

Nienke E. Lankhorst

Patellofemoral Pain

Unravelling its Course and Treatment

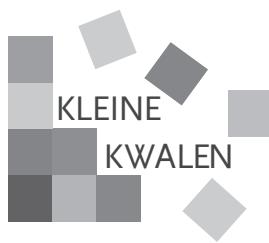
Patellofemoral Pain

Unravelling its Course and Treatment

Patellofemorale pijn

beloop en behandeling

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Patellofemoral Pain

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Chapter I

General introduction

General introduction

Symptoms of the knee are a common reason for patients to consult a general practitioner (GP).^{1,2} In general practice the prevalence of such symptoms (whether traumatic or non-traumatic) is 19 per 1000 patients per year; the majority of patients have a non-traumatic origin of their symptoms.^{2,3} Non-traumatic knee pain is an overall diagnosis of symptoms related to the knee and can consist of different diagnoses, including patellofemoral pain (PFP), tendinitis and osteoarthritis (OA), the incidence of which varies between different age groups.^{2,4} Adolescents and young adults are most likely to suffer from PFP,⁴ whereas OA of the knee is the most frequently reported diagnosis in older patients with knee complaints.³

Figure 1 shows the prevalence of non-traumatic knee complaints for different age categories in Dutch general practice. It can be seen that adolescents have a higher prevalence of non-traumatic knee complaints compared to children and young adults; thereafter there is an increase in the diagnosis of OA.

The knee joint consist of two compartments: the tibiofemoral (TF) and the patellofemoral (PF) compartment. PFP is a condition in adolescents and young adults (aged \leq than 40 years) that involves the PF region and often presents as retro-patellar or peripatellar pain of the knee (pain around the kneecap). The pain usually occurs during activities when load is put on the knee (e.g. ascending or descending stairs, squatting, running, jumping and bicycling). PFP is a diagnosis by exclusion, i.e. a diagnosis reached after elimination of other pathologies related to the anterior part of the knee (e.g. intra-articular pathologies, such as OA, meniscal tears, osteochondritis dissecans, Osgood-Schlatter disease, tendinitis or bursitis). These latter pathologies have more specific signs

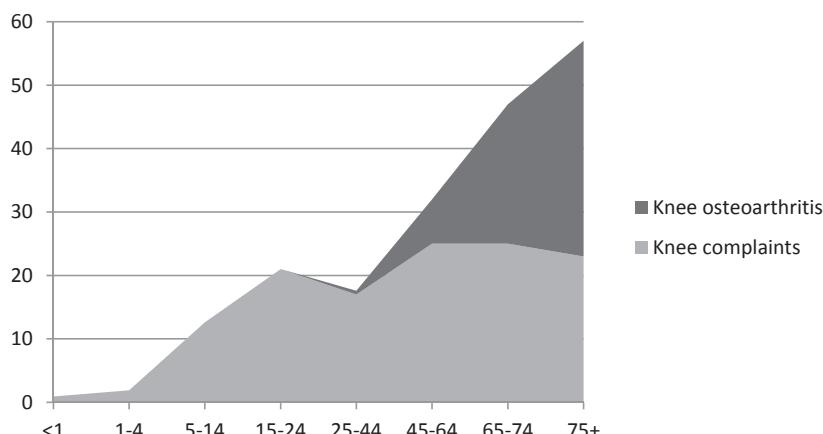


Figure 1. Prevalence of non-traumatic knee pain in Dutch general practice per 1000 persons for different age ranges. Data extracted from van der Linden et al., NIVEL/RIVM, 2004

and symptoms that are easily obtained with a medical history and physical examination. Osgood-Schlatter disease is related to the growth spurt and the pain is most likely to be reported at the tibial tuberosity, which is also enlarged. Bursitis is associated with redness and swelling of the patella and is most often occurs after knee friction due to working on the knees. Intra-articular pathology, such as osteochondritis dissecans and meniscal tears, are associated with loss of smooth passive motion or an inability to fully extend the knee, and 'snapping' of the knee.

Another intra-articular condition that can affect both the TF and the PF joint is knee OA, a progressive and disabling joint disease that has increasing prevalence with age (Figure 1). The diagnosis of OA is mainly based on symptoms (e.g. knee pain, limitation of knee movement, brief morning stiffness, and crepitus), but can also be based on radiographic signs.⁵ Signs of radiographic OA can be scored for different features, such as narrowing of the TF and/or PF joint space, presence of osteophytes, and subchondral sclerosis. If radiographic features of knee OA are present only in the PF joint, this is often described as patellofemoral osteoarthritis (PFOA). In addition, radiographic signs of PFOA are associated with symptoms such as pain and disability.⁶⁻⁹

For patients with PFP, the prevalence and incidence varies in different populations (e.g. athletes, military personnel, or the general population) and the true incidence is unknown.^{2 10-14} In a prospective cohort including military recruits, 15% of the militaries developed PFP after 14 weeks.¹³ However, in midshipmen the incidence of PFP was only 3% after a maximum of 2.5 years follow-up.¹⁵ In a retrospective cohort study among athletes, a prevalence of PFP of 16% was reported.¹² A GP in the Netherlands with a standard practice (\pm 2050 patients) sees on average 10-12 patients with PFP per year.^{4 16} Although the true incidence of PFP is unknown, there is consensus that PFP is a common problem in physically active adolescents and younger adults.¹⁴

For middle-aged patients (aged \geq 40 years) with a recent onset of retropatellar or peripatellar pain, no data are available on the true incidence of PFOA. Most studies evaluating the prevalence and incidence of radiographic PFOA included patients with chronic knee complaints,¹⁷ or a general population without knee symptoms.^{6 18} However, it is suggested that OA in the knee starts in the PF joint and then often progresses to the TF joint.¹⁹

The cause of PFP has been reported to be multifactorial.^{20 21} Various risk factors, and factors associated with PFP, have been suggested, including overuse and trauma.²² Although several reviews have specified factors associated with PFP (e.g. hip muscle weakness, kinematic gait characteristics, vastus medialis obliquus and vastus lateralis timing), there is no overview of all the potential risk factors and factors associated with PFP.²³⁻²⁵ Identification of the risk factors and factors associated with PFP is important, because these factors can be targets of interest for the treatment and prevention of PFP.²⁶

A non-surgical approach, including exercise therapy, foot insoles, orthoses, brace and taping, is the accustomed treatment option for PFP.²⁷ However, there is no consensus about the preferred non-surgical treatment option. Cochrane reviews on patellofemoral taping and orthoses have concluded that the evidence was not robust enough to draw final conclusions.^{28 29} A Cochrane review published in 2003 on the effectiveness of exercise therapy for PFP concluded that there was limited evidence that exercise therapy is more effective compared to no exercise in reducing pain and improving function in PFP.³⁰ However, since publication of this latter review, new randomized controlled trials on the effectiveness of exercise therapy for PFP have been published, indicating that an updated review is needed.

Despite reported limited evidence for the effectiveness of exercise therapy for PFP, many patients continue to have long-term complaints.^{27 31 32} An approach to improve treatment outcomes for patients with PFP might be 'personalized medicine'. For a clinician (especially first-contact practitioners) the identification of specific characteristics of patients that are more likely to respond to exercise therapy is important, because more personalized information can then be given regarding the expected effect of that therapy. Although several factors are reported to be associated with a poorer prognosis of PFP, these prognostic factors are not necessarily treatment effect modifiers.³³ To determine which patients are more likely to benefit from exercise therapy and which patients are not, we need to establish effect modifiers. In addition, this knowledge may also help to decide whether to refer the patient, or start a different or additional therapy in those that are less likely to respond to exercise therapy.

In the past, PFP was usually considered to be a 'self-limiting' disease.³⁴ More recently, however, chronic complaints are reported to be present in 20-91% of patients with PFP.^{27 32 35 36} It is important that first-line healthcare providers (i.e. GPs and physical therapists) gain more insight into the natural course of PFP, as this will help to better inform patients about their prognosis. Moreover, this can help clinicians to identify which patients are at risk to develop chronic PFP complaints. Several factors are associated with a poor prognosis of PFP.³⁷⁻⁴¹ However, most studies investigated prognostic factors for a relatively short period of time, ranging from 3 months to 1 year.^{37-39 41} Only one study on prognostic factors had a 7-year follow-up, but included some patients who had undergone an arthroscopy before start of the study; this is not current practice and could influence the natural course of PFP.⁴⁰ Furthermore, it is proposed that PFP is a precursor to patellofemoral osteoarthritis (PFOA).⁴²⁻⁴⁴ However, longitudinal evidence for a temporal relationship between PFP and PFOA is lacking, particularly with respect to high-quality cohort studies of adequate sample size.

The idea that PFP might be a precursor to PFOA is based on the fact that both conditions involve the patellofemoral joint and share common characteristics in terms of symptoms and biomechanics, such as lower limb malalignment (patella and knee),

hamstring tightness, and reduced quadriceps strength.⁴⁵⁻⁴⁷ However, most OA research that focused on PFOA included relatively older patients with a long duration of knee pain, or focused on the general population without knee pain.^{6 17 19 46 48-50} To date, no data are available on incidence and prevalence rates, and the natural course of PFOA and TFOA, in younger patients with a recent onset of knee complaints.

In the Netherlands, GPs are trained to use guidelines during the medical consultation. These guidelines consist of information covering: background of the condition, risk factors, information on the prognosis, and on therapeutic options. However, in the current guideline for non-traumatic knee complaints (including PFP), information on the aetiology, risk factors, prognosis and best treatment options are incomplete, and based on a very limited numbers of studies.⁴

For this reason, the work presented in this thesis focuses on the aetiology, prognosis and effects of the treatment of PFP.

In summary:

1. No overview is available of all the risk factors for PFP, and the factors associated with PFP.
2. An overview of the effectiveness of exercise therapy for PFP is required.
3. Identification of patients more likely to respond to exercise therapy is necessary, as not all patients seem to benefit from exercise therapy.
4. More insight in the natural course of PFP and its proposed continuum to PFOA is required, as this will help healthcare professionals to better inform their patients about the prognosis.

Therefore, the aim of this thesis is to outline and summarise: i) the risk factors and factors associated with PFP, and ii) the effects (benefits and harms) of exercise therapy aimed at reducing knee pain and improving knee function in patients with PFP, as well as to: iii) identify treatment effect modifiers in order to determine the natural course of PFP and its proposed continuum to PFOA.

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Chapter II

Risk Factors for Patellofemoral Pain Syndrome: A Systematic Review

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J Orthop Sports Phys Ther 2012;42(2):81-A12. doi:10.2519/jospt.2012.3803

Abstract

Study design

Systematic review.

Objectives

To systematically outline the risk factors for patellofemoral pain syndrome (PFPS).

Background

PFPS is the most commonly diagnosed condition in young individuals with knee complaints. High incidence among athletes suggests a possibility of prevention. The first step toward prevention is identification of possible risk factors.

Methods

Prospective studies that included 20 or more patients with PFPS and examined at least 1 possible risk factor for PFPS were included. An assessment list was applied to evaluate the quality of the studies. A meta-analysis was conducted using a random-effects model. Significant differences were based on calculated mean differences, with matching 95% confidence intervals (CIs). For dichotomous data, odds ratios or relative risks were calculated.

Results

Of the 3845 potentially relevant articles, 7 were included in this review. These studies examined a total of 135 variables, and pooling was possible for 13 potential risk factors. The pooled data showed that knee extension peak torques were significantly lower in the PFPS group than in controls. Mean differences in torque, with negative differences reflecting lower means in the PFPS group, were as follows: (a) standardized relative to body weight at 60°/s, -0.24 Nm (95% CI: $-0.39, -0.09$); (b) standardized relative to body weight at 240°/s, -0.11 Nm (95% CI: $-0.17, -0.05$); (c) standardized relative to body mass index at 60°/s, -0.84 Nm (95% CI: $-1.23, -0.44$); (d) standardized relative to body mass index at 240°/s, -0.32 Nm (95% CI: $-0.52, -0.12$); (e) non-standardized in a concentric mode at 60°/s, -17.54 Nm (95% CI: $-25.53, -9.54$); (f) non-standardized in a concentric mode at 240°/s, -7.72 Nm (95% CI: $-12.67, -2.77$).

Conclusion

Weaker knee extension strength, expressed by peak torque, appears to be a risk factor for PFPS, based on meta-analyses of pooled results from multiple studies. Because several other risk factors for PFPS were described only in single studies, these additional risk factors, as well as those with conflicting evidence, need to be confirmed in future studies.

Introduction

Patellofemoral pain syndrome (PFPS) is the most frequently diagnosed condition in patients younger than 50 years with knee complaints. While the general practitioner sees an average of 5 or 6 new patients with PFPS per year, the incidence of PFPS in the general population is still unknown.¹⁻² Women have a higher incidence of PFPS than men,³ and incidence rates of 25% to 43% have been reported in sports medicine and during basic military training.

The term patellofemoral pain syndrome is commonly used to describe a condition of anterior knee pain. Although there is no consensus on the terminology, various synonyms are used for PFPS.⁴ The guidelines of the Dutch College of General Practitioners describe PFPS as a pain in or around the patella. This pain increases after prolonged sitting, squatting, kneeling, and stair climbing.⁵ The term anterior knee pain covers all problems related to the anterior part of the knee. By excluding anterior knee pain due to intra-articular pathology, plica syndromes, Sinding-Larsen-Johansson disease, Osgood-Schlatter disease, bursitis or tendinitis, neuroma, and other rare pathologies, the remaining patients with a clinical presentation of anterior knee pain can be diagnosed with PFPS.⁶

The cause of patellofemoral pain has been reported to be multifactorial.⁶⁻⁷ Various risk factors for PFPS have been suggested, including onset timing of vasti muscles, structural abnormalities, muscle strength, and kinematic variables.⁸⁻¹⁴ However, there are discrepancies in findings among studies, as exemplified by 2 studies⁸⁻¹¹ investigating the quadriceps angle (Q-angle) as a possible risk factor. One of these studies¹¹ found a significantly larger Q-angle in individuals with PFPS than in those of a control group,¹¹ whereas the other study⁸ found no significant difference between groups. Such a discrepancy in findings also has been seen for other factors, such as the onset timing of vasti muscles⁹ and muscle strength.⁶ Other frequently cited causes for PFPS are overuse and trauma.¹⁵ However, the majority of patients with PFPS have no history of trauma.¹⁶ A brief period of overuse of the patellofemoral joint or an increase in physical activity is reported in almost all patients with PFPS.¹⁷⁻¹⁸

Because of the high incidence of PFPS, prevention is important. The first step toward prevention is identification of possible risk factors or factors associated with PFPS. Because no systematic review has been performed to summarize and outline the risk factors for PFPS, this study will systematically outline those risk factors.

Methods

Criteria for considering studies in this review

Type of Studies

Prospective cohort studies, written in English, German, French, Swedish, or Dutch, that included a minimum of 20 patients with PFPS, were eligible.

Type of participants

Adolescents and adults with PFPS who had not received operative treatment or arthroscopy were included. Due to the lack of consistent terminology for PFPS, all definitions for PFPS and its synonyms were accepted. Patients with chondromalacia patella were included if the authors intended chondromalacia patella to be a description of PFPS. Studies focusing on other knee pathologies, such as Osgood-Schlatter disease, Sinding-Larsen-Johansson disease, tendinitis or bursitis, neuromas, intra-articular pathologies, plica syndromes, and more rarely occurring pathologies were excluded. No limitations on age and setting were applied.

Type of measurement

Only studies including at least 1 possible risk factor for PFPS were included.

Search for relevant studies

The primary search was conducted in PubMed, EMBASE, Web of Science, and the Cochrane Central Register up to November 3, 2010. The following key words were used for PFPS: arthralgia AND knee joint OR anterior knee pain OR (patell* OR femoropatell* OR femoro-patell* OR retropatell*) AND (pain OR syndrome OR dysfunction). Key words used for risk factors were as follows: risk factor OR association OR relative risk OR odds ratio. APPENDIX A presents the full PubMed, EMBASE, and Web of Science search terms.

Data collection and analysis

Selection of studies

Two reviewers (N.E.L. and M.M.) independently selected articles, based on their title and abstract, following the selection criteria. For the selected references, a final decision about inclusion was made based on the full-text articles. These articles were reviewed independently. If there was a disagreement, the criteria for inclusion were discussed until consensus was reached. Methodological Quality A quality assessment list was created using criteria from the Dutch Cochrane Centre (<http://www.cochrane.nl/en/index.html>), the Newcastle-Ottawa Scale, and work by van Rijn et al¹⁹ and van Tulder et al.²⁰

Table 1 Quality assessment list

Criteria for quality score	
Study population	
1 Study groups are clearly defined	Positive if truly or somewhat representative of the average population with PFPS (females>males, athletes, primary or secondary care). Studies scored also positive if they only included women, because PFPS is more common in women than in man.
2 Number of cases ≥ 50	Positive if the total number of cases was ≥ 50
3 Adequacy of follow up of cohorts	Positive if complete follow up: all subjects accounted for and positive if subjects lost to follow up: unlikely to introduce bias, number lost < 20% in 3 months or description of those lost suggesting no different from those followed.
4 Comparable groups	Positive if the study controls are comparable for age and gender
Study design	
5 Prospective cohort studies	Positive if the study design was a prospective cohort study
6 Inclusion and exclusion criteria	Positive if inclusion and exclusion criteria were described. Inclusion: a clear definition of PFPS: At least 1 criterion for PFPS. Exclusion: a clear definition of the exclusion criteria
7 Follow-up period ≥ 6 months	Positive if follow-up period was ≥ 6 months
Assessment of outcome	
8 Definition of determinant and outcome	Positive if a clear definition of determinant and outcome was described
9 Assessment method	Positive if the assessment method was suitable
Analyzing and data presentation	
10 Data presentation	Positive if risk estimates were presented or when raw data were given that allow the calculation of risk estimates, such as: odds ratio or relative risks
11 Consideration of confounders	Positive if the confounders that were considered were described
12 Control for confounding	Positive if the method used to control for confounding was described

Abbreviations: PFPS, patellofemoral pain syndrome

Table 1 lists the criteria for the quality score, divided into 4 topics with 12 total items. The same 2 reviewers independently assessed the quality of the studies by scoring each criterion as "positive," "unclear," or "negative." Criteria scored as positive received 1 point, and those scored as negative or unclear received no points. Disagreements were solved by discussion, and Cohen kappa was calculated to measure inter-rater agreement. The quality score of each study was calculated by summing the total number of positive criteria.

Data extraction

One reviewer extracted relevant data from the publications. Information on study design (type of study, author, and year of publication), study population (number of cases/controls enrolled and analyzed), group characteristics (gender, age, and definition of PFPS), follow-up, loss to follow-up, definition of the determinants, and assessment method was extracted using a standardized form. When possible, the mean differences (MDs), with matching 95% confidence intervals (CIs), were extracted or calculated from the original studies. Other comments that could not be matched within any of the items described above and were judged to be possibly important for this review were noted.

Statistical analysis

A meta-analysis was performed to establish risk factors that had a consistent definition and results reported for the same outcome measures.²³ Statistical heterogeneity was tested with the chi-square and I^2 tests. We chose a random-effects model to inspect the forest plot. A weighted mean difference (WMD), with matching 95% CI, was calculated for the pooled data. For the meta-analysis, the software package Review Manager 5 (Nordic Cochrane Center, Copenhagen, Denmark) was used. If meta-analysis was not possible due to clinical heterogeneity, data were analyzed descriptively. For the articles that supplied adequate data, the MD with matching 95% CI was calculated. For dichotomous data, odds ratios (ORs) or relative risks (RRs) with matching 95% CIs, were calculated or abstracted from the individual study. If separate data were present for both limbs, only the data from the symptomatic limb in the symptomatic group were extracted. In the control group, random data from 1 limb were extracted. Significant differences were based on calculated MDs with matching 95% CIs. If studies did not provide sufficient information to calculate the 95% CIs, information on significant differences ($P < .05$) between the groups were extracted from the studies.

