis one pathophysiologic mechanism can be ruled out. Structural abnormalities, visible on conventional MRI or a diminished cartilage composition, are not associated with PFP. Therefore, conventional MRI should not be acquired to diagnose patients with PFP and 'chondromalacia patellae' and 'retropatellar chondropathy' should not be used as synonyms for PFP anymore.
Furthermore, based on the results of this thesis, there is no evidence to suggest that PFP pathophysiology differs between adolescent and adult patients. Both groups are comparable concerning the amount of structural abnormalities, cartilage composition and pain perception. Unfortunately, patellar bone blood perfusion could not be studied in adolescents, because we were not allowed to administer contrast to minors.

**Future research**

The next step in research would be combining the separate MR outcomes with clinical features and patient characteristics, for instance to further investigate if BMLs or other structural abnormalities coincide with higher perfusion parameters in patients. There are far more questions to be answered and combining all data to identify subgroups is even more aspiring, but unfortunately the current study lacks power to do so. In the future, conducting larger studies or pooling data, which enables application of statistics such as latent class growth analysis, would facilitate identifying potential subgroups. Thanks to rapid advancement in computational tools for analyzing large sets of data, precision medicine by phenotyping through (quantitative) imaging biomarkers combined with clinical features is also a realistic future perspective and genomic data can already be extracted from blood samples conducted in the current study.
The observed trend towards higher blood flow in PFP patients and the larger variance of $k_{trans}$ in patients warrants further research. Therefore, for PFP research, emphasis should rather be placed on DCE-MRI instead of quantitative MRI of cartilage. Standardization of our DCE-MRI method is necessary and reproducibility needs to be investigated. Whether or not clinical relevant differences could be detected with the current measurement variability indicates if further optimization of the DCE-MRI acquisition protocol is necessary. However, enhancing temporal resolution would be a serious challenge due to the dynamic nature of the DCE experiment. Another challenge would be acquiring DCE-MRI

for all knee tissues at once. Recently, DCE-MRI has been applied to measure synovitis.[102,103] Synovitis, a sign of inflammation, is linked to knee pain in multiple studies[33,46,47] and thus also a hypothetic pathophysiologic mechanism for PFF (Figure 1). It has been shown that the presence of inflammatory cytokines, such as IL-6 and TNFα, is associated with radiographic osteoarthritis and knee cartilage loss.[104,105] Because cartilage loss is not present in PFP and PFP is considered to be transient in contrast to OA, the presence of inflammatory cytokines is not the first to be expected in patients with PFP. However, it is not implausible that excessive patellofemoral stress induces certain biological cascade pathways including the release of inflammatory cytokines or growth factors. Maybe, the processes induced by the release of cytokines and growth factors can still be counterbalanced in transient PFP, whereas in OA the body's repair mechanism is not able to achieve this anymore. Synovitis, as sign of inflammation, can be measured with contrast-enhanced T1[106,107] and more recently DCE-MRI has been applied for the same purpose.[102,103] Both sequences were acquired in the current study and will be used to investigate synovitis in a later stadium. Furthermore, serological inflammatory markers can be measured in the blood samples, which were also acquired in the current study.
At the same time, it should be kept in mind for future research that multiple pathways likely coincide. For instance, both vascular and neural growth factors as well as inflammatory cytokines could be present inducing hypervascularisation, inflammation and hyperinnervation, wherein the latter could lead to an altered pain perception.

With respect to treatment, emphasis should be placed on identification of potential clinical subgroups and elucidating working mechanism of these therapies. As mentioned before, the latter will probably coincide with the aim to unravel the pathophysiology of PFP, because the link between the presence of pathology and biomechanical/kinematic factors that might predispose to PFP is still missing. Next to biomechanical/kinematic factors, differences in patellofemoral bone shape can hypothetically lead to excessive patellofemoral contact stress and therefore also needs to be studied. This approach is currently implemented in our department, where 3D patellofemoral bone shape will be compared between patients with PFP patients with OA and control subjects using statistical shape analysis.[108,109]

Besides this structural approach, more knowledge is essential on the role of altered pain mechanisms in patients with PFP. According to Noehren et al. localized and centralized pain sensitivity are related to movement mechanics. Furthermore, Rathleff et al. demonstrated that exercise therapy seems to be able to diminish pressure hyperalgesia.[25] However, the dose-response is still unknown, as is the effect of additional patient-education. The presence of altered central pain processing mechanism also warrants

further research, since these might be targeted by specific exercise therapy or even by pain modifying drugs in the future.[98]

**Conclusions**

This thesis focused on assessing the effectiveness of exercise therapy in patients with PFP and on unraveling the pathophysiology of PFP. The main conclusions can be summarized as follows:

- Exercise therapy is more effective than a control strategy (no treatment, placebo or waiting list controls). It is still unknown which type of exercise therapy is the most effective and whether this effect is present in all patients with PFP. However, a combination of hip and knee exercises seems to be more effective than knee exercises alone. Therefore, exercise therapy including knee and hip exercises should be prescribed to all patients with PFP.
- Structural joint abnormalities of the patellofemoral joint on MRI, such as bone marrow lesions, plica lesions, and patellar retinaculum lesions, are not associated with the presence of PFP. It is the question whether certain structural abnormalities are 'pathologic' or rather 'physiologic'. Retropatellar cartilage damage, both morphologic and compositional, is also not associated with PFP.
- Our tailored DCE-MRI protocol and postprocessing tool successfully extracted quantitative dynamic contrast enhancement metrics from the MRI data, and thus can be used to study patellar blood perfusion. In contrast to expected, higher, but non-significant values of patellar bone perfusion parameters, indicating hyperperfusion, were found in patients with PFP compared to healthy control subjects. Furthermore, a difference in $k_{trans}$ variance was observed. Both findings warrant further research.
- Handheld dynamometry is a reliable method to assess both the PPT and quadriceps strength in patients with PFP in clinical practice. Especially female patients with PFP showed generalized pressure hyperalgesia. No differences were found between adolescent and adult patients with PFP. Further research on the role of altered pain mechanisms in patients with PFP is warranted.
- Two other hypothetic pathophysiologic mechanisms, increased intraossesous pressure and inflammation, were not studied in the current thesis.

Figure 4 displays the current knowledge on hypothetic pathophysiologic mechanisms of PFP. Although mechanisms are presented as separate boxes, it is not unlikely that some of them coincide, as mentioned previously.