Results

Characteristics of included studies

The database search resulted in 3845 potentially relevant articles. From titles and abstracts, 167 articles were extracted for full-text review (this was not possible for 3 articles). A total of 7 studies met the inclusion criteria.^{12 20-26} Thirty-seven retrospective case control studies were excluded from this review. Because Boling et al^{21 27} published 2 articles with identical data, combined information was used for the quality measurement and data extraction. However, only the most prominent article was used for citation of these studies. Figure 1 shows the process of identifying the relevant studies. The period of follow-up ranged from 6 weeks to 3 years. The number of patients included in

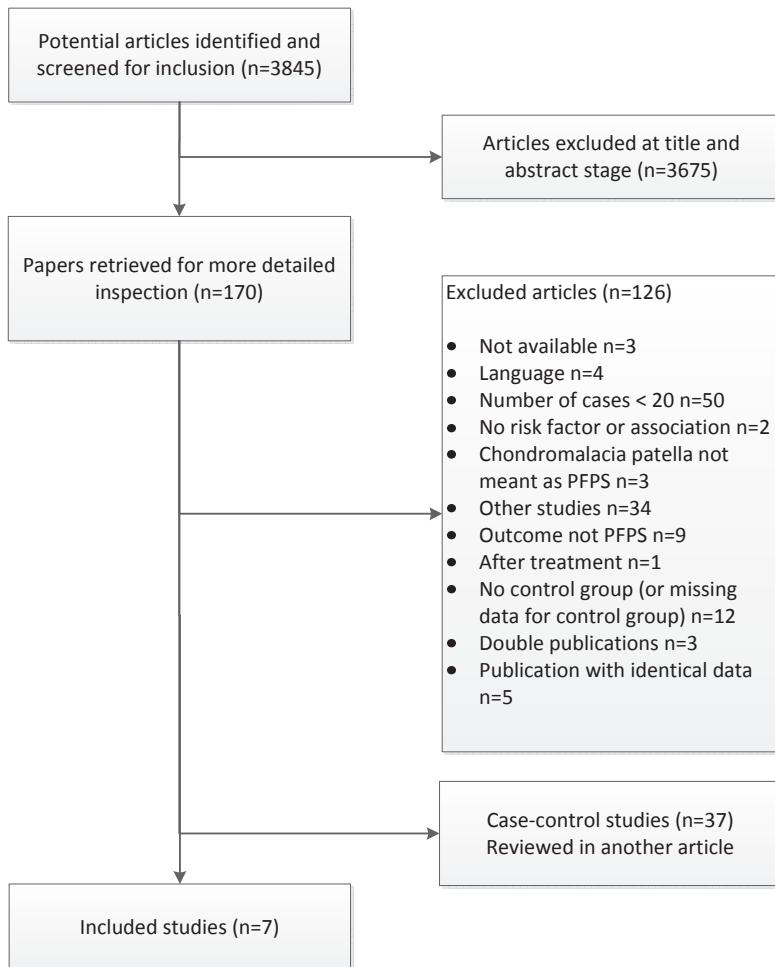


Figure 1 Flow-chart of the process to select the relevant studies

the studies ranged from 24 to 60, with a total of 243 patients with PFPS. Three studies included only male cadets or male infantry recruits.^{12 24 25} One study investigated only military females.²² Two studies examined cadets of both genders.^{21 23} One study tested students of both genders who were taking physical education classes (appendix B).²⁶

Methodological quality

Table 2 presents data on the methodological quality of the included studies. The reviewers agreed on 88% of the items among the 7 included studies (74 of 84 items, Cohen's kappa = 0.75). All initial disagreements were discussed until consensus was reached. One study included more than 50 patients with PFPS.¹² Only 2 studies included nonmilitary recruits (ie, subjects more representative of the average population), had a follow-up

duration of 6 months or more, considered possible confounders, and described the method applied to control for confounding.^{21 26}

Table 2 Methodological quality

Author, year of publication	Criteria for quality score												Total
	1	2	3	4	5	6	7	8	9	10	11	12	
Boling, 2010*	1	0	?	1	1	1	1	1	1	1	1	1	10
Duvigneaud, 2008	0	0	1	?	1	1	0	1	1	1	0	0	6
Milgrom, 1991	0	1	1	?	1	0	0	1	1	1	0	0	6
Thijs, 2007	0	0	1	1	1	1	0	1	1	1	0	0	7
Van Tiggelen, 2009	0	0	1	1	1	1	0	1	1	1	1	0	8
Van Tiggelen, 2004	0	0	1	1	1	1	0	1	1	1	0	0	7
Witvrouw, 2000	1	0	0	?	1	1	1	1	1	1	1	1	9

* 2 both studies from Boling et al

Risk factors

Demographics

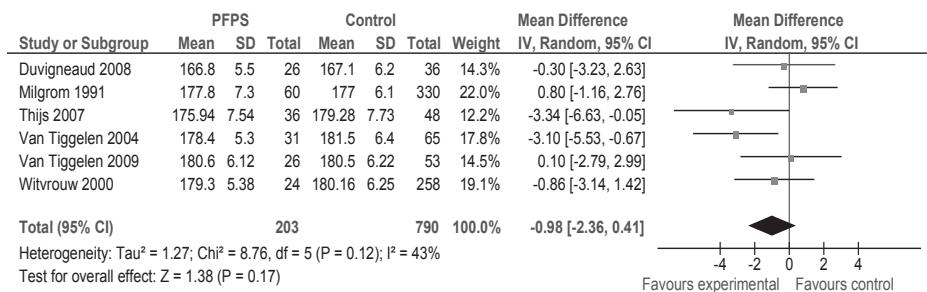
Ten anthropometric variables were considered in the included studies. Pooling of data was possible for height, body weight, body mass index (BMI), and age (Figures 2-5); none attained statistical significance.^{12 22-26} One study determined that females were at higher risk for the development of PFPS (OR: 2.23; 95% CI: 1.16, 4.10).²¹

Psychological parameters

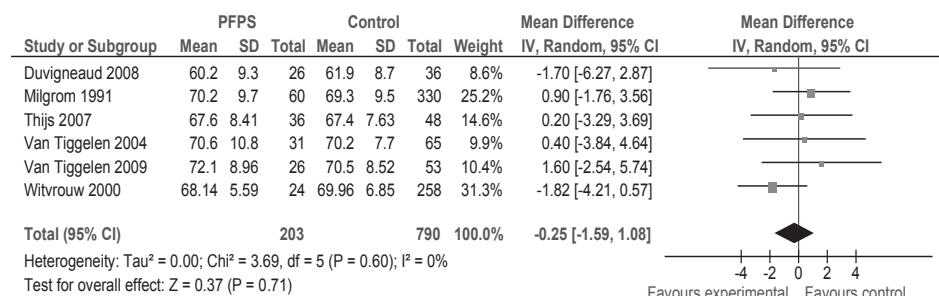
Seven psychological parameters for coping-behavior mechanisms were described in 1 study.²⁶ A significantly lower value for "looking for social support" was reported for those individuals who later developed PFPS compared to the control group (MD, -1.78; 95% CI: -3.44, -0.12).²⁶ Appendix C (available online http://www.jospt.org/doi/full/10.2519/jospt.2012.3803#.VO2qK_mG-Ps) presents all studied risk factors.

Physical Fitness

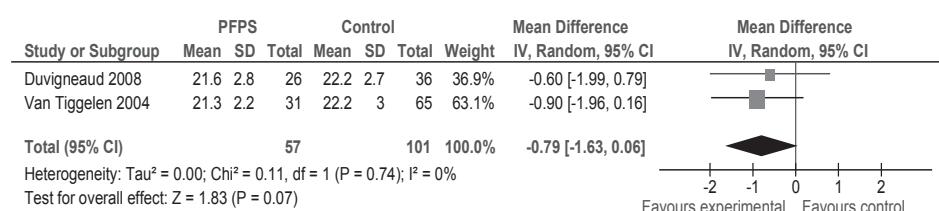
In 3 articles, data for 18 variables for physical fitness were reported.^{12 22 26} A significant difference was found for 1 variable in each study. Individuals in the control group participated in sports more hours per week compared to those who eventually developed PFPS (MD, -2.38; 95% CI: -4.03, -0.73),²² individuals who developed PFPS were able to perform a higher number of push-ups compared to controls (MD, 1.60; 95% CI: 0.22, 2.98),¹² and controls accomplished a higher vertical jump compared to those who developed PFPS in the future (MD, -3.39; 95% CI: -5.95, -0.83).²⁶

**Figure 2** Forest plot: Association between future PFPS and height (cm)

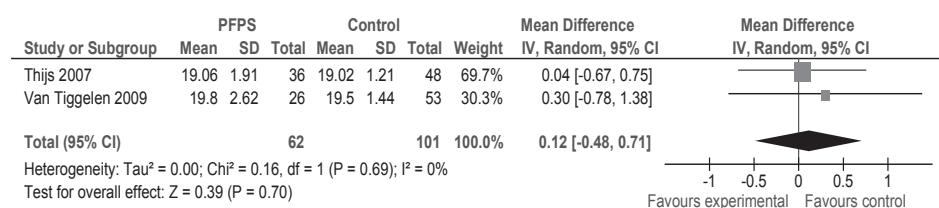
Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome.

**Figure 3** Forest plot: Association between future PFPS and body weight (kg)

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome.

**Figure 4** Forest plot: Association between future PFPS and body mass index (kg/m²)

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

**Figure 5** Forest plot: Association between future PFPS and age (y)

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

Joint angles

Eight different variables were measured in 3 studies for hip, knee, and Q-angles.^{12 21 26} Pooling was possible for the Q-angle, and no significant difference between the PFPS and control groups was found (WMD, -0.26; 95% CI: -1.93, 1.41) (Figure 6).^{21 26} No significant differences between the 2 groups were found for hip and knee angle variables.^{12 21 26}

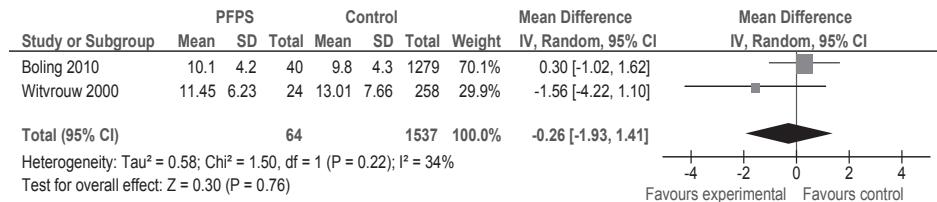


Figure 6 Forest plot: Association between future PFPS and Q-angle (°)

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

Posture

Seven posture variables were described in 3 studies.^{12 21 26} A larger medial tibial intercondylar distance was a significant risk factor for PFPS in 1 study (MD, 1.50; 95% CI: 0.60, 2.40).²² Navicular drop was significantly higher in future PFPS patients compared to controls (MD, 0.90; 95% CI: 0.04, 1.76).²¹ Patella Medial, lateral, and total patellar mobility were described in 1 study and were not significantly associated with developing PFPS in the future.²⁶

Vertical ground reaction force

Vertical ground reaction force was evaluated in 1 study and was significantly lower in the PFPS group (MD, -0.30; 95% CI: -0.58, -0.02).²¹

Plantar Pressure

Thijs et al.²³ described 37 variables for plantar pressure measurement during barefoot walking as possible causes of PFPS. Only 2 of these variables showed a significant difference between both groups. A slower maximal velocity of the change in the center of pressure in the lateromedial direction during the forefoot contact phase was significantly associated with individuals developing PFPS in the future (MD, -30.29; 95% CI: -46.01, -14.57). Also, during the forefoot contact phase, the mediolateral component of the center of pressure was more laterally directed to the heel-metatarsal II axis in future PFPS patients than in controls, who had a more medially directed mediolateral component relative to the heel-metatarsal II axis (MD, -0.67; 95% CI: -1.29, -0.04).

Electromyographic onset timing of vastus medialis obliquus (VMO) and vastus lateralis (VL)

Five variables for electromyographic onset timing of VMO and VL were described in 2 studies.^{24,26} Four variables were significantly different between groups.^{24,26} The onset timing of VMO before VL took place in 80% of controls, whereas this was the case in 42.3% of future patients with PFPS ($P < .001$).²⁴ However, the onset timing (milliseconds) of VMO before VL was not significantly associated with future patients with PFPS in 1 study (MD, -0.25 ; 95% CI: -0.33 , 0.83).²⁶ Onset of electromyographic VMO/VL activity (milliseconds) in patients with PFPS showed a significant alternation in onset timing compared to controls (MD, 6.53 ; 95% CI: 5.64 , 7.42).²⁴ In 1 study, faster reflex response times (milliseconds) of VMO and VL were seen in future individuals with PFPS (MD, -1.11 ; 95% CI: -2.04 , -0.18 and -1.36 ; 95% CI: -2.25 , -0.47 , respectively).²⁶

Flexibility

Flexibility of the hamstring, quadriceps, and gastrocnemius was considered in 1 study. Less gastrocnemius and quadriceps flexibility was significantly associated with future PFPS (MD, -3.10 ; 95% CI: -5.83 , -0.37 and -7.59 ; 95% CI: -14.35 , -0.83 , respectively).²⁶

General joint laxity

Witvrouw et al.²⁶ measured 5 variables reflective of general joint laxity. A greater range of motion for thumb-forearm mobility (MD, 18.41 ; 95% CI: 12.74 , 24.08) and knee extension mobility (MD, 3.68 ; 95% CI: 1.29 , 6.07), and a lower range of motion for elbow extension mobility (MD, -2.04 ; 95% CI: -3.80 , -0.30) were significantly associated with future occurrence of PFPS.

Strength

Eight variables for muscle strength (expressed in Newtons) were evaluated in 2 studies.^{12,21} Four variables for hip muscle strength were evaluated in 1 study, but none were significantly associated with future occurrence of PFPS.²¹ Two variables for quadriceps strength were described by Milgrom et al¹² and showed that higher isometric quadriceps strength was a risk factor for PFPS (MD, 24.60 ; 95% CI: 0.69 , 48.51); however, in the same study, quadriceps strength expressed as a function of body weight was not significantly associated with the future development of PFPS. Less knee extension strength was a significant risk factor for future PFPS in another study (MD, -0.06 ; 95% CI: -0.10 , -0.02).²¹

Joint moments

Boling et al²¹ measured 4 lower extremity joint moments, expressed as percentage body weight times height during jumping: hip abduction, hip external rotation, knee varus, and knee extension. None were significantly associated with future PFPS.

Peak torques

Three studies evaluated multiple variables of peak torques of the knee extensors and flexors during isokinetic tests (expressed in Newton meter), as a measure of muscle strength.^{22 25 26} Pooling was possible for 8 variables (Figures 7-14).^{22 25} The pooled data for concentric peak torque of the knee extensors during isokinetic testing relative to body weight, measured at 60°/s and 240°/s, were significantly lower in the group of patients who later developed PFPS than in controls (WMD, -0.24; 95% CI: -0.39, -0.09 and -0.11; 95% CI: -0.17, -0.05, respectively) (Figures 7 and 8). A lower relative concentric peak torque for the knee extensors relative to BMI, measured at 60°/s and 240°/s, was also significantly associated with future PFPS (WMD, -0.84; 95% CI: -1.23, -0.44 and -0.32; 95% CI: -0.52, -0.12, respectively) (Figures 9 and 10). Pooled data showed

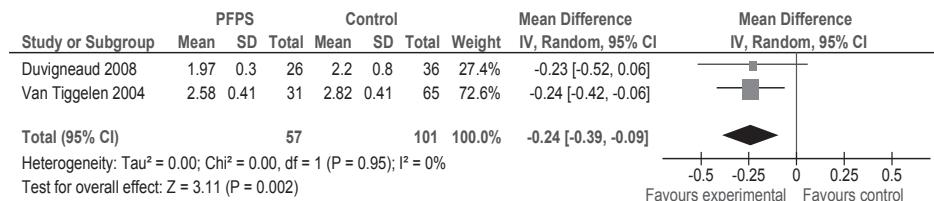


Figure 7 Forest plot: Association between future PFPS and relative knee extensors peak torque (Nm) to body Weight at 60°/s in a concentric mode.

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

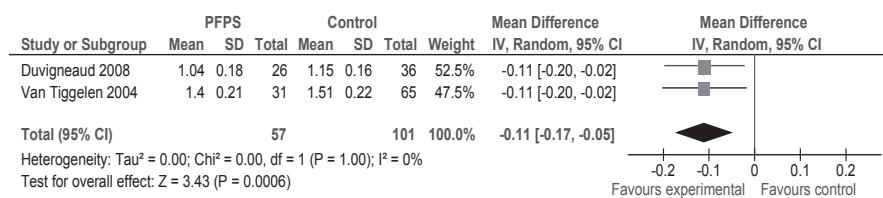


Figure 8 Forest plot of the association between future PFPS and knee extensors peak torque (Nm) relative to body weight at 240°/s in a concentric mode.

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

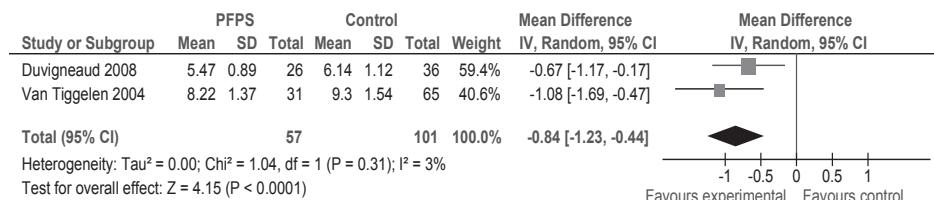


Figure 9 Forest plot of the association between future PFPS and knee extensors peak torque (Nm) relative to body mass index (kg/m²) at 60°/s in a concentric mode.

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

that concentric peak torques for the knee flexors, when measured at 60°/s and 240°/s, were not associated with future PFPS (WMD, -1.80; 95% CI: -7.65, 4.06 and -1.34; 95% CI: -5.39, 2.72, respectively) (Figures 11 and 12). Lower concentric peak torques for the knee extensors, measured at 60°/s and 240°/s, were statistically significant risk factors for future PFPS (WMD, -17.54; 95% CI: -25.53, -9.54 and -7.72; 95% CI: -12.67, -2.77, respectively) (Figures 13 and 14). Duvigneaud et al²² evaluated additional variables related to peak torques. The concentric flexor-extensor peak torque ratios measured at 60°/s and 240°/s were significantly higher in those with future PFPS compared to those in the control group (MD, 0.06; 95% CI: 0.01, 0.11 and 0.07; 95% CI: 0.01, 0.13, respectively), but no difference between groups was found for both flexor and extensor peak torque values measured at 30°/s in an eccentric mode. Due to missing data (mean and SD) for the 6 variables related to peak torques reported in the study by Witvrouw et al,²⁶ these

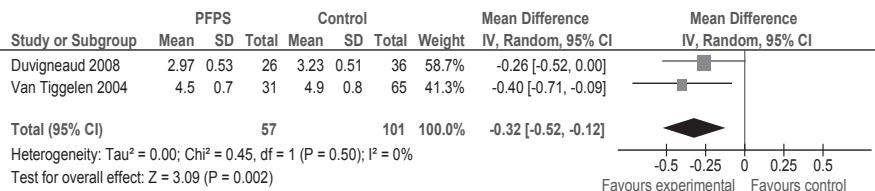


Figure 10 Forest plot of the association between future PFPS and knee extensors peak torque (Nm) relative to body mass index (kg/m^2) at 240°/s in a concentric mode.

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

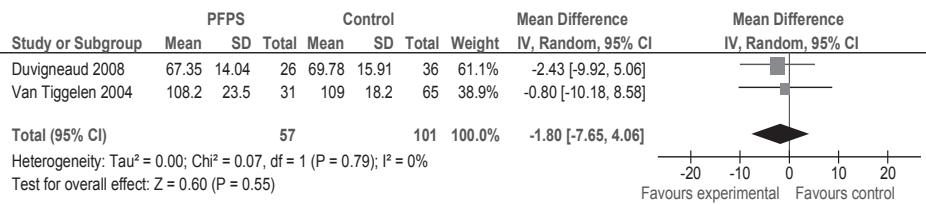


Figure 11 Forest plot of the association between future PFPS and knee flexors peak torque (Nm) at 60°/s in a concentric mode.

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

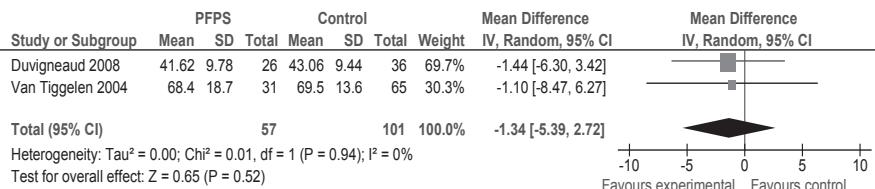


Figure 12 Forest plot of the association between future PFPS and knee flexors peak torque (Nm) at 240°/s in a concentric mode.

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

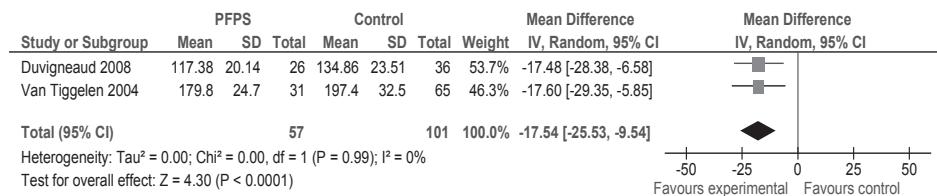


Figure 13 Forest plot of the association between future PFPS and knee extensors peak torque (Nm) at 60°/s in a concentric mode.

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

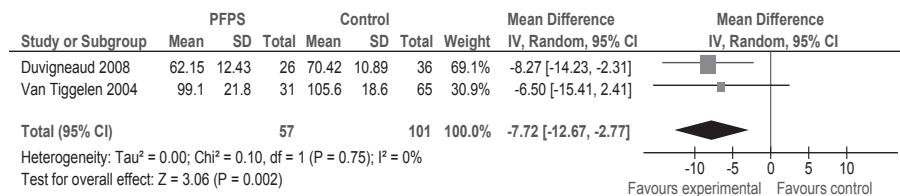


Figure 14 Forest plot of the association between future PFPS and knee extensors peak torque (Nm) at 240°/s in a concentric mode.

Abbreviations: CI, confidence interval; PFPS, patellofemoral pain syndrome

data could not be pooled. Although Witvrouw et al²⁶ found no significant differences between those who later developed PFPS and controls for the 6 evaluated variables, a positive trend was indicated by a lower concentric peak torque for the quadriceps muscles (extensors) in individuals with future PFPS compared to controls.

Discussion

This review examined risk factors for PFPS. The 7 included prospective studies evaluated 135 variables as potential risk factors for PFPS. This number of variables is noteworthy, because only 243 patients with PFPS were included in these 7 studies. None of the studies adhered to “the rule of 10,” which suggests that at least 10 individuals with PFPS should have been included for each predictive variable considered.²⁸ Pooling was possible for 13 variables (height, weight, BMI, age, Q-angle, and 8 measurements of knee strength, expressed as peak torque for the extensors or flexors). The results of these meta-analyses indicate that less knee extension strength is significantly associated with a higher risk for future PFPS. It is noteworthy that most evaluated risk factors in the 7 studies were biomechanical and neuromuscular risk factors and not structural (static) risk factors. Structural anomalies and lower extremity malalignment are often examined as associative factors for PFPS in case-control studies.^{14,29-32}

In the literature, female gender is often suggested to be a risk factor for PFPS.^{3 7 15 26} Findings of 1 prospective study included in this review support the notion that females are at higher risk for PFPS than males.

Similarly, the magnitude of the Q-angle is often suggested to be an etiological factor for PFPS, with those with a greater Q-angle being more prone to develop PFPS; but evidence for this association is lacking in the literature.^{4 6 15 32-34} The Q-angle was only considered as a potential risk factor in 2 prospective studies; after pooling, no significant difference was found between those with future PFPS and controls.^{21 26} This suggests that the Q-angle may not play a significant role in the pathogenesis of PFPS.

Contradictory findings were found for onset timing of VMO before VL in 2 studies.^{24 26} In 1 study, onset timing of VMO occurred before VL in 80% of controls, compared to 42.3% of individuals with future PFPS²⁴; these findings are in contrast to the other study, in which no significant difference in VMO-VL onset timing was found between groups.²⁶ However, in that second study, individuals with future PFPS had a significantly faster reflex response time of both VMO and VL compared to controls.²⁶ Due to methodological differences and different end points, pooling for this risk factor was not possible.^{24 26} Therefore, it remains unknown whether delayed onset timing of VMO relative to VL is a risk factor for PFPS. This is in agreement with an earlier review that showed no association between onset timing of vasti muscles and PFPS.⁹

Pooled data of 2 prospective studies^{22 25} showed that the peak torque for the quadriceps muscles is lower in individuals with future PFPS, and, although not significant, a positive trend toward a lower peak torque for the quadriceps of individuals with future PFPS was also found in 1 study.²⁶ It was not possible to pool these studies because no data were provided by Witvrouw et al.²⁶ However, because lesser strength of the knee extensors (quadriceps) appears to be a risk factor for developing PFPS in the future, it could be suggested that strength training may be an effective approach to reducing the incidence of PFPS, especially among athletes and military recruits, who have short periods of overuse. The potential of strengthening exercises for prevention appears to have some support, based on a randomized controlled trial showing the efficacy of a supervised exercise therapy program, including quadriceps training, for the treatment of PFPS.³⁵

The protective role of prior sport participation (ie, more hours of sport participation before starting basic military training) could be explained by the greater quadriceps strength in individuals with a higher amount of sport participation.²² Nevertheless, 1 study found no significant association between physical fitness before the start of physical education classes and the incidence of future PFPS.²⁶ This could be explained by the difference in follow-up duration; at a 2-year follow-up, the effect of physical fitness measured 2 years earlier may not be expected to influence the development of PFPS.²⁶ It is more likely that the effect of the number of hours of sport participation and strength of the quadriceps is still present after a follow-up of 6 weeks.²²

Two recent articles examined prevention programs for PFPS occurring during military training.^{36 37} The positive results for the standardized exercise program in 1 study³⁶ are consistent with the findings of this review (ie, strengthening and flexibility exercise of the quadriceps muscles could lead to reduction in incidence of PFPS). The positive effects of prevention programs for military recruits^{36 37} and of treatment programs for the general population^{35 38} suggest the effectiveness of such programs. These prevention programs should aim at high-risk groups, such as military recruits and athletes. However, because several significant risk factors were identified from the results of single studies, more research is needed to further delineate these potential risk factors for PFPS before prevention programs can be developed further and implemented.

Limitations

The 7 prospective studies included 243 patients with PFPS. We decided to include prospective studies only, because the primary aim of this study was to identify risk factors for PFPS. Case control studies are merely focused on the etiology of PFPS and were, therefore, excluded from this review. A total of 135 variables were used to investigate the risk factors. None of the included articles in this review adhered to the “rule of 10,” which can lead to overfitting (type I error) of the data.²⁸ By overfitting, an unimportant variable could be presented as an important predictive factor.³⁹ For instance, in 1 study of 36 participants who developed PFPS, 37 variables were examined to determine gait-related risk factors for PFPS. Of those 37 variables, only 2 showed a significant difference between individuals with and without future PFPS.²³ Given a *P* value of less than .05 for each variable, these findings could be merely statistical coincidence. This problem can be solved by examining fewer risk factors within 1 study or adjusting the level of significance to a lower *P* value. Due to the lack of a clear definition of and inclusion/exclusion criteria for PFPS,⁴ the selection of patients in the 7 studies was not truly comparable. One study provided no clear definition of the inclusion and exclusion criteria¹²; this may explain, in part, the lack of agreement among studies.

Lack of agreement among studies also may be explained by differences in the variables considered and the measurement methods used. Furthermore, only 2 of the 7 studies were somewhat representative of the general population with PFPS seen in general practice and sports medicine (ie, adolescents and adults, mainly females and athletes with PFPS).^{21 26} Pooling was possible for 13 variables due to the number of studies investigating risk factors and the variance in risk factors tested in the included studies. Such heterogeneity and type I errors make it difficult to determine the possible risk factors for PFPS and extrapolate these results to the general population with PFPS. Nevertheless, this is the first review of risk factors for PFPS to provide a systematic overview of the risk factors examined in published studies that used a prospective research design.

Conclusion

Results of this study show that being female and having lower knee extension strength (for both men and women) may be risk factors for the future development of PFPS. Because several risk factors for PFPS were described in single studies, these risk factors and other risk factors with conflicting evidence need further investigation in a variety of populations known to have high incidence of PFPS.

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Appendix A

Pubmed search:

((patellofemoral pain*[tw] OR patellofemoral syndrom*[tw] OR patello-femoral pain*[tw] OR patello-femoral syndrom*[tw] OR anterior knee pain*[tw] OR patello-femoral disorder*[tw] OR patello-femoral disorder*[tw]) OR ((arthralg*[tw] OR pain*[tw]) AND (knee joint[mesh] OR knee*[tw] OR patell*[tw] OR femoropatell*[tw] OR femoro-patell*[tw] OR retropatell*[tw] OR retro-patell*[tw] OR lateral facet*[tw] OR lateral compr*[tw] OR lateral press*[tw] OR odd facet*[tw] OR genu[tw]) AND (syndrom*[tw] OR dysfunct*[tw] OR disorder*[tw] OR chondromal*[tw] OR chondropath*[tw]))) AND (associat*[tw] OR risk*[tw] OR probabil*[tw] OR odds*[tw] OR relat*[tw] OR prevalen*[tw] OR predict*[tw] OR caus*[tw] OR etiol*[tw] OR interact*[tw]))

EMbase

((('patellofemoral pain':ti,ab,de OR 'patello-femoral pain':ti,ab,de OR 'anterior knee pain':ti,ab,de) OR ((patellofemoral OR 'patello-femoral' OR 'anterior knee') NEAR/3 (syndrom* OR disorder*)):ti,ab,de) OR (((arthralg* OR pain*) NEAR/4 (syndrom* OR dysfunct* OR disorder* OR chondromal* OR chondropath*)):ti,ab,de AND (knee* OR patell* OR femoro* OR retropatell* OR 'retro-patellar' OR 'lateral facet' OR 'lateral compression' OR 'lateral pressure' OR 'odd facet' OR genu):ti,ab,de)) AND (associat*:ti,ab,de OR risk*:ti,ab,de OR probabil*:ti,ab,de OR odds*:ti,ab,de OR relat*:ti,ab,de OR prevalen*:ti,ab,de OR predict*:ti,ab,de OR caus*:ti,ab,de OR etiol*:ti,ab,de OR interact*:ti,ab,de))

WoS

((patellofemoral OR "patello-femoral" OR "anterior knee") AND (pain* OR syndrom* OR disorder*)) OR ((arthralg* OR pain*) AND (knee* OR patell* OR femoropatell* OR retropatell* OR "retro-patellar" OR "lateral facet" OR "lateral compression" OR "lateral pressure" OR "odd facet" OR genu) AND (syndrom* OR dysfunct* OR disorder* OR chondromal* OR chondropath*)) AND (associat* OR risk* OR probabil* OR odds* OR relat* OR prevalen* OR predict* OR caus* OR etiol* OR interact*)

Appendix B

Description of study characteristics

Author, year of publication	Boling et al, 2010*
Study design, follow up	Prospective Follow up: 1-3y
Participants description	<p>N=1597 midshipmen from the United States Naval Academy were enrolled.</p> <p>Class of 2009: 438 participants 43% females baseline 2005; follow up duration: 2.5 y for the individuals who did not develop PFPS</p> <p>Class of 2010: 525 participants 42% females baseline 2006; follow up duration: 1.5 y for the individuals who did not develop PFPS</p> <p>Class of 2011: 562 participants: 35% females baseline 2007</p> <p>Follow up duration: 0.5 y for the individuals who did not develop PFPS</p> <p>No patients with a history of PFPS in the previous 6 months.</p> <p>72 did not complete 1 or more of the baseline testing stations</p> <p>206 had a history of PFPS in the previous 6 months</p> <p>Cases: 40 (60% females)</p> <p>Controls: 1279 (38% females)</p>
Description of outcome	<p>Retropatellar knee pain during at least 2 of the following activities: ascending/descending stairs, hopping/jogging, prolonged sitting, kneeling, and squatting.</p> <p>Negative findings on examination of knee ligament, menisci, bursa, and synovial plica</p> <p>Must demonstrate of the following during evaluation:</p> <p>pain on palpation of medial or lateral patellar facets or pain on palpation of the anterior portion of the medial or lateral femoral condyles</p>
Description of determinants	<ul style="list-style-type: none"> - Association between the incidence of PFPS and gender: investigated using Poisson regression. - Hip flexion angle (°) - Hip adduction angle (°) - Hip internal rotation angle (°) - Knee valgus angle (°) - Knee internal rotation angle (°) - Vertical ground-reaction force (%BW) - Hip abduction moment (%BWxht) - Hip external rotation moment (%BWxht) - Knee extension moment (%BWxht) - Knee flexion strength (%BW) - Knee extension strength (%BW) - Hip extension strength (%BW) - Hip internal rotation strength (%BW) - Hip external rotation strength (%BW) - Hip abduction strength (%BW) - Q-angle (°): standing position, using a standard goniometer, average of 3 measurements - Navicular drop (mm): difference between the navicular tuberosity height in a nonweightbearing subtalar joint neutral position and a weightbearing position, average of 3 measurements - Gender - External Sports participation - Competitive sport participation
Notes	*Both studies from Boling et al

Author, year of publication	Duvigneaud et al, 2008
Study design, follow up	Prospective, 6 weeks
Participants description	N=62 (100% females); Age range: 18y to 34y Cases: 26 (42%) Mean (SD) Height: 166.8 cm (5.5), Weight: 60.2kg (9.3), BMI: 21.6 kg/m ² (2.8) Controls: 36 (58%) Mean (SD) Height: 167.1 cm (6.2), Weight: 61.9 kg (8.7), BMI: 22.2kg/m ² (2.7)
Description of outcome	PFPS: retropatellar knee pain during at least 2 of the following activities: jumping/hopping, squatting, stairs, and running. Exhibit 2 of the following clinical criteria on assessment with a minimal VAS of 3/10: Pain on direct compression of the patella against the femoral condyle with full knee extension; tenderness on palpation of the posterior surface of the patella; pain on resisted knee extension (90° of flexion to 0°); pain during isometric quadriceps contraction against suprapatellar resistance with the knee in 15° of flexion
Description of determinants	- Anthropometric data: height, weight, and BMI - Peak torque (Nm) of the knee flexors and extensors at 60°/s and 240°/s in concentric mode. - Peak torque (Nm) of the knee flexors and extensors at 30°/s in eccentric mode - Peak torque knee extensors/BMI at 60°/s and 240°/s in a concentric mode - Peak torque knee extensors/body weight at 60°/s and 240°/s in a concentric mode - Peak torque knee flexors/peak torque knee extensors at 60°/s and 240°/s The Cybex Norm® with a single resistance pad was used to measure the isokinetic peak torques of the knee flexors and extensors. - Sports participation - Single leg hop test
Notes	Only military females
Author, year of publication	Milgrom et al, 1991
Study design, follow up	Prospective, 14 weeks
Participants description	N=390 male infantry recruits Cases: 60 ; Mean (SD) Height: 177.8cm (7.3), Weight: 70.2kg (9.7) Controls: 330; Mean (SD) Height: 177.0cm (6.1), Weight: 69.3kg (9.5)
Description of outcome	Pain in the knee, specifically anteriorly
Description of determinants	- Anthropometric data: height and weight - External rotation of hip (°) - Thigh circumference (mm) - Calf circumference (mm) - Medial tibial intercondylar distance (cm) - Tibial length (mm) - Lower limb length (mm) - Foot width (mm) - Foot length (mm) - Isometric strength of quadriceps at 85° of knee flexion (N) - Quadriceps strength/body weight - 2 km run (sec) - Push-ups (no) - Sit-ups in 60 sec (no)
Notes	Only male infantry recruits

Author, year of publication	Thijs et al, 2007
Study design, follow up	Prospective cohort study, 6 weeks
Participants description	<p>N=84 (23% females) officer cadets Mean (SD) age: 19y (1.54), Height: 177.9cm (7.78), Weight: 67.5kg (7.92)</p> <p>Cases: 36 (31% females) Mean (SD) age: 19.06 y (1.91), Height: 175.94 cm (7.54), Weight: 67.60 kg (8.41)</p> <p>Controls: 48 (17% females) Mean (SD) age: 19.02 y (1.21), Height: 179.28 cm (7.73), Weight: 67.40 (7.63)</p>
Description of outcome	Two of following clinical criteria on assessment: pain on direct compression of the patella against the femoral condyles with the knee in full extension, tenderness of the femoral condyles with the knee in full extension, tenderness of posterior surface of the patella on palpation, pain on resisted knee extension, or pain with isometric quadriceps muscle contraction against suprapatellar resistance with the knee in 15° of flexion
Description of determinants	<ul style="list-style-type: none"> - Anthropometric data: height, weight, and age - Temporal data: Time to peak pressure, instants on which the regions make contact, and instants on which the regions end contact calculated for medial heel, lateral heel, metatarsal heads I to V, and the hallux - Peak pressure data and absolute impulses (mean pressure x loaded contact time calculated for medial heel, lateral heel, metatarsal heads I to V, and the hallux) - Relative impulses (absolute impulse x 100/sum of all impulses calculated for medial heel, lateral heel, metatarsal heads I to V, and the hallux) - Mediolateral pressure distribution in the foot: calculated at the first foot contact, first metatarsal contact, forefoot flat, heel-off, and last foot contact. - Displacements of the center of pressure (COP): - x-component (mediolateral) and y-component (anteroposterior) of the center of pressure were analyzed.
Notes	Only officer cadets
Author, year of publication	Van Tiggelen et al, 2009
Study design, follow up	Prospective cohort study, 6 weeks
Participants description	<p>N=79 male cadets</p> <p>Cases: 26 (32%); Mean (SD) age: 19.5y (1.44), Height: 180.6 cm (6.12), Weight: 72.1 kg (8.96)</p> <p>Controls: 53 (68%); Mean (SD) age: 19.8y (2.62), Height: 180.5 cm (6.22), Weight: 70.5 kg (8.52)</p> <p>13 (14%) of the original 92 volunteers developed other injuries of the lower limb such as tendinopathies or stress fractures and were excluded from the study</p>
Description of outcome	Retropatellar knee pain through at least 2 of the following activities: jumping/hopping, squatting, stairs, running. Exhibit 2 of the following clinical criteria on assessment (with a minimal visual analog scale of 3/10 during the assessment): pain on direct compression of the patella against the femoral condyle with full knee extension; tenderness on palpation of the posterior surface of the patella; pain on resisted knee extension; pain with isometric quadriceps contraction against suprapatellar resistance with the knee in 15° of flexion.
Description of determinants	<ul style="list-style-type: none"> - Anthropometric data: height, weight, age - Onset timing VMO and VL
Notes	Only male cadets