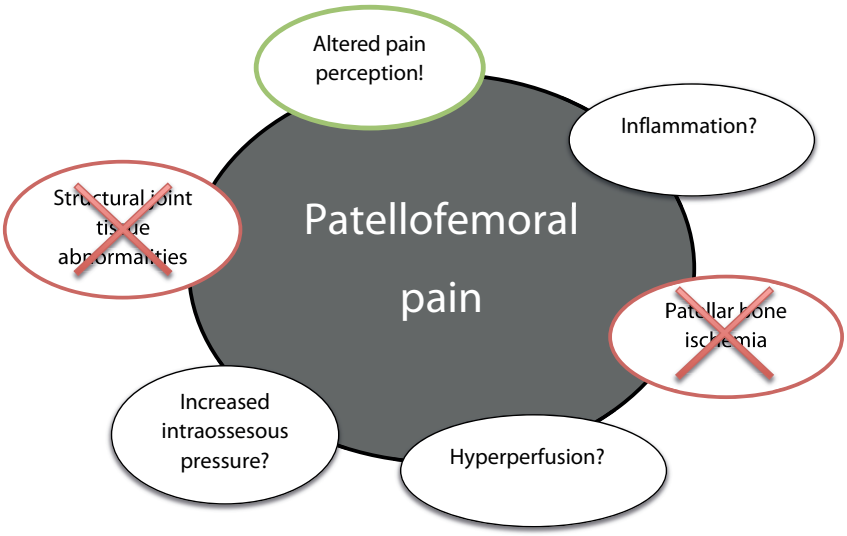


**Figure 4.** Hypothetic pathophysiologic mechanisms of patellofemoral pain

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# Summary

The aim of this thesis was to assess the effects of exercise therapy aimed at reducing knee pain and improving knee function in patients with patellofemoral pain (PFP). Furthermore, this thesis aimed to contribute to a better understanding of the pathogenesis of PFP by focusing on the association between PFP and structural abnormalities, patellar bone ischemia and altered pain perception using broad range of advanced magnetic resonance imaging (MRI) techniques.

The objective of **chapter II** was to assess the effects of exercise therapy aimed at reducing knee pain and improving knee function for people with PFP. We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (May 2014), the Cochrane Central Register of Controlled Trials (2014, Issue 4), MEDLINE (1946 to May 2014), EMBASE (1980 to 2014 Week 20), PEDro (to June 2014), CINAHL (1982 to May 2014) and AMED (1985 to May 2014), trial registers (to June 2014) and conference abstracts. Randomised and quasi-randomised trials evaluating the effect of exercise therapy on pain, function and recovery in adolescents and adults with PFP. We included comparisons of exercise therapy versus control (e.g. no treatment) or versus another non-surgical therapy; or of different exercises or exercise programmes. Two review authors independently selected trials based on pre-defined inclusion criteria, extracted data and assessed risk of bias. Where appropriate, we pooled data using either fixed-effect or random-effects methods. We selected the following seven outcomes for summarising the available evidence: pain during activity (short-term: ≤ 3 months); usual pain (short-term); pain during activity (long-term: > 3 months); usual pain (long-term); functional ability (short-term); functional ability (long-term); and recovery (long-term).
In total, 31 heterogeneous trials including 1690 participants with PFP are included in this review. There was considerable between-study variation in patient characteristics (e.g. activity level) and diagnostic criteria for study inclusion (e.g. minimum duration of symptoms) and exercise therapy. Eight trials, six of which were quasi-randomised, were at high risk of selection bias. We assessed most trials as being at high risk of performance bias and detection bias, which resulted from lack of blinding. The included studies, some of which contributed to more than one comparison, provided evidence for the following comparisons: exercise therapy versus control (10 trials); exercise therapy versus other conservative interventions (e.g. taping; eight trials evaluating different interventions); and different exercises or exercise programmes. The latter group comprised: supervised versus home exercises (two trials); closed kinetic chain (KC) versus open KC exercises (four trials); variants of closed KC exercises (two trials making different comparisons); other comparisons of other types of KC or miscellaneous exercises (five trials evaluating different interventions); hip and knee versus knee exercises (seven trials); hip versus knee exercises (two studies); and high- versus low-intensity exercises (one study). There were no trials testing exercise medium (land versus water) or duration of exercises. Where

available, the evidence for each of seven main outcomes for all comparisons was of very low quality, generally due to serious flaws in design and small numbers of participants. This means that we are very unsure about the estimates. The evidence for the two largest comparisons is summarised here.

*Exercise versus control*

Pooled data from five studies (375 participants) for pain during activity at short-term favoured exercise therapy: mean difference (MD) -1.46, 95%confidence interval (CI) -2.39 to -0.54. The CI included the minimal clinically important difference (MCID) of 1.3 (scale 0 to 10), indicating the possibility of a clinically important reduction in pain. The same finding applied for usual pain at short-term (two studies, 41 participants), pain during activity at long-term (two studies, 180 participants) and usual pain at long-term (one study, 94 participants). Pooled data from seven studies (483 participants) for functional ability at short-term also favoured exercise therapy; standardised mean difference (SMD) 1.10, 95% CI 0.58 to 1.63. Re-expressed in terms of the Anterior Knee Pain Score (0 to 100), this result (estimated MD 12.21 higher, 95% CI 6.44 to 18.09 higher) included the MCID of 10.0, indicating the possibility of a clinically important improvement in function. The same finding applied for functional ability at long-term (three studies, 274 participants). Pooled data (two studies, 166 participants) indicated that, based on the 'recovery' of 250 per 1000 in the control group, 88 more (95% CI 2 fewer to 210 more) participants per 1000 recovered in the long term (12 months) as a result of exercise therapy.

*Hip plus knee versus knee exercises*

Pooled data from three studies (104 participants) for pain during activity at short-term favoured hip and knee exercise: MD -2.20, 95% CI -3.80 to -0.60; the CI included a clinically important effect. The same applied for usual pain at short-term (two studies, 46 participants). One study (49 participants) found a clinically important reduction in pain during activity at long-term for hip and knee exercise. Although tending to favour hip and knee exercises, the evidence for functional ability at short-term (four studies, 174 participants) and long-term (two studies, 78 participants) and recovery (one study, 29 participants) did not show that either approach was superior.

In conclusion, this review has found very low quality but consistent evidence that exercise therapy for PFP may result in clinically important reduction in pain and improvement in functional ability, as well as enhancing long-term recovery. However, there is insufficient evidence to determine the best form of exercise therapy and it is unknown whether this result would apply to all people with PFP. There is some very low quality evidence that hip plus knee exercises may be more effective in reducing pain than knee exercise alone. Further randomised trials are warranted but in order to optimise research effort and engender the large multicentre randomised trials that are required to inform

practice, these should be preceded by research that aims to identify priority questions and attain agreement and, where practical, standardisation regarding diagnostic criteria and measurement of outcome.

The following chapters focused on hypothetic pathophysiologic mechanisms of PFP.
A cross sectional case-control study was conducted between January 2013 and September 2014 and included a healthy control group and patients with PFP with minimum symptom duration of two months to a maximum of two years. All participants were aged between 14 and 40 years. Patients who visited their general practitioner, physiotherapist or sports physician were included if they were diagnosed with PFP based on the presence of at least 3 of the following symptoms: crepitus or pain while stair climbing, squatting, running, cycling, or sitting for a prolonged period with the knee flexed. Patients were excluded if they currently had a defined pathological knee condition of the affected knee (eg, osteoarthritis or patellar tendinopathy), 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. Control subjects consisted of team members, friends or colleagues of the included patients with PFP. We aimed to match control subjects on age, Body Mass Index (BMI), sex and activity level. Control subjects were excluded if they had current or past PFP, if they previously had a traumatic injury or surgery on both knees or if they were first-grade family members of patients.