Author, year of publication	Van Tiggelen et al, 2004
Study design, follow up	Prospective cohort study, 6 weeks
Participants description	N=96 male cadets; Age range: 17-21y Cases: 31 (48%); Mean (SD) Height: 178.4 cm (5.3), Weight: 70.6 (10.8), BMI: 22.2kg/m ² (3.0) Controls: 65 (52%); Mean (SD) Height: 181.5cm (6.4), Weight: 70.2kg (7.7), BMI: 21.3kg/m ² (2.2)
Description of outcome	Retropatellar knee pain through at least 2 of the following activities: jumping/hopping, squatting, stairs, running. Exhibit 2 of the following clinical criteria on assessment (with a minimal visual analog scale of 3/10 during the assessment): pain on direct compression of the patella against the femoral condyle with full knee extension; tenderness on palpation of the posterior surface of the patella; pain on resisted knee extension; pain with isometric quadriceps contraction against suprapatellar resistance with the knee in 15° of flexion.
Description of determinants	- Anthropometric data: height, weight, and BMI - Peak torque flexors (Nm) at 60°/s in a concentric mode - Peak torque flexors (Nm) at 240°/s in a concentric mode - Peak torque extensors (Nm) at 60°/s in a concentric mode - Peak torque extensors (Nm) at 240°/s in a concentric mode The Cybex Norm® with a single resistance pad was used in order to evaluate prospectively the isokinetic peak torques of the knee flexors and extensors.
Notes	Only male cadets

Author, year of publication	Witvrouw et al, 2000
Study design, follow up	Prospective cohort study, 2 year
Participants description	N=480 students; 198 (41%) lost to follow up 282 (46% females) remaining; Mean age: 18.6y (range 17-21y) Cases: 24 (9%) (54% females) Mean (SD) Height: 179.3 cm (5.38), Weight: 68.14 kg (5.59) Controls: 258 (81%) Mean (SD) Height: 180.16 cm (6.25), Weight: 69.96 kg (6.85)
Description of outcome	For patellofemoral pain, subjects had to have a characteristic history and symptoms of patellofemoral pain syndrome for more than 6 weeks: retropatellar pain during physical activities such as jumping, running, squatting, and going up or down stairs. Exhibit 2 of the following clinical criteria on assessment: pain on direct compression of the patella against the femoral condyles with the knee in full extension, tenderness of the posterior surface of the patella on palpation, pain on resisted knee extension, and pain with isometric quadriceps muscle contraction against suprapatellar resistance with the knee in 15° of flexion.

Description of determinants

- Anthropometric data: height, weight, endomorphism, ectomorphism, mesomorphism, fat percentage, ponderal index
- Physical fitness test: flamingo balance (sec), vertical jump (cm), standing broad jump (cm), bent arm hang (cm), shuttle run (sec), plate tapping (no. repetitions), arm pull (no. repetitions), leg lifts (no. repetitions), sit and reach (no. repetitions), sit ups (no. repetitions), maximal O₂-uptake (ml/kg/min)
- General joint laxity: extension little finger (°), mobility shoulders (cm), extension elbow (°), thumb-forearm (°), extension knee (°), medial patellar mobility (cm), lateral patellar mobility (cm), total patellar mobility (cm)
- Flexibility of different muscles: hamstring, quadriceps, gastrocnemius (°)
- Response time of VMO and VL (ms)
- Psychological parameters: neurotic unstable; psychosomatic unstable, extroversion, active behavior, palliative reaction, avoiding behavior, looking for social support, passive reaction pattern, expression of emotions, reassuring thoughts
- Static patellofemoral alignment: Q-angle (°), genu varum/valgum
- Peak torques (Nm) of hamstrings and quadriceps at 60°, 180° and 240°: using Cybex 350 dynamometer in a concentric mode

Notes

Abbreviations: BMI (body mass index); BW (body weight); cm (centimeter); ° (degrees); ht (height); kg (kilogram); m (meter); mm (millimeter); ms (milliseconds); N (Newton); Nm (Newton meter); no (number); s (seconds); SD (standard deviation); y (year).

Chapter III

Factors associated with patellofemoral pain syndrome: A systematic review

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Abstract

Objective

This review systematically summarises factors associated with patellofemoral pain syndrome (PFPS).

Methods

A systematic literature search was conducted. Studies including ≥ 20 patients with PFPS that examined ≥ 1 possible factor associated with PFPS were included. A meta-analysis was performed, clinical heterogeneous data were analysed descriptively.

Results

The 47 included studies examined 523 variables, eight were pooled. Pooled data showed a larger Q-angle, sulcus angle and patellar tilt angle (weighted mean differences (WMD) 2.08; 95% CI 0.64, 3.63 and 1.66; 95% CI 0.44, 2.77 and 4.34; 95% CI 1.16 to 7.52, respectively), less hip abduction strength, lower knee extension peak torque and less hip external rotation strength (WMD -3.30; 95% CI -5.60, -1.00 and -37.47; 95% CI -71.75, -3.20 and -1.43; 95% CI -2.71 to -0.16, respectively) in PFPS patients compared to controls. Foot arch height index and congruence angle were not associated with PFPS.

Conclusion

Six out of eight pooled variables are associated with PFPS, other factors associated with PFPS were based on single studies. Further research is required.

Introduction

The most frequently diagnosed condition in adolescents and adults with knee complaints is patellofemoral pain syndrome (PFPS).¹ A general practitioner (GP) registers (on average) five or six patients a year with PFPS and women have a higher incidence than men.^{2,3} In sports medicine PFPS is diagnosed in about 25% of all running injuries.⁴ Treatment for PFPS is especially promising for the short term; long-term results for treatment of PFPS are less successful.^{1,5,6} After 7 years, 30% of the non-recovery PFPS patients had persistent complaints.⁶

PFPS is a commonly used term to describe a condition of anterior knee pain, which covers all the problems related to the anterior part of the knee.⁷ Although there is no consensus on the terminology, various synonymous are used for PFPS.^{8,9} PFPS is commonly described as a pain in/around the patella. This pain increases after prolonged sitting, squatting, kneeling and stair climbing.¹⁰

It is suggested that the aetiology of PFPS is multifactorial.^{1,7} However, there is no agreement with regard to which factors contributing to or relating to PFPS.¹¹ The risk

factors for PFPS are outlined in a systematic review on risk factors for PFPS.¹² This review concludes that being women and having lower knee extension strength in both men and women seem to be risk factors for the future development of PFPS. However, only seven studies were included in this review and the majority of the research done on factors associated with PFPS is done by case-control studies. Several case-control studies also described the association between PFPS and muscle strength, but malalignment, LE muscle imbalance, delayed onset of vastus medialis obliquus (VMO), overuse, trauma, cartilage damage, muscular flexibility and vascular disturbance are also discussed as possible causes for PFPS.^{7 13-19} Two systematic reviews have summarized the available evidence for kinematic gait characteristics and for the VMO and vastus lateralis (VL) timing.^{20 21} Another review, focusing on hip muscle weakness, concludes that females with PFPS demonstrate a decrease in abduction, external rotation and extension strength compared to controls.²² However, there is a lack in overview of all the factors studied in case-control studies and therefore there is need for one review encompassing all factors. The lack of a clear classification of the factors contribute to or are related to PFPS could be a possible reason for the less successful outcomes of long-term complaints in patients with PFPS.

Therefore, the aim of this study is to systematically summarise the factors associated with PFPS, described in case-control studies.

Methods

Criteria for considering studies for this review

Type of studies

Case-control or cross-sectional studies writing in English, French, German, Swedish or Dutch, including a minimum of 20 patients with PFPS, were eligible. The choice of including studies with a minimum of 20 patients with PFPS was primarily based on the likeliness of publication bias occurring in case-control studies with small numbers of subjects. To reduce this chance, studies with <20 patients with PFPS were excluded.

Type of participants

Adolescents and adults suffering from PFPS and not receiving operative treatment or arthroscopy were included. Owing to the lack of consistent terminology for PFPS, all definitions for PFPS and its synonyms were included. Patients with chondromalacia patella (CP) were included if the authors intended CP to be a description for PFPS. Studies focusing on other named knee pathologies (such as Osgood Schlatter disease, Sinding Larsen Johansson's disease, tendinitis or bursitis, plural of neuroma's (sic), intra-articular

pathologies, plica syndromes and more rarely occurring pathologies) were excluded. No limitations on age and setting were applied.

Type of outcome measurement

Only studies including at least one possible factor associated with PFPS were included in this review.

Search for relevant studies

The primary search was conducted in Pubmed (MEDLINE), Embase, Web of Science (WoS), MEDLINE (OVID) and the Cochrane Central Register up to 3 of November 2010. The following keywords were used: Arthralgia AND knee joint OR anterior knee pain OR (patell* OR femoropatell* OR femoropatell* OR retropatell*) AND (pain OR syndrome OR dysfunction) AND risk factor OR association OR relative risk OR. Appendix 1 presents the full Pubmed, Embase, WoS and MEDLINE (OVID) search. References of included studies, but also of excluded studies due to the small sample size and systematic reviews on patellofemoral pain, were screened for relevant citations.

Data collection and analysis

Selection of studies

Two reviewers (NL and MM) independently selected the articles based on title and abstract, according to the criteria. For the selected references a final decision about inclusion was made based on the full-text article. These articles were reviewed independently. In the case of disagreement, conditions of entrance were discussed until consensus was reached.

Methodological quality

A quality assessment list was created using criteria from the Dutch Cochrane Centre (<http://www.cochrane.nl/en/index.html>). Table 1 presents the criteria for the quality score: the list is divided into three topics with a total of eight items. Two reviewers (NL and MM) independently measured the quality of the studies by scoring each of the study criteria as 'positive', 'unclear' or 'negative'. Positive scored criteria received one point. Disagreements were solved by discussion and Cohen's kappa was calculated to measure inter-rater agreement. The quality score of each study was calculated by summing up the total number of positive criteria.

Data extraction

One reviewer (NL) extracted relevant data from the studies. Information on study design (type of study, author and year of publication), study population (number of cases/con-

trols enrolled and analysed), characteristics of the groups (gender, age and definition of PFPS), definition of the factors investigated and assessment method were extracted, applying a standardized form. Other comments that could not be arranged within the items described above, and might be important for this review, were described in 'notes'. Studies are presented in the following sub-divisions: static measures, kinematic measures, kinetic measures, muscle function measures and other measures.

Table 1 Quality assessment list

Criteria for quality score	
Study population	
1	Study groups are clearly defined
	Positive if truly or somewhat representative of the average population (females>males, athletes, patients from primary or secondary care). Studies received also one point if they only included women, because the PFPS is more common in women than in man. Described recruitment of included patients.
2	Number of cases ≥ 50
	Positive if the total number of cases was ≥ 50
3	Comparable groups
	Positive if the study controls are comparable for age en gender
4	Inclusion and exclusion criteria
	Positive if inclusion and exclusion criteria were described. Inclusion: a clear definition of PFPS Exclusion: a clear definition of the exclusion criteria
Assessment of outcome	
5	Definition of determinant
	Positive if a clear definition of outcome measure (variable that might be associated with PFPS) was described
Analysing and data presentation	
6	Data presentation
	Positive if risk estimates were presented or when raw data (numbers and percentages for dichotomous variables and means and SDs for continuous variables) were given that allow the calculation of risk estimates (odds ratio or relative risks) and mean differences
7	Control for confounding
	Positive if the method used to control for confounding was described
Blinding	
8	Blinding
	Positive if the outcome assessor was blinded on health status (PFPS versus controls) subjects

Statistical analysis

A meta-analysis was performed to establish factors associated with PFPS that had a consistent definition, and whether results were reported for the same outcome measures. Statistical heterogeneity was tested with the χ^2 and I^2 test. We chose for a random effects model for inspection of the forest plot. Weighted mean differences (WMD) with matching 95% CI were calculated for the pooled data. For the meta-analysis the software package Review Manager 5 was used. If a meta-analysis was not possible due to clinical heterogeneity, data were analysed descriptively. For the articles that supplied adequate data, the mean difference (MD) with matching 95% CI was calculated. If the SD was

not reported, we estimated the SD comparing MD's and group sample sizes (PFPS and control group) of comparable studies. For dichotomous data odds ratio (OR) or relative risk (RR) with matching 95% CI was calculated or abstracted from the individual studies. If a meta-analysis was not possible due to clinical heterogeneity, data were analysed descriptively. If separate data were present for both legs, only the data from the symptomatic leg in the case group were extracted. In the control group random data from one leg were extracted. If data were presented in figure form or were missing (eg, SD), the corresponding author was contacted and was asked for the raw original data. If the corresponding author did not have the raw data or did not respond, we measured the mean outcomes with (if given) accompanying SD.²³ Significant differences were based on calculated MDs with matching 95% CI. If studies did not provide sufficient information to calculate the 95% CI, information on significant differences ($p < 0.05$) between the groups were extracted from the studies (supplementary online appendix 2 <http://bjsm.bmjjournals.org/content/47/4/193/suppl/DC1>).

Results

Characteristics of the included studies

The database search resulted in 4664 potentially relevant articles. From titles and abstracts, 213 articles were extracted for full-text review (this was not possible for three articles). A total of 47 studies met the inclusion criteria (figure 1).^{13 20 24-72} Multiple publications with identical data were found for Dierks et al,^{31 73} Jensen et al,^{36 66} Powers et al^{50 69} and Willson et al,^{57 71 72} combined information were used for the quality measurement and data extraction. But only the most prominent or first published articles were used for citation of these studies (supplementary online appendix 3 <http://bjsm.bmjjournals.org/content/47/4/193/suppl/DC1>).

Methodological quality

The two reviewers agreed on 88% of the items among the 47 included studies (332 from 376 items). All initial disagreements were discussed until a consensus was reached. The quality score ranged from 2 to 7 and the median quality score for the 47 studies was 6. Only 12 studies scored positive on item 2 including more than 50 cases and 34 studies (72%) scored positive on the representativeness of the study population. Remarkable was that all studies described a clear definition of outcome measure (variable that might be associated with PFPS), except for the study from Al-Rawi et al.⁶¹

In only five studies the outcome assessor was blinded on health status (PFPS versus controls) of the subjects^{20 37 39 46 61} (table 2).

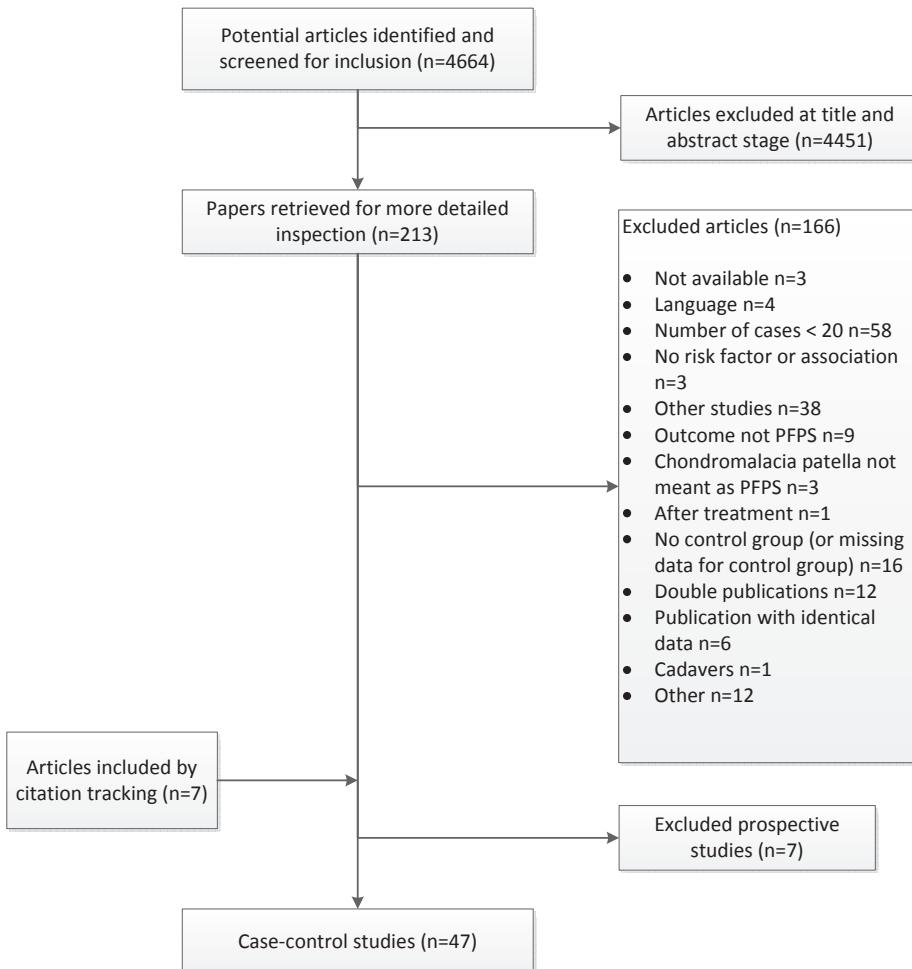


Figure 1 Flow-chart of the process to select the relevant studies.