In total 64 patients and 70 control subjects were included; 40 participants (equally distributed between groups) were adolescents The mean age was 23.2 ± 6.4 years, mean BMI was 22.9 ± 3.4 kg/m2 and 56.7% of the participants were female. Participants were asked to fill in an online questionnaire, including questions on demographics (age, sex, BMI), sports participation at the time of inclusion and before onset of pain (yes or no) and knee complaints (duration of complaints, pain at rest and during activity (Numerical Rating Scale (NRS) 0-10) and function (Anterior Knee Pain (AKP) score 0-100)). Subsequently, they were invited for a physical examination (including crepitation during squatting (present or not), palpation of the medial patellar facet (painful or not) and the Clarke compression test (positive or negative)) and 3 Tesla MRI scan at our university medical center. The MRI protocol comprised sagittal, axial and coronal fast spin echo (FSE) proton density weighted sequences, a 3 dimensional (3D) high resolution sagittal SPGR sequence with high spatial resolution with and without fat-saturation, a 3D sagittal FSE $T1_{\rho}$ mapping sequence, a 3D sagittal FSE T2 mapping sequence, a 3D sagittal inversion recovery non-fat-saturated SPGR sequence for delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and a sagittal, anterior-posterior frequency-encoded, fat suppressed 3D SPGR sequence for dynamic contrast-enhanced (DCE)-MRI. The last two sequences were only acquired in adults due to the need of contrast administration.

**Chapter III** aimed to investigate the presence of structural abnormalities of the patellofemoral joint on high-resolution MRI in patients with PFP compared to healthy control subjects. No previous study has investigated if PFP is associated with structural abnormalities of the patellofemoral joint using high-resolution MRI. All images were scored using the Magnetic Resonance Imaging Osteoarthritis Knee Score with the addition of specific patellofemoral features. Associations between PFP and the presence of structural abnormalities were analysed using logistic regression analyses, adjusted for age, BMI, sex and sports participation.
Full thickness cartilage loss was not present. Minor patellar cartilage defects, patellar bone marrow lesions (BMLs) and high signal intensity of Hoffa's fat pad were frequently seen in both patients (23%, 53% and 58% respectively) and control subjects (21%, 51% and 51% respectively). After adjustment for age, BMI, sex and sports participation, none of the structural abnormalities were statistically significantly associated with PFP.
In conclusion, structural abnormalities of the patellofemoral joint have been hypothesized as a factor in the pathogenesis of PFP, but our findings suggest that structural abnormalities of the patellofemoral joint on MRI are not associated with PFP

**Chapter IV** aimed to investigate differences in patellofemoral cartilage composition between patients with PFP and healthy control subjects using quantitative MRI. Retropatellar cartilage damage has been suggested as an etiological factor for PFP, but, to date, there is no conclusive evidence for an association between cartilage defects and PFP. Nowadays, advanced quantitative MRI techniques enable estimation of cartilage composition. Differences in relaxation times of patellar and femoral cartilage were compared between groups by linear regression analyses, adjusted for age, body mass index, sex, sports participation, and time of image acquisition. Higher T2 en $T1_{\rho}$ and lower $T1_{GD}$ relaxtion times mean less content.
For delayed gadolinium-enhanced MRI of cartilage, the mean $T1_{GD}$ relaxation times of patellar (657.8 vs 669.4 ms) and femoral cartilage (661.6 vs 659.8 ms) did not significantly differ between pa- tients and controls. In addition, no significant difference was found in mean $T1_{\rho}$ relaxation times of patellar (46.9 vs 46.0 ms) and femoral cartilage (50.8 vs 50.2 ms) and mean T2 relaxation times of patellar (33.2 vs 32.9 ms) and femoral cartilage (36.7 vs 36.6 ms) between patients and controls. Analysis of prespecified medial and lateral subregions within the patellofemoral cartilage also revealed no significant differences.
In conclusion, there was no difference in composition of the patellofemoral cartilage, estimated with multiple quantitative MRI techniques, between patients with PFP and healthy control subjects. However, clinically relevant differences could not be ruled out for $T1_{\rho}$ in the adolescent population. Retropatellar cartilage damage has long been hy-

pothesized as an important factor in the pathogenesis of PFP, but study findings suggest that diminished patellofemoral cartilage composition is not associated with PFP.

**Chapter V and VI** focused on patellar bone tissue ischemia. Vascular problems, like bone ischemia or increased intraosseous hydrostatic pressure due to venous outflow obstruction, might play a role in PFP. DCE-MRI enables quantitative measurement of patellar bone blood perfusion. However, application of DCE-MRI for bone has been limited due to the sparse vascularization of bone and the typical low contrast enhancement compared to surrounding tissues. Therefore, our first aim was to develop a robust analysis method for quantifying patellar bone blood perfusion with DCE-MRI **(chapter V)**. DCE-MRI acquisition was optimized and the optimal combination of pharmacokinetic model and arterial input function (AIF) for quantitative analysis of blood perfusion in the patellar bone using DCE-MRI was identified. The method design study used a random subset of five control subjects. We systematically investigated the reproducibility of pharmacokinetic parameters for all combinations of Orton and Parker AIF models with Tofts, Extended Tofts (ETofts), and Brix pharmacokinetic models. We evaluated if the AIF should use literature parameters, be subject specific, or be group specific. Model selection was based on the goodness-of-fit and the coefficient of variation of the pharmacokinetic parameters. The vascular component in the ETofts model could not reliably be recovered and the Brix model parameters showed high variability. A subject specific AIF performed worse than a group specific AIF, but better than an AIF with literature parameters. The best reproducibility and goodness-of-fit were obtained by combining Tofts' pharmacokinetic model with the group specific Parker AIF.
In conclusion, we identified several good combinations of pharmacokinetic model and AIF for quantitative analysis of perfusion in the patellar bone. The recommended combination was Tofts pharmacokinetic model combined with group specific Parker's AIF model.

This DCE-MRI method was than applied in **chapter VI** in our case-control study. Quantitative MR perfusion parameters (i.e. $k_{ep}$, $k_{trans}$) of manually segmented patellar bone were derived from motion-compensated DCE MRI-data by fitting Tofts' model to the measured data in each voxel. Differences in perfusion parameters of patellar bone were compared between groups by linear regression analyses, adjusted for age, body mass index (BMI), gender, and sports participation. Lower values of patellar bone perfusion parameters, suggestive for local tissue ischemia or venous outflow obstruction, were expected in patients with PFP compared to healthy control subjects.
35 adult patients and 44 adult controls were included. Mean age was 26.1 ± 5.0, mean BMI was 24.1 ± 3.4 kg/m2 and 49% was female. Mean $k_{ep}$ was 0.189 ± 0.147 $min^{-1}$ for patients and 0.154 ± 0.114 $min^{-1}$ for controls. Mean $k_{trans}$ was 0.019 ± SD 0.015 $min^{-1}$ for

patients and 0.014 ± SD 0.009 $min^{-1}$ for controls. Both perfusion parameters were not significantly different between groups. However, a significant difference in variance between populations was observed for $k_{trans}$.
In conclusion, in contrast to expected, higher values of patellar bone perfusion parameters were found in patients with PFP compared to healthy control subjects, but these differences were not statistically significant. This result, and the observed difference in $k_{trans}$ variance warrant further research.