Factors associated with PFPS

Static measures

Foot and ankle characteristics

Foot and ankle characteristics were reported in seven studies, including 47 variables.^{20 24 31 40 54 58 65} The ratio of the dorsum height (at 50% foot length) divided by the truncated foot length, expressed as the arch height index, was measured in three studies^{31 54 58} and pooling was possible for two.^{31 58} No association between arch height index and PFPS was found after pooling (WMD 0.01; 95% CI -0.01 to 0.03) (figure 2)^{31 58} and Thomeé et al⁵⁴ also found no significant difference between both study groups. Ten

Table 2 Methodological quality

Author, year of publication	Criteria for quality score ^a								Total number
	1	2	3	4	5	6	7	8	
Aglietti, 1983 ⁶⁰	?	1	0	0	1	1	?	?	3
Alberti et al, 2010 ²⁴	1	0	1	1	1	1	1	?	6
Al-Rawi, 1997 ⁶¹	1	1	1	?	0	1	?	1	5
Anderson, 2003 ⁶²	1	0	1	1	1	1	?	0	5
Baker et al, 2002 ²⁵	1	0	?	1	1	1	?	?	4
Barton et al, 2010 ²⁰	1	0	1	1	1	1	1	1	7
Besier et al, 2008 ²⁶	1	0	?	1	1	1	1	?	5
Boling et al, 2009 ²⁷	1	0	1	1	1	1	1	?	6
Callaghan, 2004 ⁶³	1	1	1	1	1	1	?	?	6
Caylor et al, 1993 ²⁸	1	1	1	0	1	1	1	?	6
Cowan et al, 2001 ²⁹	1	0	1	1	1	1	1	?	6
Cowan et al, 2002 ⁵⁹	1	0	1	1	1	1	1	?	6
Crossley et al, 2003 ³⁰	1	0	?	1	1	1	?	?	4
Dierks et al, 2008 ^{*31}	1	0	1	1	1	1	1	?	6
Dorotka et al, 2002 ³²	0	1	1	0	1	1	1	?	5
Draper, 2006 ¹³	1	0	0	0	1	1	0	?	3
Draper, 2009 ⁶⁴	1	0	1	1	1	1	0	?	5
Duffey et al, 2000 ⁵⁸	0	1	1	1	1	1	1	?	6
Eckhoff et al, 1994 ³³	?	0	?	1	1	0	0	?	2
Emami et al, 2007 ³⁴	1	1	1	1	1	0	1	?	6
Haim, 2006 ⁶⁵	0	1	0	1	1	1	?	0	4
Jan et al, 2009 ³⁵	1	1	1	1	1	1	1	0	7
Jensen et al, 2008 ^{*66}	1	1	1	1	1	1	?	?	6
Joensen et al, 2001 ³⁷	0	0	1	1	1	1	1	1	6
Keser et al, 2008 ³⁸	1	1	1	1	1	1	1	?	7
Laprade et al, 2003 ³⁹	0	0	1	1	1	1	1	1	6
Livingston et al, 2003 ⁴⁰	1	0	0	1	1	1	0	?	4
MacIntyre et al, 2006 ⁴¹	0	0	1	1	1	?	1	?	4
Magalhaes et al, 2010 ⁴²	1	1	1	1	1	1	1	0	7
McClinton et al, 2007 ⁴³	0	0	1	1	1	1	1	?	5
Morrish, 1997 ⁶⁷	1	0	1	1	1	1	?	?	5
Muneta et al, 1994 ⁴⁴	?	1	1	1	1	1	1	?	6
Näslund et al, 2007 ⁴⁵	1	0	0	1	1	1	0	?	4
Ota et al, 2008 ⁴⁶	1	0	1	0	1	1	1	1	6
Owings, 2002 ⁶⁸	?	0	0	0	1	1	?	?	2
Patil et al, 2010 ⁴⁸	1	0	1	1	1	1	1	?	6
Patil et al, 2010 ⁴⁷	1	0	1	1	1	1	1	?	6

Table 2 Methodological quality (continued)

	Criteria for quality score ^a								
	1	0	1	1	1	1	1	0	6
Piva et al, 2005 ⁴⁹	1	0	1	1	1	1	1	0	6
Powers et al, 2000 ⁵⁰	1	0	1	1	1	1	1	?	6
Powers et al, 1996 ⁵¹	1	0	1	1	1	1	1	?	6
Salsich et al, 2007 ⁵²	1	0	1	1	1	1	1	?	6
Souza, 2009 ⁶⁹	1	0	1	1	1	1	1	0	6
Stefanyshyn et al, 2006 ⁵³	?	0	?	1	1	1	0	?	3
Thomee et al, 1995 ⁵⁴	1	0	1	1	1	1	1	?	6
Tuncyurek et al, 2010 ⁵⁵	?	0	1	1	1	1	1	?	5
Werner et al, 1995 ⁵⁶	1	0	1	0	1	1	1	?	5
Willson et al, 2008 ⁵⁷	1	0	1	1	1	1	1	?	6

* Multiple studies included for methodological quality assessment

^a1: open population study groups or recruited from primary and secondary care. Studies received also one point if they only included women, because the PFPS is more common in women than in men 2: Number of cases \geq 50. 3: Study groups comparable for age and gender. 4: Clear definition of inclusion and exclusion criteria was described. 5: Positive if a clear definition of outcome measure (variable that might be associated with PFPS) was described 6: Risk estimates were presented or raw data were given that allow the calculation of risk estimates, such as: odds ratio, or relative risk. 7: Method used to control for confounding was described. 8: Blinding of outcome assessor on health status (PFPS versus control) subjects.

variables for the measurement of foot posture in PFPS patients were reported in one study. A significantly greater pronated foot posture in relaxed stance was found in PFPS patients compared to controls in eight measurement methods (supplementary online appendix 2 <http://bjsm.bmjjournals.com/content/47/4/193/suppl/DC1>).²⁰ No significant difference was found between the number of PFPS patients with pes cavus or pes planus and the control subjects.⁶⁵ Three variables for static rear foot angles were described in one study and data for men and women were reported separately; however, none were significantly different.⁴⁰

Leg length differences

Two studies examined leg length differences between PFPS patients and control subjects expressed by five variables.^{58 61} Absolute and relative leg length differences were measured in one study. Both were not associated with PFPS.⁵⁸ Leg length differences of half till 1 cm, shorter or longer, in the dominant leg were not associated with PFPS as well as no differences in leg length at all.⁶¹

Q-angle in weight bearing position

Nine studies described the relation between quadriceps angle (Q-angle) and PFPS.^{28 34 47 48 54 57 58 60 65} Pooled data showed a significantly larger Q-angle in the PFPS group compared to the control group (WMD 2.08 95% CI 0.64 to 3.63) (figure 3) Sig-

nificantly more PFPS patients had a Q-angle larger than 20° (p value <0.001) compared to controls in one study.⁶⁵ Another study examined the Q-angle at 0° and at 30° knee flexion and found no difference in Q-angle between PFPS patients and controls in both measurements.⁵⁴

Malalignment

Misalignments by genu varum and genu valgum were not associated with PFPS in one study.⁶⁵

Patella

Differences in physical examination and radiographic examination of the patella between PFPS patients and controls were examined in 12 studies, including 39 variables.^{13 33 37-39 45 50 52 55 60 64 65} Pooling was possible for three variables. Pooled data showed that PFPS patients had a significantly larger patellar tilt angle (WMD 4.34 95% CI 1.16

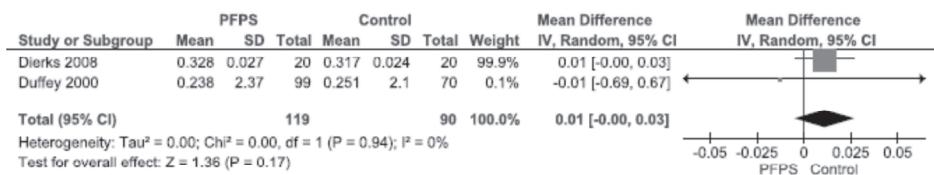


Figure 2 Forest plot: association patellofemoral pain syndrome and arch height index.

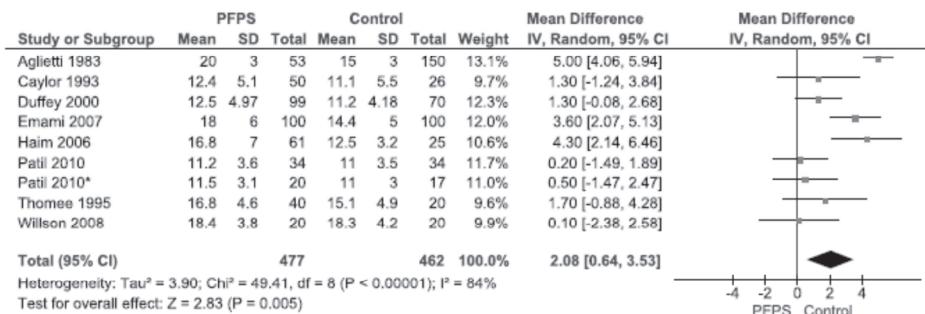


Figure 3 Forest plot: association patellofemoral pain syndrome and Q-angle in weight-bearing position (°).

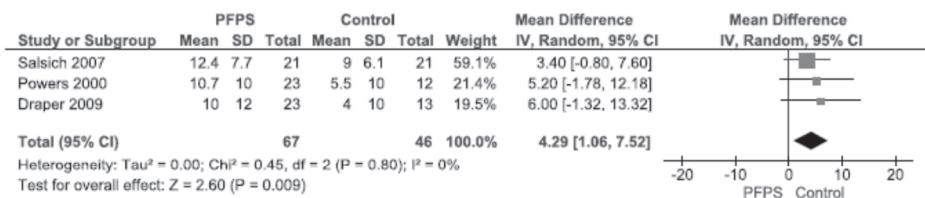


Figure 4 Forest plot: association patellofemoral pain syndrome and patellar tilt angle (°).

to 7.52) (figure 4) and a significantly larger sulcus angle (WMD 1.61 95% CI 0.44 to 2.77) (figure 5). After pooling no significant difference was found between congruence angle in PFPS patients and controls (figure 6). Due to missing data, the study from Eckhoff et al, was not pooled. However, this study also found no association between the sulcus angle and congruence angle and PFPS.³³ Three studies evaluated the association between bisect offset and PFPS, and conflicting results are found.^{50 52 64} In one study PFPS patients had a greater bisect offset compared with controls (MD 0.07 95% CI 0.01 to 0.13)⁵² and in another study 10% larger differences in bisect offset were found between PFPS patients and controls during knee flexion between 0° and 50° (p value: 0.03).⁶⁴ No association between bisect offset and PFPS was found in the study by Powers et al.⁵⁰ Salsich et al also evaluated the contact area of total patellofemoral joint, representing the length of cartilage contact on the medial and lateral facets and patellar width, using MRI. Both were significantly smaller in the PFPS group compared to the control group (MD -28.70; 95% CI -54.59, -2.81 and -2.90; 95% CI -4.85 to -0.95, respectively).⁵² Significantly more PFPS patients had patellar glide as a percentage of patellar width compared to controls in one study (-8.00 95% CI -14.6 to -1.40).⁶⁵ Patellar height ratio was significantly greater in PFPS patients compared to controls when measured with the Insall-Savati method (0.04 95% CI 0.01 to 0.07), although no association between patellar height ratio and PFPS was found when this was measured with the Blackburne method.⁶⁰ In one study PFPS patients had an increased lateral and medial retinacular sensitivity (OR 88.7 95% CI 17.1 to 459.9 and OR 21.90 95% CI 4.70 to 102.0, respectively), and increased patellofemoral crepitations (OR 27.5 95% CI 5.85 to 128.9) compared to

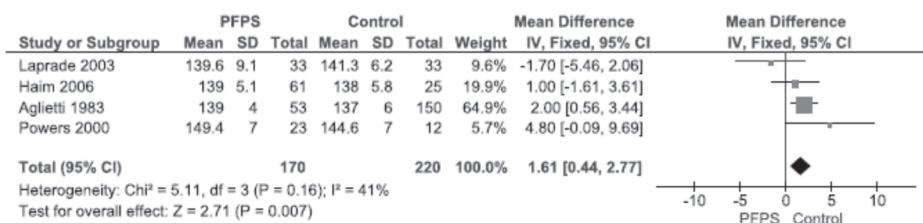


Figure 5 Forest plot: association patellofemoral pain syndrome and sulcus angle (°).

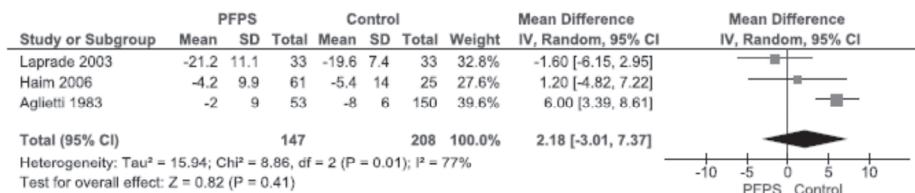


Figure 6 Forest plot: association patellofemoral pain syndrome and congruence angle (°).

controls. In the same study the patellar tracking instability test was positive in 25% of the PFPS patients compared with none of the controls (p value: 0.004).⁶⁵ The pulsatile blood flow in the patella before and after passive knee flexion (90°) was investigated in one study. A significant reduction of blood flow in the patella after passive knee flexion was found in PFPS patients compared to controls ($p < 0.0002$).⁴⁵ The presence of articular cartilage lesions of the patella was examined by Joensen et al³⁷ and significantly more lesions were found in patients with PFPS compared to controls (OR 7.9; 95% CI 1.9 to 33). The articular cartilage thickness was examined by Draper et al¹³ and data for male and females were presented separate. In male PFPS patients the superior cartilage thickness was significantly lower compared to male control subjects (MD males: -0.90 95% CI -1.78 to -0.02). Keser et al³⁸ reported a significantly higher incidence of trochlear dysplasia in knees of the patients with PFPS compared to the knees of the controls (OR 7.12; 95% CI 1.6 to 31.7) and significantly less lateral trochlear inclination in PFPS patients compared to controls (MD -4.20; 95% CI -6.04 to -2.36). None of the other evaluated variables were associated with PFPS.^{13 33 39 55 60 64 65}

Angles

Static LE angles were evaluated by 18 variables in eight studies.^{33 44 47 48 52 54 58 71} One study described a significantly smaller tibial tubercle rotation angle in PFPS patients compared to controls (MD -2.50; 95% CI -4.56 to -0.44).⁴⁴ Another study reported a statistically significant greater hip external rotation angle and smaller hip internal rotation angle in PFPS subjects compared to controls ($p < 0.001$ and $p = 0.01$, respectively).⁴⁸ Knee hyperextension angle was significantly greater in PFPS patients compared to controls (MD 2.40; 95% CI 1.25 to 3.55) in Thomeé et al.⁵⁴ No other significant differences were found among the 14 studied variables.^{33 44 47 48 52 54 58}

Characteristics of vastus medialis obliquus muscle

Insertion level, fibre angle and volume of VMO muscle were evaluated in one study, and all were significantly smaller in PFPS patients compared to controls (table 3).³⁵

Characteristics of quadriceps muscles

In one study quadriceps atrophy was examined expressed as the quadriceps cross-sectional area, no significant differences between the PFPS patients and control group were found.⁶³

Table 3 Significant different variables between both groups in the individual studies.

Author	Variables	MD (95% CI)
Static measures		
Foot and ankle characteristics		
Barton, 2010 ²⁰	Longitudinal arch angle (LAA) (°) Relaxed stance	-6.80 (-11.57,-2.03)
	Foot posture index (FPI) (°) Relaxed stance	2.40 (0.19,4.61)
	Normalized Vertical Navicular Height (NVNH) (%foot length) Relaxed stance	-2.00 (-3.93,-0.07)
	Normalized navicular drop (NNDrop) (% foot length) Foot posture relative, Subtalar joint neutral	1.60 (0.57,2.63)
	Normalized dorsal arch height (NDAH) difference (% foot length) Foot posture relative, Subtalar joint neutral	0.70 (0.25,1.15)
	Normalized navicular drift (% foot length) (NNDrift) Foot posture relative, Subtalar joint neutral	1.60 (0.49,2.71)
	LAA Difference (°) Foot posture relative, Subtalar joint neutral	3.00 (0.86,5.14)
	CA Difference (°) Foot posture relative, Subtalar joint neutral	2.60 (0.45,4.75)
Patella		
Joensen, 2001 ³⁷	Articular cartilage lesions	OR: 7.9 (1.9,33)
Keser, 2008 ³⁸	Lateral trochlear inclination (LTI)	-4.20 (-6.04,-2.36)
	Trochlear dysplasia (n)	OR: 7.12 (1.60,31.70) *
Näslund, 2007 ⁴⁵	Pulsatile blood flow in the patella	P<0.0002
Salsisch, 2007 ⁵²	Contact area of total patellofemoral joint (mm2)	-28.70(-54.59,-2.81)
	Bisect offset index (patellar width)	0.07 (0.01,0.13)
	Patellar width (mm)	-2.90 (-4.85,-0.95)
Haim, 2006 ⁶⁵	Positive Active instability test (patellar tracking) (number and %)	P value: 0.004
	Patellofemoral joint crepitations (n and %)	OR: 27.5 (5.85, 128,9)
	Medial retinacular sensitivity (n and %)	OR: 21.90 (4.70,102,0)
	Lateral retinacular sensitivity (n and %)	OR: 88.7 (17.1, 459.9)
	Patellar glide as percentage of patellar width (%)	-8.00 (-14.6, -1.40)
Aglietti, 1983 ⁶⁰	Patellar height ratio Insall-Salvati method	0.04 (0.01, 0.07)
Draper, 2009 ⁶⁴	Differences in Bisect offset between knee flexion angles 0° and 50° (%)	P value: 0.03
Lower extremity angles		
Muneta, 1994 ⁴⁴	Tibial tubercle rotation angle (°)	-2.50 (-4.56,-0.44)
Patil, 2010 ⁴⁸	External hip rotation (°)	P<0.001
	Internal hip rotation (°)	P=0.01
Thomee, 1995 ⁵⁴	Knee hyperextension angle (°)	2.40 (1.25,3.55)

Table 3 Significant different variables between both groups in the individual studies. (continued)

Author	Variables	MD (95% CI)
Characteristics of VMO		
Jan, 2009 ³⁵	Insertion level of vastus medialis obliquus (cm)	-0.40 (-0.63,-0.17)
	Fiber angle of the VMO (°)	-5.40 (-8.08,-2.12)
	Volume of VMO (cm3)	-1.20 (-1.92,-0.48)
Kinetic measures		
Foot and ankle characteristics		
Alberti, 2010 ²⁴	Contact area Medial Rearfoot (cm2)	1.80 (0.03,3.57)
	Contact area Midfoot (cm2)	3.60 (1.05,6.15)
	Peak pressure medial rearfoot (kPa)	-10.0 (-19.27,-0.73)
	Peak pressure central rearfoot (kPa)	-20.0 (-24.7,-15.28)
	Peak pressure lateral rearfoot (kPa)	-20.0 (-29.44,-10.56)
	Peak pressure midfoot (kPa)	-10.0 (-15.79,-4.21)
	Peak pressure medial forefoot (kPa)	-45.0 (-56.57,-33.43)
	Peak pressure lateral forefoot (kPa)	-20.0 (-28.11,-11.89)
Duffey, 2000 ⁵⁸	Calcaneus-tibia touchdown angle (°)	2.80 (0.46,5.14)
	Pronation through first 10% of stance (°)	-1.30 (-2.27,-0.33)
	Initial pronation velocity (°xs-1)	-70.0 (-120.13,-19.87)
	Maximum pronation velocity (°xs-1)	-79.0 (-130.25,-27.75)
Ground reaction force		
Duffey, 2000 ⁵⁸	Maximum lateral force (BW) during running	-0.09 (-0.11,-0.07)
Dierks, 2008 ³¹	Knee internal rotation excursion (°) during single leg jump	-2.70 (-4.99,-0.41)
	Hip internal rotation velocity (°/s)	-71.50 (-135.73,-7.27)
	Peak stance-phase knee flexion during stair descent	5.5 (1.7;9.4) *
Peak moments		
Besier, 2009 ²⁶	Knee flexion-extension moment during running [Nm/kg]	-0.38 (-0.64,-0.12)
Peak torques		
Duffey, 2000 ⁵⁸	Extension peak torque at 60° (Nm)	-21.40 (-34.49,-8.31)
	Extension peak torque at 240°(Nm)	-8.80 (-17.51,-0.09)
	Flexion peak torque 60° (Nm)	-9.40 (-16.04,-2.76)
	Flexion peak torque at 240° (Nm)	-9.40 (-16.03,-2.77)
	Extension peak torque at 60°/BW (%)	-9.70 (-14.41,-4.99)
	Flexion peak torque 60°/BW (%)	-4.40 (-7.46,-1.34)
	Flexion peak torque at 240°/BW (%)	-4.10 (-6.79,-1.41)
	Flexion/extension peak torque ratio at 240° (%)	-4.70 (-9.32,-0.08)
Werner, 1995 ⁵⁶	60°/s peak torque during knee extension (Nm)	-56.50 (-81.07,-31.93)
	Peak torque 60°/s concentric during knee extension (Nm)	-52.90 (-73.56,-32.24)
	Peak torque 60°/s eccentric during knee extension (Nm)	-72.80 (-99.87,-45.73)
	Peak torque 180°/s concentric during knee extension (Nm)	-39.00 (-56.00,-22.00)
	Peak torque 180°/s eccentric during knee extension (Nm)	-72.70 (-101.20,-44.20)