**Chapter VII and VIII** focused on pain perception. It has been suggested that repeated overload might sensitize local nociceptors causing local hyperalgesia. This might also lead to an altered central processing of nociceptive information. In order to identify pressure hyperalgesia, the pressure pain threshold (PPT) can be measured. Therefore, our first aim was to determine the inter-rater reliability of handheld dynamometry to test PPT in patients with PFP. Quadriceps strength was also conducted, because it can be easily assessed with the same device. A reliability study took place in 22 PFP patients and 16 matched controls of the case-control study mentioned previously **(Chapter VII)**. Measurements comprised three quadriceps strength and one PPT measurements performed by two independent investigators. Inter-rater reliability was analyzed using intraclass correlation coefficients (ICC) and Bland-Altman plots.
Inter-rater reliability of quadriceps strength testing was fair to good in PFP patients (ICC= 0.72) and controls (ICC=0.63). Bland-Altman plots showed an increased difference between assessors when average quadriceps strength values exceeded 250 Newton. Inter-rater reliability of PPT was excellent in patients (ICC=0.79) and fair to good in controls (ICC=0.52).
In conclusion, handheld dynamometry seems to be a reliable method to test both quadriceps strength and PPT in PFP patients. Inter-rater reliability was higher in PFP patients compared to control subjects. With regard to quadriceps testing, a higher variance between assessors occurs when average quadriceps strength values exceeded 250 Newton.
This method was than applied in **chapter VIII** in a case-control study to investigate differences in PPT between patients with PFP and healthy control subjects and study associations between PPT and patients characteristics. The PPT was measured with a handheld dynamometer with algometry tip on three locations: most painful spot at the affected knee (medial facet in controls), same spot contralateral knee and at the contralateral forearm. Differences between groups were tested with linear regression analyses adjusted for age, gender, BMI and sports participation.
Patients had significantly lower PPTs compared to controls at all locations. Beta's were -13.98(95%CI -18.62;-9.33) at the affected knee, -6.91(95%CI -11.84;-1.97)) at the contralateral knee and -7.57(95%CI -12.07;-3.07) at the arm. A significant interaction effect was

found between participant status and female with respect to the PPT at the contralateral arm. (β -9.95, 95%CI -18.74;-1.16). Female gender was significantly associated with a lower PPT in the patient population.
In conclusion, local, distal and generalized pressure hyperalgesia, suggesting alterations in both peripheral and central pain mechanisms, were present in patients with PFP. Females with PFP were most likely to suffer from generalized hyperalgesia.

**Chapter IX** discusses the main findings and places them in a wider prospective. Methodological strengths and challengers are discussed. Furthermore, clinical implications and future research prospectives are given.

# Nederlandse samenvatting

Het doel van dit proefschrift was het vaststellen van de effectiviteit van oefentherapie gericht op vermindering van kniepijn en verbetering van de kniefunctie in patiënten met patellofemorale pijn (PFP). Ook beoogde dit proefschrift om bij te dragen aan een beter begrip van de pathogenese van PFP door middel van het bestuderen van associaties tussen PFP en structurele afwijkingen, ischemie van het bot van de patella en een veranderde pijnperceptie. Dit werd gedaan met een grote selectie aan geavanceerde beeldvormende technieken gebaseerd op magnetische resonantie (MRI).

**Hoofdstuk II** beschrijft een systematisch literatuuronderzoek naar de effectiviteit van oefentherapie gericht op vermindering van kniepijn en verbetering van de knie functie in patiënten met PFP. We doorzochten daarvoor verschillende databases o.a. van de Cochrane Bone, Joint and Muscle Trauma Group (Mei 2014) en Cochrane Central Controlled Trials. Gerandomiseerde en quasi-gerandomiseerde studies, die het effect van oefentherapie op pijn, functie en herstel in adolescenten en volwassenen met PFP hadden onderzocht werden geincludeerd. De studies deden dit door middel van vergelijkingen van oefentherapie versus een controle strategie (bijv. geen behandeling) of versus een andere niet-operatieve therapie, en vergelijkingen van verschillende oefeningen of oefenprogramma's, werden geïncludeerd. We selecteerden de volgende zeven uitkomsten om het beschikbare bewijs in samen te vatten: pijn tijdens activiteit (korte termijn: ≤ 3 maanden), dagelijkse pijn (korte termijn), pijn tijdens activiteit (lange termijn: > 3 maanden), dagelijkse pijn (lange termijn), fysiek functioneren (korte termijn), fysiek functioneren (lange termijn) en herstel (lange termijn).
In totaal, zijn er 31 studies met in totaal 1196 patiënten met PFP geïncludeerd. Er was sprake van een behoorlijke variatie in patiënt karakteristieken (bijv. in activiteiten niveau en diagnostische criteria voor inclusie in de studie (bijv. minimale klachtenduur)) en in de soort oefentherapie tussen studies. De geïncludeerde studies, waarbij sommige bijdroegen aan meer dan een vergelijking, verschaften bewijs voor de volgende vergelijkingen: oefentherapie versus controle strategie, oefentherapie versus andere conservatieve interventies (bijv. tapen), en verschillende oefeningen of oefenprogramma's. De laatste groep bevatte gesuperviseerde oefeningen versus oefeningen thuis, gesloten kinetische keten oefeningen versus open kinetische keten oefeningen, varianten van gesloten kinetische keten oefeningen, andere vergelijkingen of andere types van gesloten keten oefeningen of ander soort oefeningen, heup- en knie oefeningen versus knie oefeningen, heup versus knie oefeningen en hoge intensiteit- versus lage intensiteit oefeningen. Het bewijs voor alle zeven belangrijkste uitkomsten was van erg lage kwaliteit. Dit kwam vooral door serieuze gebreken in de studie opzet, zoals bijvoorbeeld het niet blinderen van patiënten en behandelaars voor de behandeling waarin de patiënt geplaatst was, en door het kleine aantal deelnemers in de studies.

Dit betekent dat de validiteit van de uitkomsten discutabel is. Het bewijs voor de twee grootste vergelijkingen hebben we samengevat in de volgende paragrafen.

**Oefentherapie versus controle strategie:**

Samengevoegde data van vijf studies voor pijn tijdens activiteit op de korte termijn toont aan dat oefentherapie meer leidt tot een afname van pijn dan een controle strategie; gemiddeld verschil van -1.46, 95% betrouwbaarheids interval (BI) -2.39 tot -0.54. Dit verschil is klinisch relevant. Hetzelfde was het geval bij dagelijkse pijn op de korte termijn, pijn tijdens activiteit op de lange termijn en dagelijkse pijn op de lange termijn. Samengevoegde data van zeven studies toont aan dat voor fysiek functioneren op de korte termijn oefentherapie meer leidt tot een verbetering in functie; met een gestandaardiseerd gemiddeld verschil van 1.10, 95% BI 0.58 tot 1.63. Uitgedrukt in de 'Anterior Knee Pain Score' (schaal 0 tot 100) was het gemiddelde verschil 12.21 (95% BI 6.44 tot 18.09). Dit is klnisch relevant. Dezelfde bevinding werd gedaan voor fysiek functioneren op de lange termijn. Samengevoegde data van twee studies liet ook zien dat, gebaseerd op een herstel van 250 per 1000 in de controle groep, er 88 (95% BI 2 minder tot 210 meer) meer deelnemers per 1000 op de lange termijn (12 maanden) herstelden in de oefentherapie groep.

**Heup- en knie oefeningen versus knie oefeningen:**

Samengevoegde data van drie studies voor pijn tijdens activiteit op de korte termijn gaf een voorkeur aan heup- en knie oefeningen versus alleen knie oefeningen, met een gemiddel verschil van -2.20 (95% BI -3.80 tot -0.60). Dit verschil is klinisch relevant effect. Hetzelfde is van toepassing op dagelijkse pijn op de korte termijn. Een studie vond een klinisch relevante afname in pijn tijdens activiteit op de lange termijn voor heup- en knie oefeningen. Ook al neigde het bewijs voor fysiek functioneren op de korte termijn , lange termijn en herstel naar heup- en knie oefeningen, toch was geen van beide aanpakken superieur aan de ander.

Concluderend geeft dit systematische literatuuronderzoek bewijs van erg lage, maar wel consistente kwaliteit, dat oefentherapie in patiënten met PFP kan resulteren in een klinische relevante afname in pijn en verbetering van de knie functie, als ook in meer herstel op lange termijn. Er is echter onvoldoende bewijs om vast te kunnen stellen welke vorm van oefentherapie de beste is en of dit resultaat op alle patiënten met PFP van toepassing is. Er is ook bewijs, zij het van erg lage kwaliteit, dat heup- en knie oefeningen effectiever zouden zijn in het verminderen van pijn dan knie oefeningen alleen. Meer gerandomiseerde studies zijn nodig. Maar om onderzoeksinspanningen te optimaliseren, moet er eerst onderzoek worden gedaan naar de belangrijkste vragen en overeenstemming bereikt worden wat betreft diagnostische criteria en uitkomstmaten.

De volgende hoofstukken richtten zich op het ontrafelen van de pathofysiologische mechanismen van PFP. Een cross-sectionele case-controle studie heeft plaatsgevonden van Januari 2013 tot September 2014. Hierbij werden een gezonde controle groep en patiënten met PFP met een klachtenduur tussen de twee maanden en twee jaar geïncludeerd. Alle patiënten waren tussen de 14 en 40 jaar oud. Patiënten die hun huisarts, fysiotherapeut of sportarts bezochten, werden geïncludeerd als ze gediagnosticeerd werden met PFP gebaseerd op drie van de volgende symptomen: crepitatie (kraken van het gewricht bij buigen) of pijn bij traplopen, hurken, rennen, fietsen of langdurig met de knieën gebogen zitten. Patiënten werden geëxcludeerd als ze momenteel reeds vastgestelde pathologie van de aangedane knie hadden (zoals artrose of patellotendinopathy), als ze een eerdere operatie of blessure aan de aangedane knie hadden gehad, als ze meerdere episodes van PFP meer dan twee jaar geleden hadden gehad of als PFP was ontstaan na een trauma. Controlepersonen waren teamgenoten, vrienden of collega's van de geïncludeerde patiënten met PFP.

In totaal zijn er 64 patiënten en 70 controlepersonen geïncludeerd, waarbij 40 deelnemers (evenredig verdeeld over de groepen) adolescenten waren. De gemiddelde leeftijd was 23.2 ± 6.4 jaar, het gemiddelde BMI was 22.9 ± 3.4 kg/m2 en 56.7% van de deelnemers was vrouw. Deelnemers werd gevraagd om een online vragenlijst in te vullen betreffende demografische gegevens (leeftijd, geslacht, BMI), sportdeelname tijdens inclusie en voordat de pijn begon (ja of nee) en knieklachten (duur, pijn tijdens rust en tijdens activiteit (Numerical Rating Scale (NRS) 0-10) en functie (Anterior Knee Pain (AKP) score 0-100)). Daarna werden ze uitgenodigd voor een lichamelijk onderzoek (met o.a. crepitatie tijdens hurken (aanwezig of niet), palpatie van het mediale patellaire facet (pijnlijk of niet) en de Clark compressie test (positief of negatief)) en een 3 Tesla MRI scan in het Erasmus universitair medisch centrum. Het MRI protocol bevatte proton density sequenties, hoge resolutie sequenties, quantitatieve sequenties voor het meten van kraakbeen ($T1_{GD}$ (delayed gadolinium-enhanced MRI of cartilage (dGEMRIC)), T2 en $T1_{\rho}$) en een quantitatieve sequentie om de doorbloeding te meten (dynamic contrast-enhanced (DCE)-MRI) De laatste twee sequenties zijn alleen gemaakt in volwassen, omdat hierbij contrast toegediend moest worden.

In **hoofdstuk III** wordt de aanwezigheid van structurele afwijkingen van het patellofemorale gewricht op hoge-resolutie MRI tussen patiënten met PFP en gezonde controlepersonen vergeleken. Geen enkele eerdere studie heeft onderzocht of PFP geassocieerd is met structurele afwijkingen van het patellofemorale gewricht met behulp van hoge-resolutie MRI. Alle beelden werden gescoord volgens de Magnetic Resonance Imaging Osteoarthritis Knee Score, waarbij er enkele specifieke patellofemorale items werden

toegevoegd. Associaties tussen PFP en de aanwezigheid van structurele afwijkingen werden getest met logistische regressie analyses, welke geadjusteerd werden voor leeftijd, BMI, geslacht en sportdeelname.
Volledige dikte kraakbeenverlies was niet aanwezig. Kleine patellaire kraakbeendefecten, patellaire beenmerglesies (BMLs) en een hoge signaalintensiteit van Hoffa's vetlichaam werd veelvuldig waargenomen, zowel in patiënten (23%, 53% en 58% respectievelijk) als controlepersonen (21%, 51% en 51% respectievelijk). Na adjustering voor leeftijd, BMI, geslacht en sportdeelname, was geen van de structurele afwijkingen statistisch significant geassocieerd met PFP.
Concluderend is het verondersteld dat structurele afwijkingen van het patellofemorale gewricht bijdragen aan de pathogenese van PFP, maar onze resultaten suggereren dat structurele MRI afwijkingen van het patellofemorale gewricht niet geassocieerd zijn met PFP.

In **hoofdstuk IV** worden verschillen in patellofemorale kraakbeen-samenstelling tussen patiënten met PFP en gezonde controlepersonen onderzocht met behulp van kwantitatieve MRI technieken. Retropatellaire kraakbeenschade wordt verondersteld een etiologische factor voor PFP te zijn, maar tot op heden is er niet afdoende bewijs voor een associatie tussen PFP en kraakbeendefecten. Met behulp van geavanceerde, kwantitatieve MRI technieken ($T1_{GD}$, T2 en $T1_{\rho}$) is het tegenwoordig mogelijk om de kraakbeensamenstelling te bepalen. Verschillen in relaxatietijden van patellair en femoraal kraakbeen werden vergeleken tussen de groepen met lineaire regressie analyses, welke waren geadjusteerd voor leeftijd, BMI, geslacht, sportdeelname en het tijdstip waarop de MRI scan gemaakt was. Een hogere T2 en $T1_{\rho}$ en lagere $T1_{GD}$ relaxatietijd betekent minder bestanddelen in het kraabeen en het dus minder stevig, gezond kraakbeen.
De gemiddelde $T1_{GD}$ relaxatie tijd van het patellaire kraakbeen (657.8 vs 669.4 ms) en van het femorale kraakbeen (661.6 vs 659.8 ms) was niet significant verschillend tussen patiënten en controles. Ook was er geen significant verschil in de gemiddelde $T1_{\rho}$ relaxatietijden van patellair- (46.9 vs 46.0 ms) en femoraal kraakbeen (50.8 vs 50.2 ms) en de gemiddelde T2 relaxatietijden van patellair- (33.2 vs 32.9 ms) en femoraal kraakbeen (36.7 vs 36.6 ms) tussen patiënten en controles.
Analyses van vooraf gedefinieerde mediale en laterale subregio's binnen het patellofemorale kraakbeen lieten ook geen significante verschillen zien.
Concluderend was er geen verschil in patellofemorale kraakbeensamenstelling, bepaald met multiple kwantitatieve MRI technieken, tussen patiënten met PFP en gezonde controlepersonen. Voor $T1_{\rho}$ in de adolescenten kunnen klinisch relevante verschillen echter niet worden uitgesloten. Het is lang verondersteld dat retropatellaire kraakbeenschade een belangrijke factor is in de pathogenese van PFP, maar onze resultaten suggereren

dat een verminderde patellofemorale kraakbeensamenstelling niet geassocieerd is met PFP.