Table 3 Significant different variables between both groups in the individual studies. (continued)

Author	Variables	MD (95% CI)
Souza, 2009 ⁷⁰	Peak torque hip extension during isometric strength testing (Nm/kg)	-0.37(-0.65, -0.09)
	Peak torque hip abduction during isometric strength testing (Nm/kg)	-0.23 (-0.45, -0.01)
Callaghan, 2004 ⁶³	Peak torque knee extension at 90°/s at full knee extension (Nm)	-31.10(-55.57, 6.63)
Kinematic measures		
Lower extremity angles		
Crossley,2004 ³⁰	Knee flexion at heel-strike during stair ascent (°)	6.8 (0.8;12.9) *
	Knee flexion at heel-strike during stair descent (°)	2.5 (0.2;4.9) *
Dierks, 2008 ³¹	Hip adduction peak angle (°)	-3.10 (-6.04,-0.16)
McClinton, 2010 ⁴³	Knee flexion (°)	P value: 0.038
Willson, 2008 ⁵⁷	Knee internal rotation plane angle (°) during single leg jump	-5.47; -10.46,-0.48
	Hip adduction plane angle (°) during single leg squat	3.75; 0.69, 6.81
	Hip adduction plane angle (°) during running	2.86; 0.25,5.48
	Hip adduction plane angle (°) during single leg jump	3.66; 0.20,7.12
	Hip internal rotation angle (°) during single leg squat	-4.17;-6.90,-1.43
	Hip internal rotation angle (°) during single leg jump	-4.67;-8.36,-0.98
	Frontal plane pelvis angle at peak knee extension moment during single leg jump (°)	-2.30; -4.30,-0.30
	Hip abduction at peak knee extension moment during single-leg jump (°)	3.70; 0.21,7.19
	Hip Internal rotation at peak knee extension moment during single-leg jump (°)	-4.68; -8.36,-1.00
	Peak hip adduction angle (°) during running	0.20; -2.53,2.93
Souza, 2009 ⁷⁰	Peak Hip adduction (°) during drop jump	2.20; -1.18, 5.58
	Peak Hip adduction (°) during step-down	2.90; -0.58, 6.38
Velocity		
Dierks, 2008 ³¹	Hip adduction velocity (°/s)	-70.50 (-121.41,-19.59)
	Hip internal rotation velocity (°/s)	-71.50 (-135.73,-7.27)
Anderson, 2003 ⁶²	Break in Torque on eccentric quadriceps contraction 30°/s (%)	OR: 5.67 (1.25, 25.6)
	Perturbations in isokinetic torque curves (%)	OR: 2.25 (0.36, 14.0)
	Break in knee angular velocity curves during stair descent (%)	OR: 8.50 (1.86, 38.8)
Excursion		
Willson, 2008 ⁵⁷	Hip internal rotation excursion (°) during single leg squat	-3.24 (-5.43,-1.05)
	Knee internal rotation excursion (°) during single leg jump	-2.67(-5.29,-0.05)
Peak stance-phase		
Crossley, 2004 ³⁰	Peak stance-phase knee flexion during stair ascent (°)	6.0 (0.6;11.4) *

Table 3 Significant different variables between both groups in the individual studies. (continued)

Author	Variables	MD (95% CI)
Muscle function measures		
Muscle flexibility		
Patil, 2010 ⁴⁸	Popliteal angle (°) (hamstring tightness)	P=0.04
Piva, 2005 ⁴⁹	Quadriceps length (°)	-11.4 (-17.06,-5.74)
	Hamstring length (°)	-9.50 (-15.19,-3.81)
	Gastrocnemius length (°)	-10.20 (-13.10,-7.30)
	Soleus length (°)	-6.90 (-9.38,-4.42)
Muscle Strength		
Besier, 2009 ²⁶	Normalized peak forces in vastus lateralis during walking	P value: 0.032
	Normalized peak force in vastus intermedius during walking	P value: 0.044
	Peak semitendinosus force during walking	P value: 0.044
	Peak force in the medial gastrocnemius during walking	P value: <0.001
	Peak medial gastrocnemius force during running	P value: <0.002
Dierks, 2008 ³¹	Hip abduction strength (kgxcm/bw)	-2.00 (-3.54,-0.46)
Magalhaes, 2010 ⁴²	Strength of Hip abductors ((kg strength/kg body weight) x100)	-2.90 (-4.91,-0.89)
	Strength of Hip adductors ((kg strength/kg body weight) x100)	-1.00 (-3.70,1.70)
	Strength of Hip extensors ((kg strength/kg body weight) x100)	-2.70 (-7.34,1.94)
	Strength of Hip flexors ((kg strength/kg body weight) x100)	-3.10 (-5.98,-0.02)
Willson, 2008 ⁵⁷	Isometric strength of Lateral trunk flexion (%BW)	-6.50 (-11.98,-1.02)
	Isometric strength of Hip external rotation (%BW)	-1.63 (-3.21,-0.05)
Morrish, 1997 ⁶⁷	Force developed of quadriceps during knee extension (N)	-50.50 (-80.82,-20.18)
Muscle endurance		
Duffey, 2000 ⁵⁸	Extension total work at 240° (Nxm)	-238.8 (-459.37,-18.23)
	Flexion total work at 240° (Nxm)	-284.0 (-521.68,-46.32)
	Extension work first 6 reps at 240° (Nxm)	-69.60 (-123.58,-15.62)
	Flexion work first 6 reps at 240° (Nxm)	-80.10 (-138.88,-21.32)
	Extension work last 6 reps at 240° (Nxm)	-50.90 (-85.01,-16.79)
	Flexion work last 6 reps at 240° (Nxm)	-40.10 (-79.49,-0.71)
	Extension average power at 240° (Watts)	-22.20 (-48.65,4.25)
	Flexion average power at 240° (Watts)	-22.90 (-40.35,-5.45)
Muscle timing		
Cowan, 2001 ²⁹	Onset of VL/VMO during concentric task (%)	OR: 5.33 (1.86,15.30)
	Onset of VL before onset of VMO during eccentric task (%)	OR: 11.61 (3.66,36.78)
	Onset of VL/VMO during concentric task (ms)	-15.65 (-27.48,-3.82)
	Onset of VL/VMO during eccentric task (ms)	-22.18 (-35.37,-8.99)

Table 3 Significant different variables between both groups in the individual studies. (continued)

Author	Variables	MD (95% CI)
Cowan, 2002 ⁵⁹	VL-VMO timing difference during lifting toes and contracting tibialis anterior muscle (rock task) (ms)	-31.95 (-47.95,-15.95)
	VL-VMO timing difference during rising toes by contracting triceps surea muscle (rise task) (ms)	-14.68 (-25.51,-3.85)
	Onset VMO- onset tibialis anterior during rock task	31.60 (9.35,53.85)
	Onset VL-onset soleus during rise task	-63.20 (-90.31,-36.09)
McClinton, 2007 ⁴³	Activation duration ratio VMO/VL	0.15 (0.05,0.25)
Owings, 2002 ⁶⁸	Normalized activation level of VMO	0.55(0.22,0.88)
	Normalized activation level of VL	0.74 (0.28, 1.20)
Powers, 1996 ⁵¹	Onset of VML during fast walking (% of gait cycle)	5.00 (1.26,8.74)
	Onset of VI during fast walking (% of gait cycle)	5.80 (1.08,10.52)
	Cessation of VMO during stair descent (% gait cycle)	2.20 (0.20,4.20)
	Cessation of VML during stair descent (% gait cycle)	5.70 (1.37,10.03)
	Cessation of VI during stair descent (% gait cycle)	6.40 (3.10,9.70)
	Onset of VMO during ramp ascent (% of gait cycle)	4.60 (1.37,7.83)
	Onset of VMO during stair ascent (% of gait cycle)	3.60 (0.08,7.12)
	Onset of VMO during ramp descent (% of gait cycle)	4.30 (0.43,8.17)
	Onset of VL during ramp descent (% of gait cycle)	3.60 (0.46,6.74)
	Onset of VML during ramp descent (% of gait cycle)	5.00 (0.90,9.10)
	Onset of VI during ramp descent (% of gait cycle)	5.70 (1.96,9.44)
	Intensity of EMG activity of VMO during free-speed walking (% maximal muscle test)	-5.20 (-9.94,-0.46)
	Intensity of EMG activity of VMO during fast walking (% maximal muscle test)	-6.70 (-12.60,-0.80)
	Intensity of EMG activity of VL during stair descent (% maximal muscle test)	-7.20 (-11.96,-2.44)
	Intensity of EMG activity of VMO during ramp ascent (% maximal muscle test)	-5.40 (-9.66,-1.14)
	Intensity of EMG activity of VL during ramp ascent (% maximal muscle test)	-5.50 (-9.80,-1.20)
	Intensity of EMG activity of VMO during ramp descent (% maximal muscle test)	-4.90 (-9.68,-0.12)
	Intensity of EMG activity of VL during ramp descent (% maximal muscle test)	-5.00 (-8.49,-1.51)
Patil, 2010 ⁴⁸	Vastus muscles intensity during free speed walking (%MIMT)	-5.60 (-10.91,-0.29)
	Vastus muscles intensity during fast walking (%MIMT)	-8.10 (-14.86,-1.34)
	Vastus muscles intensity during ramp ascent (%MIMT)	-5.80 (-10.40,-1.20)
	Vastus muscles intensity during ramp (%MIMT) descent	-4.60 (-8.83,-0.37)
	Lateral hamstring-medial hamstring onset timing difference (ms)	-53.80 (-105.66,-1.94)

Table 3 Significant different variables between both groups in the individual studies. (continued)

Author	Variables	MD (95% CI)
Morrish, 1997 ⁶⁷	VMO lag factor	0.32 (0.20, 0.44)
	VLO lag factor	0.29 (0.02, 0.55)
	RF lag factor	0.20 (0.09, 0.31)
	Time for 80% tension development for quadriceps (msec)	100.0 (0.05, 199.95)
Besier, 2009 ²⁶	Co-contracting of quadriceps and hamstrings at heel strike during walking	P value: 0.025
Souza, 2009 ⁷⁰	Average gluteus maximus EMG signal during step-down (%) Maximum voluntary isometric contraction (%MVIC)	5.90; 1.39, 10.4
	Average gluteus maximus EMG signal during running (%MVIC)	21.0; 6.22, 35.8
Other measures		
Joint position sense		
Baker, 2002 ²⁵	Non-Weightbearing joint position sense at 60° knee flexion (°)	1.20 (0.12,2.28)
Joint mobility		
Al-Rawi, 1997 ⁶¹	Hyper mobile joints (%)	OR: 4.27(3.39,7,61)
	Normal mobile joints (%)	OR: 0.23 (0.13,0.42)
Psychological factors		
Jensen, 2008 ⁶⁶	Coop-Wonca Chart	0.82 (0.45,1.19)
	Hopkins Symptoms Checklist-25 (HSCL-25)	0.38 (0.17,0.59)
Neurologic factors		
Jensen, 2008 ⁶⁶	Detection threshold of warmth (°C)	P value: <0.05
	Detection threshold of cold (°C)	P value: <0.05
	Tactile perception threshold (g/mm ²)	P value: <0.05
Extrinsic factors		
Dorotka, 2002 ³²	Duration of sport participation (months)	-16.40 (-30.58,-2.22)
	Sports activity before military training (%)	OR: 2.28 (1.36,3.83)
	In basis training from the military training (%)	OR: 2.00(1.20,3.32)
	Previous injury to the knee (%)	OR: 6.84 (3.01,15.3)
Duffey, 2000 ⁵⁸	Shoe mileage (miles)	-157.0 (-267.06,-46.94)
Jensen, 2008 ⁶⁶	Triple jump test (cm)	55.0 (29.39,80.61)
Piva, 2005 ⁴⁹	Activities of Daily Living Scale score	-35.30 (-42.03,-28.57)
Thomee, 1995 ⁵⁴	Total competitive sports activities (times/week)	P<0.0001

* MD (95%CI) were calculated by Crossley et al. as: mean controls – mean cases.

All other MD (95%CI) were calculated as: mean cases – mean controls

Kinetic measures

Foot and ankle characteristics

Three studies examined a total of 31 variables for dynamic rear foot motion during running and stair descending.^{24 31 58} One study reported a larger contact area of medial and mid-foot rear foot and lower peak pressure in the rear foot expressed by six variables in PFPS patients compared to controls during stair descending (table 3).²⁴ Duffey et al reported lower pronation velocity expressed in two variables in PFPS patients compared to controls (table 3).⁵⁸ In this study, PFPS patients had also a significant less calcaneus-tibia touchdown angle (MD 2.80 95% CI 0.46 to 5.14) and less foot pronation angle during first 10% of stance during running (MD -1.30; 95% CI -2.27 to -0.33) compared to controls.⁵⁸

Ground reaction force

Two studies examined 21 variables for ground reaction force during running, single leg squat and single leg jump.^{57 58} Only a significantly lower maximum lateral force during running in the PFPS group compared to the control group was found in one study (MD -0.09; 95% CI -0.11 to -0.07).⁵⁸

Peak moments

Peak moments in LE muscle were examined by eight variables.^{26 53 57} Only knee flexion-extension moment during running was significantly lower in the PFPS group compared to the control group in one study (MD -0.38; 95% CI -0.64 to -0.12).²⁶

Peak torques

The peak torques of the LE muscles were examined in five studies, including 30 variables.^{27 56 58 63 70} Peak torques were expressed in Newton metre (Nm) per unit of time. Pooling was possible for one variable; PFPS patients had a significantly lower knee extension peak torque at 60° (Nm) compared to control subjects (WMD: -37.47 95% CI -71.75 to -3.20) (figure 7).^{56 58} In four studies PFPS patients had a significantly lower peak torque compared to controls expressed by 14 variables (table 3).^{56 58 63 70} No significant associations were found among the other 15 studied variables.^{27 58}

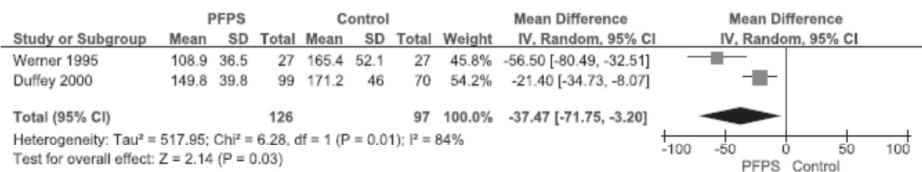


Figure 7 Forest plot: association patellofemoral pain syndrome and peak torque knee extension 60° (Nm).

Kinematic measures

Patella

Patella joint kinematics and mobility were described by 15 variables.^{41 46 65} In one study no statistical significant associations were found for patella joint kinematics and PFPS.⁴⁶ Another study included PFPS patients without malalignment and a subgroup of PFPS patients with malalignment and evaluated the difference in patella joint kinematics and mobility between these groups and the controls. Although no significant association was found between PFPS patients without malalignment compared to controls, the PFPS patients with malalignment had a more laterally shifted patella during flexion ($p=0.049$) and had a significantly lower rate of posterior shift during knee flexion compared to control subjects ($p=0.01$).⁴¹ In one study none of the control subjects had positive active patellar instability tested compared with 25% of the PFPS patients (p value: 0.004). The other five examined variables were not associated with PFPS.⁶⁵

Angles

Six studies reported a total of 36 variables on dynamic LE angles.^{30 31 43 51 57 70} The dynamic LE angles were measured during different physical activities and two studies found smaller flexion angles expressed by eight variables for knee, hip adduction, hip internal rotation and frontal plane pelvis in PFPS patients compared to controls (table 3).^{30 57} Larger angles were found for hip adduction during single leg squat, hip abduction at peak knee extension moments during single leg jump (MD 3.84; 95% CI 0.85, 6.83 and 3.75; 95% CI 0.17 to 7.33, respectively),⁵⁷ peak hip internal rotation during running and during step-down (MD 7.60 95% CI 4.14, 11.06 and 6.40 95% CI 1.85 to 10.95, respectively)⁷⁰ and knee flexion at footstep contact across different step heights ($p=0.038$)⁴³ in PFPS patients compared to controls in two studies.^{43 57} Another study evaluated maximum knee flexion angle during free speed walking, fast walking, ramp descent, ramp ascent, stair ascending and stair descending expressed in seven variables; however none were significantly associated with PFPS.⁵¹

Velocity

Two studies measured velocities (degrees/second), described by 10 variables.^{31 62} One study measured the velocities for six joint motions, expressed in the maximum velocity that occurred during the stance phase while running. The joint motions for hip adduction and hip internal rotation velocity were significantly lower in PFPS patients compared to controls (MD -70.50; 95% CI -121.41, -19.59 and -71.50; 95% CI -135.73 to -7.27, respectively).³¹ PFPS patients were unable to perform a smoothly controlled eccentric quadriceps contraction during stair descent at slow velocities and knee angular velocities.⁶² No significant associations were found among the other five variables studied.^{31 62}

Excursion

Fifteen variables for LE excursions were measured in two studies and calculated as the peak angle during the first half of stance minus the minimum angle preceding the peak during running,^{31 57} single leg squat and single leg jump.⁵⁷ No significant association between LE excursion and PFPS were found in one study;³¹ however, a greater hip internal rotation excursion in PFPS patients compared to controls during a single leg squat (MD 3.50; 95% CI 1.21 to 5.79) and a lower knee internal rotation excursion (MD -2.70 95% CI -4.99 to -0.41) in PFPS patients compared to control subjects during single leg jump were found in another study.⁵⁷

Peak stance-phase

Two variables tested the peak knee flexion in the stance phase and were significantly lower at heel-strike during stair ascent and descent in PFPS patients compared to the control participants (MD 6.0; 95% CI 0.6 to 11.4 and 5.5; 95% CI 1.7 to 9.4).³⁰

Muscle function measures

Flexibility

Lower-extremity (LE) muscle flexibility was expressed by nine variables^{20 48 49} and five variables showed a significantly decreased flexibility of the LE muscles in PFPS patients

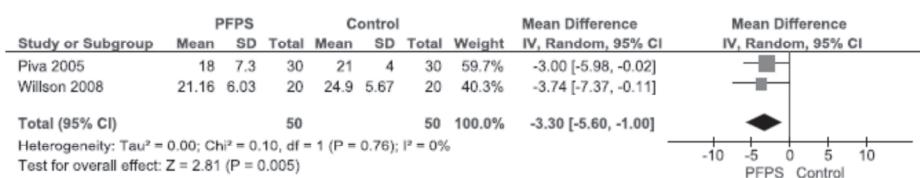


Figure 8 Association patellofemoral pain syndrome and hip abduction strength (relative to % body weight).



Figure 9 Forest plot: association patellofemoral pain syndrome and hip external rotation strength (relative to % body weight).