**Hoofdstuk V en VI** richtten zich op ischemie, een verminderde doorbloeding, van het bot van de patella. Vasculaire problemen, zoals ischemie van het bot van de patella of een verhoogde inta-ossale druk in de patella door een veneuze afvloeiingsobstructie, kunnen een rol spelen in PFP. Met DCE-MRI is het mogelijk om de doorbloeding, de perfusie, van het patella bot te meten. Vanwege de lage vascularisatie van bot en lage signaalintensiteit ten opzichte van omliggende weefsels is DCE-MRI in bot nog weinig toegepast. Daarom, was ons eerste doel om een robuuste analyse methode te ontwikkelen waarmee we de perfusie van het patella bot met DCE-MRI kunnen kwantificeren **(hoofdstuk V)**. De acquisitie van DCE-MRI is eerst geoptimaliseerd en daarna hebben we de optimale combinatie van farmacokinetisch model en arteriële input functie (AIF) onderzocht. De studie om de methode te ontwikkelen, bevatte vijf random controlepersonen. In deze studie werd de reproduceerbaarheid van de farmacokinetische parameters onderzocht voor alle combinaties van AIF, zoals voorgesteld door Orton en Parker, in combinatie met het farmacokinetische model van Tofts, Extended Tofts en Brix. We evalueerden of de AIF gebaseerd moest zijn op literatuur parameters, of geschat moest worden per subject of over de gehele groep. Voor elke combinatie van modellen, werden de variatiecoëfficiënt, als maat van reproduceerbaarheid van de geschatte perfusie parameters, en de goodness of fit onderzocht.
De vasculaire component in het Extended Tofts model kon niet betrouwbaar worden verkregen en het model van Brix had een hoge variabiliteit. Een op het subject gebaseerde AIF was minder goed dan de groep-specifieke AIF, maar beter dan de op literatuur parameters gebaseerde AIF. De beste reproduceerbaarheid en goodness of fit werd verkregen door Tofts farmacokinetisch model te combineren met de groep-specifieke Parker AIF.
Concluderend werden verschillende goede combinaties van farmacokinetisch model en AIF voor de kwantitatieve analyse van doorbloeding van patella bot geïdentificeerd. De uiteindelijk aangeraden combinatie was Tofts farmacokinetisch model gecombineerd met de groeps-specifieke Parker AIF.
Deze DCE-MRI methode werd vervolgens toegepast in **hoofdstuk VI** in onze case-controle studie. Kwantitatieve MRI perfusie parameters ($k_{ep}$, $k_{trans}$) van manueel gesegmenteerd patella bot werden verkregen uit beweging gecompenseerd DCE-MRI data waarop Tofts' model gefit was op voxel niveau. Verschillen in perfusie parameters van patella bot tussen de groepen werden vergeleken met lineaire regressie analyses, welke geadjusteerd waren voor leeftijd, BMI, geslacht en sportdeelname. Lagere perfusie waarden, suggestief voor ischemie van het bot van de patellar of een veneuze afvloeiingsobstructie, werden verwacht in patiënten met PFP vergeleken met controlepersonen.

In totaal weren 35 volwassen patiënten en 44 volwassen controlepersonen geïncludeerd. De gemiddelde leeftijd was 26.1 ± SD 5.0 jaar, het gemiddelde BMI was 24.1 ± 3.4 kg/m2 en 49% was vrouw. De gemiddelde $k_{ep}$ was 0.189 ± 0.147 $min^{-1}$ in patiënten en 0.154 ± 0.114 $min^{-1}$ in controlepersonen. De gemiddelde $k_{trans}$ was 0.019 ± 0.015 $min^{-1}$ in patiënten en 0.014 ± 0.009 $min^{-1}$ in controlepersonen. Beide perfusieparameters waren niet significant verschillend tussen de groepen. Een significant verschil in variantie tussen de populaties was echter aanwezig.
Concluderend werden er, in tegenstelling tot verwacht, hogere waarden gevonden voor de perfusieparameters van het patellabot in patiënten met PFP in vergelijking met gezonde controlepersonen, maar deze verschillen waren niet statistisch significant. Gezien dit resultaat en het gevonden verschil in variantie in $k_{trans}$ is verder onderzoek nodig.

**Hoofdstuk VII en VIII** richtten zich op pijnperceptie. Het wordt gesuggereerd dat locale nociceptors gesensitiseerd kunnen worden door herhaalde overbelasting. Dit resulteert in hyperalgesie en kan ook leiden tot een verstoorde centrale pijnverwerking. Druk hyperalgesie kan gemeten worden met de pressure pain threshold (PPT). Daarom was ons eerste doel om de betrouwbaarheid vast te stellen wanneer de PPT wordt gemeten in patiënten met PFP met een dynamometer die met de hand wordt vastgehouden door verschillende onderzoekers. De kracht van de quadriceps spier werd gelijktijdig gemeten, omdat dat eenvoudig kan met hetzelfde apparaat. Deze betrouwbaarheidsstudie vond plaats in 22 patiënten en 16 controlepersonen van de eerder genoemde case-controle studie **(Hoofdstuk VII).** De kracht van de quadriceps spier werd drie keer gemeten en de PPT een keer door twee onafhankelijke onderzoekers. De betrouwbaarheid tussen deze onderzoekers werd geanalyseerd met intraclass correlation coefficients (ICC) en Bland-Altman plots.
De betrouwbaarheid tussen onderzoekers voor het meten van de quadriceps kracht was redelijk tot goed in patiënten (ICC= 0.72) en controlepersonen (ICC=0.63). De Bland-Altman plots lieten een toename in het verschil tussen onderzoekers zien wanneer de gemiddelde quadriceps kracht meer dan 250 Newton bedroeg. De betrouwbaarheid tussen onderzoekers voor de PPT was uitstekend in patiënten (ICC=0.79) en redelijk tot goed in controlepersonen (ICC=0.52).
Concluderend, is met de hand toegepaste dynamometrie een betrouwbare methode om zowel de quadriceps kracht als de PPT in patiënten met PFP te meten. De betrouwbaarheid tussen onderzoekers was hoger in patiënten dan in controlepersonen. Wat het meten van de quadriceps kracht betreft, bleek dat er een groter verschil tussen onderzoekers optrad wanneer de gemiddelde quadriceps kracht meer dan 250 Newton bedroeg.
Deze methode is vervolgens toegepast in **hoofdstuk VIII** in de case-controle studie om verschillen in PPT tussen patiënten met PFP en gezonde controlepersonen te onder-

zoeken en om te bestuderen welke patiënt karakteristieken geassocieerd zijn met PFP. De PPT is gemeten met de dynamometer met speciale algometrie opzetstuk op drie locaties: meest pijnlijke plek op de aangedane knie (mediale facet bij controlepersonen), dezelfde plek op de contralaterale knie en een plek op de contralaterale onderarm. Verschillen tussen groepen werden getest met lineaire regressie analyses, welke waren geadjusteerd voor leeftijd, BMI, geslacht en sportdeelname.
Patiënten hadden een lagere PPT vergeleken met controlepersonen voor alle locaties; aangedane knie β -13.98 (95% BI -18.62;-9.33), contralaterale knie β -6.91 (95% BI -11.84;-1.97)) arm β -7.57 (95% BI -12.07;-3.07). Er werd een significant interactie effect gevonden tussen deelnemers status (patiënt of controle) en vrouw zijn wat betreft de PPT van de contralaterale arm (β -9.95, 95%BI -18.74;-1.16). Vrouwelijk geslacht was significant geassocieerd met een lagere PPT.
Concluderend waren lokale, distale en gegeneraliseerde druk hyperalgesie, suggestief voor zowel perifere- als centrale pijnmechanismes, aanwezig in patiënten met PFP. Vooral vrouwen met PFP hadden gegeneraliseerde druk hyperalgesie.

**Hoofstuk IX** geeft een overzicht en beschouwing van de belangrijkste bevindingen. Methodologische sterke punten en uitdagingen worden bediscussieerd. Verder, worden implicaties voor de kliniek uiteengezet en aanbevelingen gedaan voor verder onderzoek.

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Mieke, wat lief dat je me op kwam zoeken met die maffe Binkie op de momenten dat het nodig was. Jij bent iemand die heel begaan is en goed aanvoelt wat de ander nodig

heeft. Dat vind ik echt mooi aan je! Die mountainbike toertocht komt er echt nog wel van en anders verzinnen we gewoon iets anders, zoals skydiven of motorrijden ofzo….
Mijn schoonfamilie, Jan, Coby, Monique, Onno en Eline, bedankt voor jullie interesse in mijn proefschrift en de gezellige familie samenkomsten. Hier zien jullie nu eindelijk wat ik al die tijd heb gedaan. Jan en Coby, ook bedankt voor het veelvuldige aanbieden van hulp om mij op die manier iets uit handen te nemen.
Mijn paranimfen, Alyt en Kristel, ik vind het heel fijn dat jullie deze taak op jullie wilden nemen. Jullie hebben mij de afgelopen jaren al bijgestaan tijdens lastige periodes, dus ik zie mijn verdediging helemaal zitten met jullie achter me. Alyt, jij bent me reeds voorgegaan met promoveren en hebt een mooi voorbeeld gegeven van hoe het moet. We hebben elkaar goed gevonden qua sportieve drang en ambitie. Al zitten we wat het eerste betreft nu beiden op het reservebankje, zit het gelukkig met het tweede wel goed en is het mooi om te zien dat je als postdoc je onderzoek kan voortzetten. Het is fijn dat je begrijpt hoe vervelend het is om je ei niet kwijt te kunnen met sporten, maar goed dat je me helpt relativeren en dat we ons ook prima kunnen vermaken met hele leuke onsportieve dingen, zoals de Sneekweek en de Swan market. Kristel, jij zal me zeker opvolgen wat promoveren betreft. Ook al werken je muizen of de mensen eromheen niet altijd mee, toch zet je door, ook in het weekend. Het heeft me zeker geholpen om mijn perikelen wat betreft planningen die misliepen door onvoorziene zaken met je te delen. Verder waren onze uitstapjes helemaal mooi, ook al liepen die soms ook een beetje anders dan gepland: kano's die omslaan waardoor ik bijna verzuip en Basel was misschien ook een beetje te, maar wel memorabel.
Dan natuurlijk mijn familie. Opaatje, bedankt voor de steun, dat je maar 100 mag worden! Maritte en Katelijne, mijn twee superslimme en ambitieuze zusjes. Alhoewel zusjes… eigenlijk zijn jullie nu toch echt wel volwassen (en dienen jullie je daar dus ook naar te gedragen he). Bedankt voor de afleiding tijdens de gezellige zussenavonden, die we alle drie hard nodig hebben, want jullie zijn ook hard bezig met je verdere ontwikkeling. Maritte, ik hoop dat er spoedig iemand op je pad komt die je kwaliteiten ziet en je de kans zal geven om je verder te ontwikkelen tot gezondheidszorgpsycholoog. Katelijne, veel succes met het afronden van je coschappen. En als je weer eens te maken hebt met een doorgedraaide dokter tijdens zijn/haar spreekuur, bedenk dan dat je je altijd nog kan bedenken en toch radioloog kan worden. Dat zijn tenminste heel normale mensen ;) Ik ben trots op jullie! Mijn ouders, Alfred en Hanneke, jullie zijn erg belangrijk voor me. Bedankt voor de onvoorwaardelijke steun en het vertrouwen in mijn kunnen. Pap, bedankt voor het ook altijd belichten van de zakelijke kant van het verhaal in lastige situaties. Dit kan je natuurlijk heel goed door je ervaring als rector. Door omstandigheden hebben we de laatste tijd wat minder gefietst, maar laten we dat weer snel oppakken, want ik vind dat erg leuk om samen te doen ter ontspanning (en momenteel ga ik toch niet hard ;) ). Mam, de elfde stelling is voor jou. Wat heb jij een sterke geest, wat heb ik

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Lieve Dennis, je bent me heel dierbaar. Wat is het een fijn en geruststellend gevoel dat jij er altijd bent om me bij te staan. En het is helemaal fijn en super leuk dat jij er altijd bent om het leven mee te vieren of we nou gaan mountainbiken, naar een concert van Machine Head gaan of tapas gaan eten in Spanje. Op nog vele jaren samen!

# About the author

Rianne Aileen van der Heijden was born in Rotterdam, the Netherlands on the 22th of June in 1986. She attended secondary school at 'Emmauscollege' in Rotterdam. After graduating in 2003, she started her medical study at Erasmus University Medical Center Rotterdam. Besides her career, sports has always been Rianne's passion. In her earlier years, Rianne has performed judo on a high level and more recently she has been a determined mountainbiker. Complementary to her personal interest, the musculoskeletal system has received her special interest while studying Medicine. She, therefore, chose to write her master thesis on the subject of cam impingement in professional soccer players at the department of Orthopedics, Erasmus MC, Rotterdam. Because of promising progress, this project was prolonged for a year in between her internships and eventually resulted in an article in a high impact journal. After graduating in May 2011, Rianne started her career as a youth health care physician, which she could combine with pursuing her ambition as semiprofessional mountainbiker. After a period dedicated to her cycling passion, a longing for musculoskeletal research made her apply for a PhD position at the Erasmus MC. In May 2012 she started her PhD project, which was a joined project of the Department of General Practice and the Department of Radiology, under supervision of prof. dr. S. Bierma-Zeinstra, dr. M. van Middelkoop, and dr. E.H.G. Oei. She was appointed for 2.5 years, which was prolonged for half a year, thanks to a RSNA seed grant awarded to dr. E.H.G. Oei for the promising results Rianne had achieved together with the BIGR group concerning the development of a quantitative method to measure bone blood perfusion. Multiple advanced magnetic resonance imaging techniques were applied in patients with patellofemoral pain (PFP), who were referred by their general practitioner, sports physician or physiotherapist, in order to clarify the pathophysiology of PFP. The research carried out during this period led to multiple publications in high impact journals and was covered by the Volkskrant, one of the largest newspapers of the Netherlands. In May 2016, Rianne started as a resident in Radiology&Nuclear Medicine at Erasmus MC.