(table 3).^{48 49} None of the other evaluated variables were significantly different between both study groups.^{20 49}

Muscle strength

Muscle strength was described in six studies, including 33 variables.^{26 31 42 49 57 67} Pooling was possible for two variables. Pooled data showed less hip abductor strength (percentage body weight, %BW) (WMD -3.30; 95% CI -5.60 to -1.00) (figure 8)^{49 57} in PFPS patients compared to controls and less hip external rotation strength (%BW) (WMD -1.43; 95% CI -2.71 to -0.16) in PFPS patients compared to controls (figure 9).^{49 57} Less strength of the LE muscles was found in PFPS patients compared to controls in three studies, expressed by four variables (table 3).^{31 42 57} One study examined peak forces in the LE muscles during running and walking expressed by 21 variables; patients with PFPS had greater peak force in VL, vastus intermedius (VI) and semitendinosus muscles during walking and greater peak force in gastrocnemius muscle during running compared to controls (table 3). The maximum force developed of the quadriceps during knee extension was significantly lower in PFPS patients compared to control subjects in one study (-50.50 95% CI -80.82 to -20.18).⁶⁷ Also PFPS patients had a significantly greater co-contraction of quadriceps and hamstrings at heel strike during walking ($p=0.025$).²⁶ No significant difference between both study groups was found for the other 20 evaluated variables.^{26 31 42 49}

Muscle endurance

One study evaluated 10 variables for muscles endurance, expressed by the product of the torque (the force that the subjects exerted at a given distance perpendicular to the dynamometer axis) and the range of motion through which it was applied (Newton metre per unit of time). Significantly less muscle endurance in the PFPS group was found compared to the control group, expressed by eight variables (table 3).⁵⁸

Muscle timing

A total of 97 variables for muscle timing of the LE muscles were evaluated in nine studies.^{29 43 47 50 51 59 67 68 70} Electromyographic (EMG) onset timing of VMO during concentric

task, eccentric task, lifting toes, rising toes, stair descent, ramp descent, stair ascent and ramp ascent was delayed in PFPS patients compared to control subjects expressed by 10 significantly associated variables (table 3)^{29 51 59} and EMG cessation of VMO was delayed during stair descent (MD 5.70; 95% CI 1.37 to 10.03).⁵¹ Seven variables for onset timing of VL during different physical activities were reported.^{50 51 59} Onset of VL occurred earlier than the soleus muscle activation in PFPS patients (MD -63.20 (-90.31 to -36.09);⁵⁹ however, the onset of VL was delayed during ramp descent in PFPS patients compared to controls (MD 3.60; 95% CI 0.46 to 6.74).⁵¹ EMG onset and cessation of VL and vastus medialis longus (VML) were measured in Powers et al during six different physical activities that is, free speed walking, fast walking, stair ascent and descent and ramp ascent and descent; cessation of both muscles was delayed during stair descent and onset of both muscles was delayed during ramp descent in PFPS patients (table 3).⁵¹ Powers et al also described the mean intensity of all vasti muscle and the intensity of EMG activity for VMO and VL (% of maximal muscle test) contraction during six different physical activities and those were both significantly lower during all physical activities, except for stair ascending and descending, in PFPS patients compared to control subjects. Intensity of the VL muscle (EMG activity) was significant lower during ramp ascent, ramp descent and stair descent in the patients with PFPS compared to controls.⁵¹ In one study, activation levels during maximum voluntary knee extension initiated with the knee flexed were measured for VMO and VL muscles, both normalised activation levels were greater in PFPS patients compared to control subjects.⁶⁸ Maximum voluntary isometric contraction of the average gluteus maximus and medius muscles were measured during running, step-down and drop jump. In one study the activation of VMO, VL and rectus femoris muscles relative to the main bulk of the muscle were significantly slower than for the control subjects.⁶⁷ Average gluteus maximus EMG signal was greater in PFPS patients during step-down and running compared to controls (MD 5.90; 95% CI 1.39, 10.4 and 21.0; 95% CI 6.22 to 35.8). No significant differences were found among the other four studied variables.⁷⁰ One study described significant less onset timing difference between lateral hamstring and medial hamstring muscle in PFPS patients compared to controls (MD -53.80; 95% CI -105.66 to -1.94).⁴⁷ No significant associations were found among the other 55 studied variables.^{43 50 59 68}

Other measures

Joint position sense

Four variables for joint position sense in the knee were measured in one study. The error between demonstrated and performed action was significantly greater in PFPS patients in weight-bearing joint position sense at 60° knee flexion compared to the control group (MD 1.20; 95% CI 0.12 to 2.28).²⁵

Joint mobility

In one study the percentage of hypermobile and normal mobile joints in PFPS patients were compared with the number of hypermobile and normal mobile joints in the control group. In the group with PFPS patients more joints were hypermobile compared to the control group (OR: 4.27; 95% CI 3.39 to 7.61).⁶¹ In the control group more normal mobile joints were found compared to PFPS patients (OR: 0.23; 95% CI 0.13 to 0.42).⁶¹

Joint effusion

No significant differences in joint effusion were found between PFPS patients and control subjects.⁶⁵

Psychological factors

Two psychological variables and their relationship with PFPS were evaluated in one study. PFPS patients had reduced 'self-perceived health status' and increased 'mental distress' compared to controls (MD 0.82; 95% CI 0.45, 1.19 and 0.38; 95% CI 0.17 to 0.59, respectively).³⁶

Neurological

Five variables to measure neurological signals were studied in one study.⁶⁶ The detection threshold of warmth was higher in PFPS patients compared to controls (p value: <0.05); hence the detection threshold of cold was lower in PFPS patients compared to controls (p value: <0.05). The tactile perception threshold (Von Frey) in the painful area of the knees from PFPS patients was increased compared to the control group (p value: <0.05). No differences between both groups were found for the sum of detection thresholds (limen) and for the heat pain thresholds.⁶⁶

Extrinsic factors

Extrinsic factors were examined by 29 variables.^{32 36 49 54 58} Duffey et al evaluated 18 training variables using a runners' history questionnaire that inquired about past running injuries, training regimen, running terrain, running shoes, stretching and running experience. Only mileage accumulated in shoes before discarding was significantly lower in the PFPS group (MD -157.0; 95% CI -267 to -47).⁵⁸ One study described a significantly shorter period of sport participation before military training (MD -16.40; 95% CI -30.6 to -2.22), a significantly higher number of sport participants before basic military (OR 2.28; 95% CI 1.36 to 3.83), a significantly higher number of previous knee injuries in PFPS (OR 6.84; 95% CI 3.01 to 15.3) and significantly more PFPS patients were in basic training of the military training compared to controls (OR 2.00; 95% CI 1.20 to 3.32).³² Thomeé et al found a higher number of PFPS patients participating in competitive sports compared to controls (p<0.0001).⁵⁴ One study used the triple jump test to evaluate the functional

demands of weight bearing and jumping. Subjects had to stand on one foot and jumped three times on the same lower extremity, first on the pain-free LE and then on the LE with the painful knee. The difference between the lower extremities in centimetre was recorded as the final score. PFPS patients demonstrated a greater difference between involved an uninvolved LE during the triple jump test compared to controls (MD 55.0; 95% CI 29.4 to 80.6).³⁶ One study reported lower activities of daily living score in PFPS patients compared to controls (MD -35.30; 95% CI -42.0 to -28.6).⁴⁹ No other evaluated extrinsic factors were significantly associated with PFPS.^{32 54 58}

Discussion

This review examined the factors associated with PFPS. The 47 included studies evaluated 523 variables for PFPS. Pooling was possible for eight variables and a significantly larger Q-angle, larger sulcus angle, larger patellar tilt angle, lower peak torque knee extension, significantly lower hip abduction strength and significantly lower hip external rotation strength were found in the PFPS patients compared to controls. No difference was found for arch height index and congruence angle.

The pooled data showed a significant larger Q-angle in PFPS patients. The pooled analysis showed a large statistical heterogeneity between the studies. This might partly be explained by the methodological difference among the studies and due to the lack of consensus of the measurement method of the Q-angle. A recent systematic review concludes that the considerable disagreement on the reliability and validity of the clinical Q-angle measurements might be due to the lack of standardization in the measurement procedure. This might also be one of the causes for the heterogeneity found in our statistical analysis.⁷⁴ One study found larger, although not significant, Q-angles during the measurement at 0° compared to the 30° measurement.⁵⁴ To reduce the chance on heterogeneity, data from the Q-angle at 30° were not used for pooling and in most included studies the Q-angle was measured with the knees in full extension. It is apparent the Q-angle is not significantly associated with future PFPS, as shown in the systematic review on risk factors for PFPS.¹² Considering that the Q-angle is not expected to change after the onset of PFPS, it is not expected that the Q-angle is a consequence of PFPS. Nevertheless, the pooled data of our review shows that a larger Q-angle is associated with current PFPS. Since the recent systematic review could not recommend the best suitable method to measure the Q-angle, more research is required to establish a standardized clinical Q-angle protocol.⁷⁴

The pooled data of two studies showed lower knee extension peak torques at 60°/s (Nm) in PFPS patients, although a large statistical heterogeneity was seen between these studies. This might be explained by the difference in the PFPS patient groups;

that is, in the study done by Duffey et al 31% of the PFPS patients were female, while in the study by Werner et al 52% of the PFPS patients were female.^{56 58} Nevertheless, lower extension peak torque was confirmed as a risk factor for PFPS in two prospective studies.^{75 76} This suggests that a lower knee extension peak torque at 60°/s is associated with PFPS, and might even be apparent before development of PFPS. This is confirmed by the results of a recent published review, in which a meta-analysis showed that future PFPS patients have lower knee extension peak torque at 60°/s, indicating a lower concentric peak torque for the knee extensors. In these studies the evaluated peak torques were expressed as a measure for strength of the lower-extremity muscles. Therefore, it seems that PFPS patients have less quadriceps strength and this even seems to be a risk factor for PFPS.^{12 56 58 75 76}

Pooled data showed significantly less hip abduction strength (%BW) and less hip external rotation strength (%BW) in PFPS patients compared to the control subjects.^{49 57} In contrast, a prospective study on risk factors reported no significant differences in hip abduction strength (%BW) and hip external rotation strength (%BW) between future PFPS patients and control subjects.⁷⁷ owing to patellofemoral pain a large percentage of patients are forced to stop sports activities⁷⁸ and therefore might cause decreased lower-extremity muscle strength in PFPS patients. Hence, more prospective research is needed to clarify whether less hip abduction strength (%BW) and hip external rotation strength (%BW) rather is a consequence of PFPS than a cause.

Conflicting evidence was found for dynamic hip internal rotation angle in two studies.^{57 70} One study found a smaller hip internal rotation angle during a single leg squat and a single leg jump.⁵⁷ Whereas another study found a greater hip internal rotation angle during running and step-down tasks.⁷⁰ A possible explanation for the different results may be attributed to the methodological and measurement differences. Additionally, the question remains as to whether the differences found are a consequence of the pain by compensation or related to the cause of pain.

Delayed EMG onset timing of VMO in PFPS patients during different physical activities was described in three studies, expressed by 10 variables.^{29 51 59} Although pooling was not possible due to the difference in tasks during the measurements, the results of three studies imply that the VMO is delayed in PFPS patients compared to controls during different physical activities.^{29 51 59} Noteworthy is that for the 94 evaluated variables on muscle timing of the vasti muscles, 55 variables were not associated with PFPS. Especially the cessation timing of all vasti muscles and the onset of VL, VML and VI were not significantly different between both study groups during almost all activities. This suggests that only the onset timing of VMO is delayed and had less activity in PFPS patients compared to controls.⁵¹ It is however questionable as to whether the small differences found are also clinically relevant. Discrepancy in outcomes was found for EMG onset timing of VMO relative to VL; two studies did not find a significant difference in

EMG onset timing between VMO and VL between PFPS and control group,^{43 50} while in both studies from Cowan the VMO onset was significantly delayed in PFPS patients.^{29 59} In another study the normalised activation levels of VMO and VL were both greater in PFPS patients compared to controls.⁶⁸ This discrepancy in outcomes was also seen in the systematic review from Chester et al where an association between EMG onset timing of vasti muscles and PFPS is not demonstrated, although they describe a trend for delayed onset of VMO relative to VL in PFPS patients compared to the control subjects.²¹ Conflicting evidence was also seen in two prospective studies investigating risk factors for PFPS.^{78 79} The results of the studies that examined the onset timing of VMO^{21 29 59 78 79} suggest the possible role of delayed onset of VMO relative to VL in PFPS patients. A case-control study on treatment for PFPS patients compared patellar taping with no tape and found that the onset timing of VMO and VL changed in patients with patellar taping.⁸⁰ The mechanism by which knee taping may affect neuromotor control was examined in another study, suggesting that taping reduced the pain in PFPS patients and consequently leads to changes in onset timing.⁸¹ Therefore, the changed onset timing might be a consequence of pain and it remains unclear as to which mechanism is involved in the development of pain in PFPS and therefore further research is necessary.

The clinical relevance of the significant differences between both groups studied in this systematic review is often debatable. For example, the sulcus angle is on average 1.61 degrees larger in the PFPS group, indicating a very small, but significant difference between both study groups. One might argue whether this small difference will have clinical relevance, also taking the measurement errors into account. The same probably counts for the muscle strength findings, finding small significant differences in strength, expressed in percentage of body weight.

Limitations

We performed our literature search in Pubmed (MEDLINE), MEDLINE (OVID), Embase and the WoS and checked all reference lists of included studies, but also of the studies that were excluded based on the study sample. Since there are other literature databases available that were not included in our search strategy, there is a very small chance that relevant literature was missed. We decided to exclude case-control studies including <20 PFPS subjects. This choice was primarily based on the likeliness of publication bias occurring in case-control studies with small numbers of subjects. Therefore, the published small case-control studies are likely to be not representative for all studies performed on factors associated with PFPS. Since the chance on such a bias is relatively large in small case-control studies, we decided to exclude studies with <20 subjects included. As a consequence, we have excluded 58 small case-control studies (figure 1) and therefore might have excluded additional data on factors associated with PFPS. Owing to the magnitude number of variables tested in the included studies, we were unable

to discuss the individual findings of all variables (table 3). Because these findings were based on single studies, further research is required to confirm the possible association with PFPS. Remarkable was that in only five studies the outcome assessor was blinded on health status (PFPS versus controls) of the subjects.^{20 37 39 46 61} Five studies^{35 42 49 65 70} described that the outcome assessor was not blinded and in the other 37 studies it was unclear as to whether the outcome assessor was blinded or not. Therefore, it is likely that detection bias has occurred in those 42 studies. Hereby, there is a major potential that this confounds the results of those studies. To reduce the chance of detection bias, blinding of the examiner in future studies is recommended.

A total of 523 variables were tested in the 47 included studies. Thirteen studies^{28 30 32 34 35 38 40 44 45 53 60 61 63} adhered to 'the rule of ten' (type I error), meaning that in these studies not more than one variable per 10 PFPS patients were examined.⁸² The other 34 studies evaluated more than one variable per 10 cases, which leads to a higher chance on coincident significant findings. Therefore, an unimportant variable could be presented as an important association.⁸³ From the 13 studies that adhered to 'the rule of ten', 10 studies included 50 or more patients with PFPS. Owing to the dissimilarity of the examined variables in the studies, pooling was only possible for eight variables. A meta-analysis for the other 515 evaluated variables was not feasible, because of the difference in outcome measures, methodological measurements, missing data and due to statistical heterogeneity. The lack of consensus for the methodological measurement and the magnitude variability of these factors evaluated in the included studies make it difficult to compare the outcomes and determine the possible associations and implement these on the patients in the primary or secondary care. Furthermore, 13 studies were not truly or somewhat representative for the average population that is, adolescents and adults, mainly females and athletes with PFPS in general practice and sports medicine. This makes it also difficult to translate the results to these patients in primary or secondary care. Nevertheless, this is the first review that provides a systematic overview of all the associated factors examined in published studies.

In conclusion, our review provides indications that PFPS is associated with a larger Q-angle, larger sulcus angle, larger patellar tilt angle, less hip abduction strength conveyed as a percentage body weight and less knee extension strength expressed by peak torque. Other factors that were statistically significant different between PFPS patients and control subjects were based on single studies, and therefore further research is required in high-risk groups that is, athletes and military recruits in a prospective cohort study design.

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Appendix I

Pubmed search:

((patellofemoral pain*[tw] OR patellofemoral syndrom*[tw] OR patello-femoral pain*[tw] OR patello-femoral syndrom*[tw] OR anterior knee pain*[tw] OR patello-femoral disorder*[tw] OR patello-femoral disorder*[tw]) OR ((arthralg*[tw] OR pain*[tw]) AND (knee joint[mesh] OR knee*[tw] OR patell*[tw] OR femoropatell*[tw] OR femoropatell*[tw] OR retropatell*[tw] OR retro-patell*[tw] OR lateral facet*[tw] OR lateral compr*[tw] OR lateral press*[tw] OR odd facet*[tw] OR genu[tw]) AND (syndrom*[tw] OR dysfunct*[tw] OR disorder*[tw] OR chondromal*[tw] OR chondropath*[tw]))) AND (associat*[tw] OR risk*[tw] OR probabil*[tw] OR odds*[tw] OR relat*[tw] OR prevalen*[tw] OR predict*[tw] OR caus*[tw] OR etiol*[tw] OR interact*[tw]))

EMbase

((('patellofemoral pain':ti,ab,de OR 'patello-femoral pain':ti,ab,de OR 'anterior knee pain':ti,ab,de) OR ((patellofemoral OR 'patello-femoral' OR 'anterior knee') NEAR/3 (syndrom* OR disorder*)):ti,ab,de) OR (((arthralg* OR pain*) NEAR/4 (syndrom* OR dysfunct* OR disorder* OR chondromal* OR chondropath*)):ti,ab,de AND (knee* OR patell* OR femoro* OR retropatell* OR 'retro-patellar' OR 'lateral facet' OR 'lateral compression' OR 'lateral pressure' OR 'odd facet' OR genu):ti,ab,de)) AND (associat*:ti,ab,de OR risk*:ti,ab,de OR probabil*:ti,ab,de OR odds*:ti,ab,de OR relat*:ti,ab,de OR prevalen*:ti,ab,de OR predict*:ti,ab,de OR caus*:ti,ab,de OR etiol*:ti,ab,de OR interact*:ti,ab,de)

WoS

((patellofemoral OR "patello-femoral" OR "anterior knee") AND (pain* OR syndrom* OR disorder*)) OR ((arthralg* OR pain*) AND (knee* OR patell* OR femoropatell* OR retropatell* OR "retro-patellar" OR "lateral facet" OR "lateral compression" OR "lateral pressure" OR "odd facet" OR genu) AND (syndrom* OR dysfunct* OR disorder* OR chondromal* OR chondropath*))) AND (associat* OR risk* OR probabil* OR odds* OR relat* OR prevalen* OR predict* OR caus* OR etiol* OR interact*)

Chapter IV

Exercise for treating patellofemoral pain syndrome (Review)

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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 Schlat-ter 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 orthoses⁸, patellar taping⁹ 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)
 - a. Exercise therapy versus unimodal conservative interventions
 - b. Exercise therapy versus multimodal conservative interventions
3. Comparisons of different exercises or exercise therapy programmes:
 - a. Delivery of exercises or exercise programmes (e.g. supervised versus home exercise; group versus individual supervision)
 - b. Medium of exercises or exercise programmes (water versus land-based exercise)
 - c. Types of exercises or exercise programmes (e.g. closed versus open kinetic chain exercises; dynamic versus static)

- d. Target of exercises or exercise programmes (strengthening of hip or abdominal muscles versus quadriceps muscles)
- e. Duration of exercises or exercise programmes (e.g. long duration (more than three months) versus shorter duration (three months or less))
- f. 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 scale²⁵). 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 Crossley 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 (available online <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010387.pub2/full>). 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 review¹⁰, 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 protocol³¹, 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 incorrectly 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 χ^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 χ^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. We used the GRADE approach for systematic reviews³³⁻³⁶ 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; > 3 months); usual pain (long-term); functional ability (short-term); functional ability (long-term); recovery (long-term); see Types of outcome measures) (Higgins³²; 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; Table 1 (available online)

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 (online available); 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 six⁵⁸ to 65.²⁷

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 practices⁵⁸, rehabilitation services^{46 47}, athletic trainer practices⁴⁵, sports medicine practices²⁷, rheumatology department⁴³, department of community health⁴⁸, institute of sports⁴⁸, poster advertisements in public places⁵⁸, screening of all female students at the physiotherapy clinic affiliated to the rehabilitation faculty⁵⁵, or via bulletin board posters and word of mouth⁵² (see Table 1 (online available)). 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); Spain (one); Sweden (one); Switzerland (one); Taiwan (one); The Netherlands (one); Turkey (one); UK (three); and USA (three) (see Table 1 (online available)).