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# PhD portfolio

**Name PhD student:** R.A. van der Heijden
**Erasmus MC Departments:** General Practice and Radiology & Nuclear Medicine
**PhD period:** 2012-2016
**Promotor:** S.M.A. Bierma-Zeinstra
**Copromotors:** M. van Middelkoop, E.H.G. Oei

| General courses and workshops | Year | Workload (ECTS) |
|---|---|---|
| - During previous employment: | | |
| Biostatistics for clinicians (NIHES) | 2009 | |
| Introduction to clinical research (NIHES) | 2009 | |
| - Basiscursus regelgeving en organisatie van klinische trials/good clinical practice (Molmed) | 2012 | 1.0 |
| - MRI safety and scanning course (Department of Radiology, Erasmus MC) | 2013 | 2.0 |
| - Media contacts for researchers (Press office, Erasmus MC) | 2014 | 0.5 |
| **(Inter)national oral presentations** | **Year** | **Workload (ECTS)** |
| - Annual meeting of the Dutch society for sports medicine, Ermelo, The Netherlands | 2012 | 1.0 |
| - Patellofemoral pain research retreat, Vancouver, Canada | 2013 | 2.0 |
| - Annual meeting of the Dutch society for sports medicine, Ermelo, The Netherlands | 2013 | 1.0 |
| - European congress of radiology, Vienna, Austria | 2014 | 2.0 |
| - Nordic meeting on quantitative imaging, Kuopio, Finland | 2014 | 1.5 |
| - Annual meeting of the Dutch society for sports medicine, Ermelo, The Netherlands ($3^{d}$ price abstract competition) | 2014 | 1.0 |
| - Danish sports medicine congress, Kopenhagen, Denmark,(top 6 competitor abstract competition) | 2015 | 1.5 |
| - Patellofemoral pain research retreat, Manchester, United Kingdom (2x) | 2015 | 2.5 |
| - Radiologendagen, Rotterdam, The Netherlands | 2015 | 1.0 |
| - Annual meeting of the Dutch society for sports medicine, Ermelo, The Netherlands | 2015 | 1.0 |
| **(Inter)national electronic poster presentations** | **Year** | **Workload (ECTS)** |
| - Annual meeting of the radiologic society of North America, Chicago, United States of America | 2015 | 2.0 |
| - Annual meeting of the international society for magnetic resonance in medicine, Singapore | 2016 | 0.5 |
| **(Inter)national paper poster presentations** | **Year** | **Workload (ECTS)** |
| - Annual meeting of the international society for magnetic resonance in medicine, Milan, Italy | 2014 | 0.5 |
| - European congress of radiology, Vienna, Austria | 2015 | 0.5 |
| - Osteoarthritis research society international world congress. Seattle, United States of America | 2015 | 0.5 |
| - Dutch general practice scientific meeting, Rotterdam, The Netherlands | 2015 | 0.5 |

| | | | |
|---|---|---|---|
| - | Osteoarthritis research society international world congress Amsterdam, the Netherlands | 2016 | 0.5 |

| **Teaching activities** | | **Year** | **Workload (ECTS)** |
|---|---|---|---|
| - | Lecturing MRI assistants | 2013 | 0.5 |
| - | Lecturing general practice trainees | 2013 | 0.5 |
| - | MRI scan training of fellow PhD students | 2014-2015 | 0.5 |
| - | Supervising MSc theses:4 medical students and 1 biomedical engineering student | 2012-2015 | 10.0 |

| **Other** | | **Year** | **Workload (ECTS)** |
|---|---|---|---|
| - | Media coverage in 5 issues of the Volkskrant, a large newspaper in the Netherlands | 2013-2014 | 3.0 |
| | | | |
| **Total** | | | **37.5** |

# Publication list

## THIS THESIS

**van der Heijden RA**, Vollebregt T, Bierma-Zeinstra SMA, van Middelkoop M. Strength and Pain Threshold Handheld Dynamometry Test Reliability in Patellofemoral Pain.
*Int J Sports Med. 2015 Dec;36(14):1201-5. doi: 10.1055/s-0035-1555855. PMID: 26158920*

**van der Heijden RA**, Lankhorst NE, van Linschoten R, Bierma-Zeinstra SMA, van Middelkoop M. Exercise for treating patellofemoral pain syndrome.
*Cochrane Database Syst Rev. 2015 Jan 20;1:CD010387. doi: 10.1002/14651858.CD010387.pub2. PMID: 25603546*

**van der Heijden RA**, Oei EHG, Bron EE, van Tiel J, van Veldhoven PLJ, Klein S, Verhaar JAN, Krestin GP, Bierma-Zeinstra SMA, van Middelkoop M. No Difference on Quantitative Magnetic Resonance Imaging in Patellofemoral Cartilage Composition Between Patients With Patellofemoral Pain and Healthy Controls.
*Am J Sports Med. 2016 May;44(5):1172-8. doi: 10.1177/0363546516632507. PMID: 26951075*

**van der Heijden RA**, de Kanter JLM, Bierma-Zeinstra SMA, Verhaar JAN, van Veldhoven PLJ, Krestin GP, Oei EHG, van Middelkoop M. Structural abnormalities on MRI in patients with patellofemoral pain: a cross-sectional case-control study.
*Am J Sports Med. 2016 May 20. pii: 0363546516646107. [Epub ahead of print] PMID: 27206691*

Poot DHJ, **van der Heijden RA**, van Middelkoop M, Oei EHG, Klein S. Dynamic contrast-enhanced MR imaging of the patellar bone: how to quantify perfusion
*Submitted*

**Van der Heijden RA**, Poot DHJ; Ekinci M, van Veldhoven PLJ, Klein S, Verhaar JAN, Krestin GP, Bierma-Zeinstra SMA, van Middelkoop M, Oei EHG. Blood perfusion of patellar bone measured by dynamic contrast-enhanced MRI in patients with patellofemoral pain: a case-control study.
*Submitted*

**van der Heijden RA**, Rijndertse MM, Bierma-Zeinstra SMA, van Middelkoop M. Pain pressure thresholds especially lower in female patellofemoral pain patients: a cross-sectional case-control study
*Submitted*

## OTHER PUBLICATIONS:

Agricola R, Bessems JH, Ginai AZ, Heijboer MP, **van der Heijden RA**, Verhaar JA, Weinans H, Waarsing JH. The development of Cam-type deformity in adolescent and young male soccer players. *Am J Sports Med. 2012 May;40(5):1099-106. doi: 10.1177/0363546512438381. Epub 2012 Mar 13. PMID: 22415206*

**van der Heijden RA**, Lankhorst NE, van Linschoten R, Bierma-Zeinstra SMA, van Middelkoop M. Exercise for treating patellofemoral pain syndrome. An abridged version of Cochrane Systematic Review. *Eur J Phys Rehabil Med. 2016 Feb;52(1):110-33. PMID: 26158920*

Collins NJ, Vicenzino B, **van der Heijden RA**, Middelkoop M. Pain during prolonged sitting is a common problem in people with patellofemoral pain. *J Orthop Sports Phys Ther. 2016 Jul 3:1-19. [Epub ahead of print] PMID: 27374012*