Participants

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

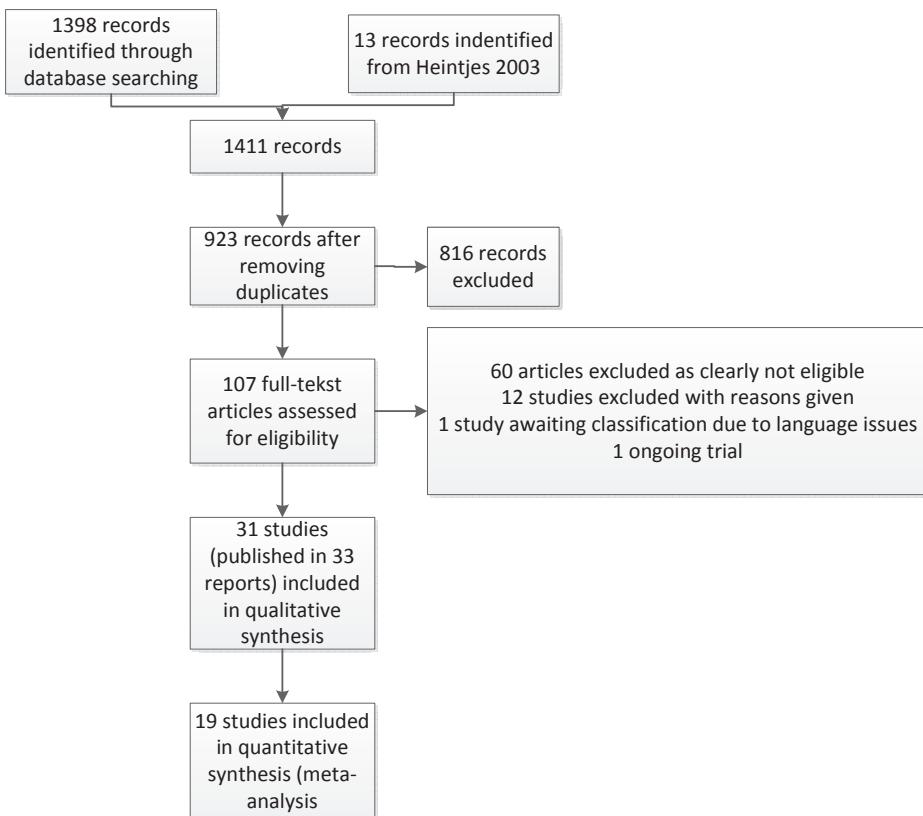


Figure 1 Study flow diagram

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 weeks⁵² 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 (online available)).^{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} Eighteen 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 (online available)). The duration of complaints ranged from four weeks⁵⁴ 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:
 - a. Exercise therapy versus unimodal conservative interventions
 - b. Exercise therapy versus multimodal conservative interventions
3. Different types of exercise therapy
 - a. Delivery of exercises or exercise programmes (e.g. supervised versus home exercise; group versus individual supervision)
 - b. Medium of exercises or exercise programmes (water versus land-based exercise)
 - c. Types of exercises or exercise programmes (with the primary categorisation being by the type of kinetic chain involved)
 - d. Target of exercises or exercise programmes (strengthening of hip and knee muscles versus knee muscles)
 - e. Duration of exercises or exercise programmes (e.g. long duration (more than three months) versus shorter duration (three months or less))
 - f. 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 weeks⁴¹ to four months⁵³ 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 (online available).

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. Her-rington 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 propriocep-tive 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 3 (online available).

Exercise therapy versus unimodal conservative interventions

Four trials compared exercise therapy with different unimodal conservative interven-tions.^{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, 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 inter-ventions 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 4 (online available).

Delivery of exercises or exercise programmes

Two studies compared supervised exercise programmes with home exercise pro-grammes (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 (online available), 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 score²⁰ 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 (online available). 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 scale⁶⁹, patient specific function score, patellofemoral scale, Bessette and Hunter score⁷⁰, WOMAC Osteoarthritis Index²³, Patellofemoral Joint Evaluation Scale⁷¹, Lysholm score²⁵) 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 scale²⁷, number of patients no longer troubled by symptoms⁴³, number of patients with more than 50% improved on pain scale⁶¹, improvement percentage⁶², patients' impression of change (ordinal scale of three)⁵⁰, subjective success (yes or no)⁴⁸, number of patients participating in sports with or without pain⁶⁶, 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 months⁴⁴ 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 al⁷⁶ 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 conventional 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 blinding 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-

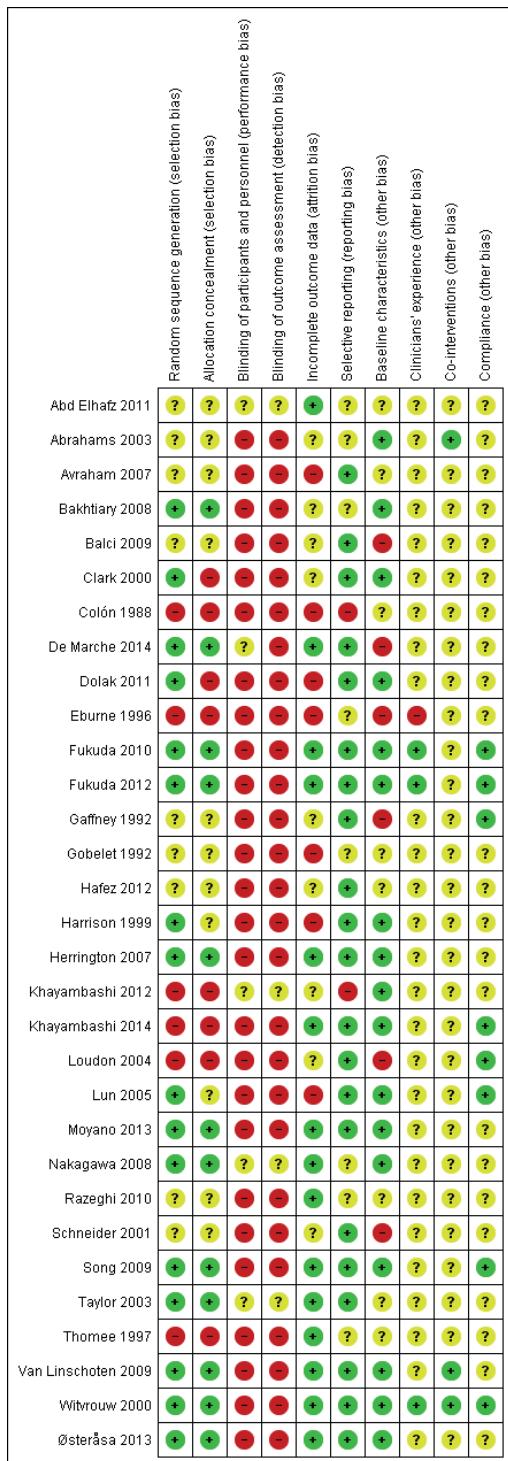


Figure 2 'Risk of bias' summary: review authors' judgement about each risk of bias item for each included study

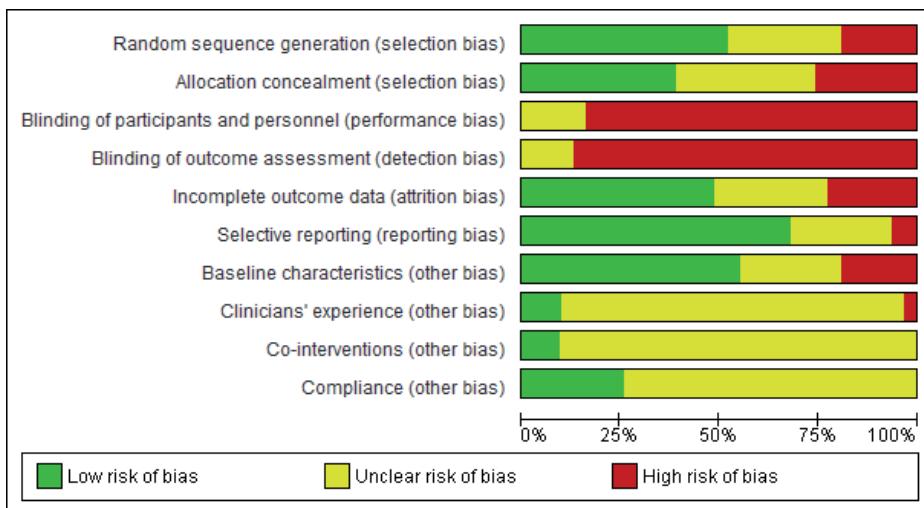


Figure 3 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentage across all included studies

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 Khayam-bashi 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 al¹⁷ 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** (online available). Exercise therapy compared with a control strategy (no treatment, placebo or waiting list controls) for patellofemoral pain syndrome; **Summary of findings 2** (online available) Supervised exercises compared with home exercises for patellofemoral pain syndrome; **Summary of findings 3** (online available) Closed kinetic chain exercises compared with open kinetic chain exercises for patellofemoral pain syndrome; **Summary of findings 4** (online available) Target of exercise: hip + knee versus knee exercises for treating patellofemoral pain syndrome; **Summary of findings 5** (online available) Target of exercise: hip versus knee exercises for treating patellofemoral pain syndrome; **Summary of findings 6** (online available) 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 function⁵¹ 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)

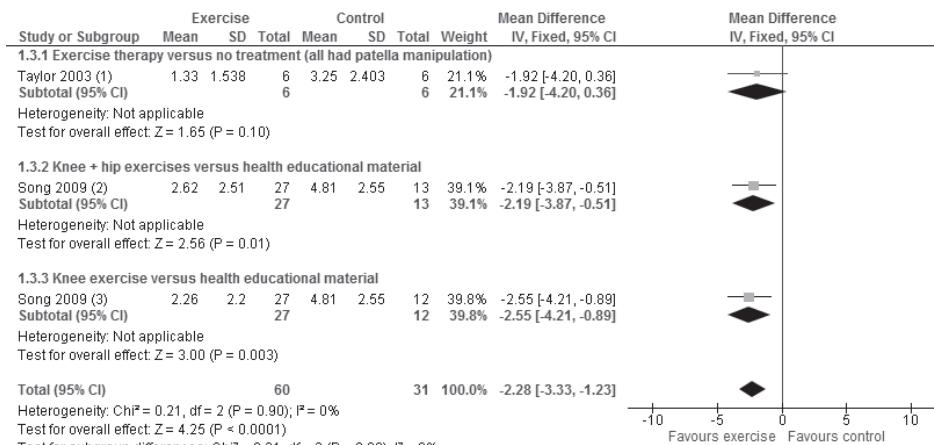
Pooled data from five studies^{27 43 46 51 52} (375 participants) showed a mean difference (MD) of -1.46 favouring exercise therapy, 95% confidence interval (CI) -2.39 to -0.54, P value = 0.002, random-effects model used due to statistical heterogeneity (P value = 0.0003; $I^2 = 74\%$); very low quality evidence due to risk of bias, imprecision and inconsistency; see Analysis 1.1 (online available) and Figure 4. The results were homogeneous (P value = 0.55 and $I^2 = 0\%$) 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).

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 (online available).

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)

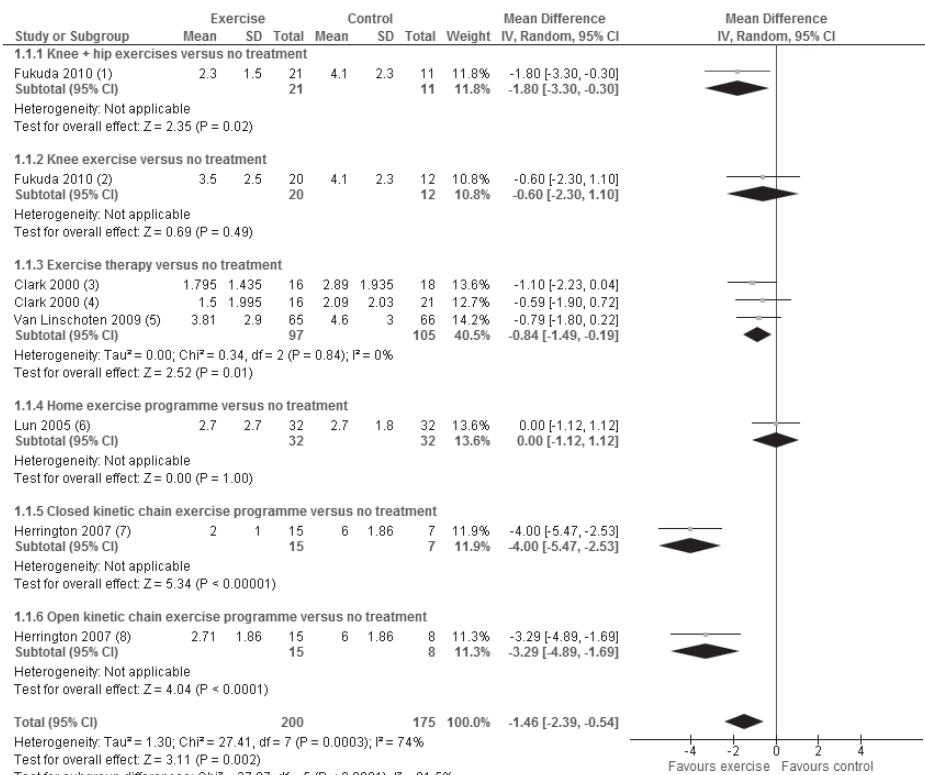
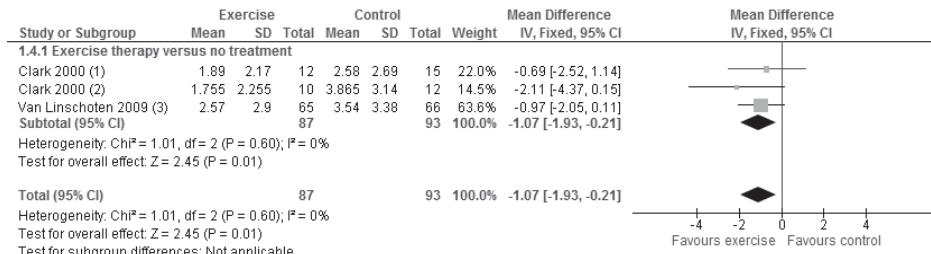


Figure 4 Analysis 1.1: Exercise therapy versus control, outcome: 1.1 Sum: pain during activity continuous short-term

Knee pain in the long term

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

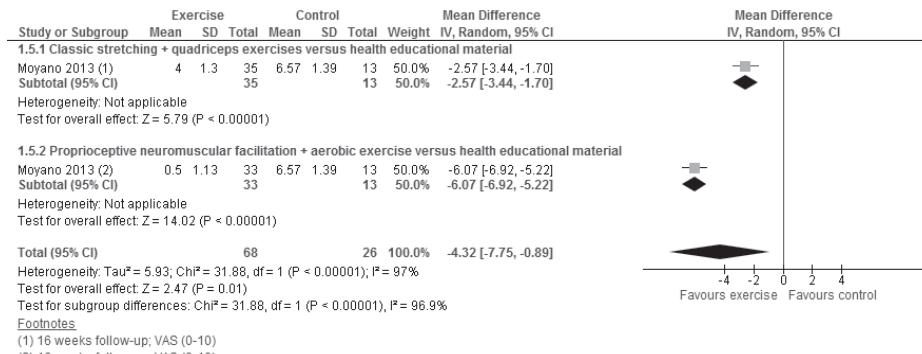
Pooled data from two studies^{27 43} (180 participants) resulted in a MD of -1.07 favouring exercise therapy, 95% CI -1.93 to -0.21, P value = 0.01; very low quality evidence due to serious risk of bias and imprecision; see Analysis 1.4.

**Footnotes**

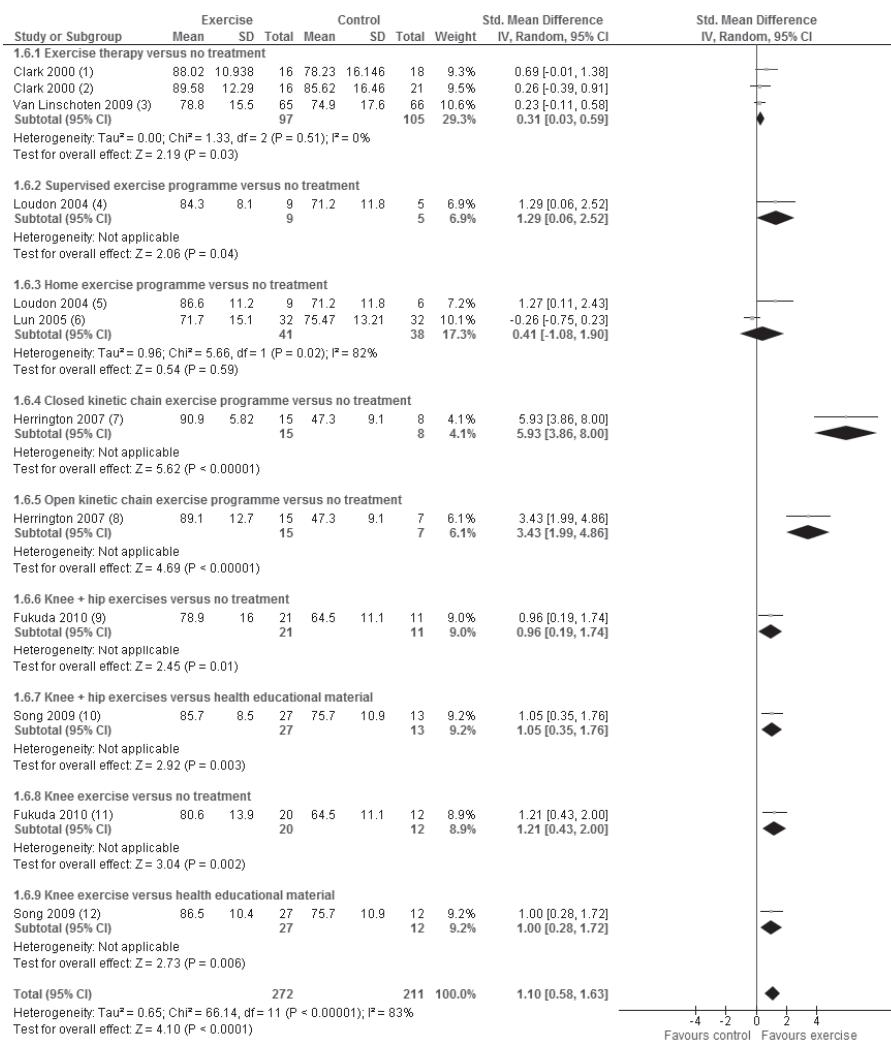
- (1) 12 months follow-up; VA (0-200) scaled to 0-10
- (2) 12 months follow-up; VA (0-200) scaled to 0-10
- (3) 12 months follow-up; VAS (0-10)

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 study⁵³ (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 and Figure 5. The results did not become homogeneous after excluding any single study.



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

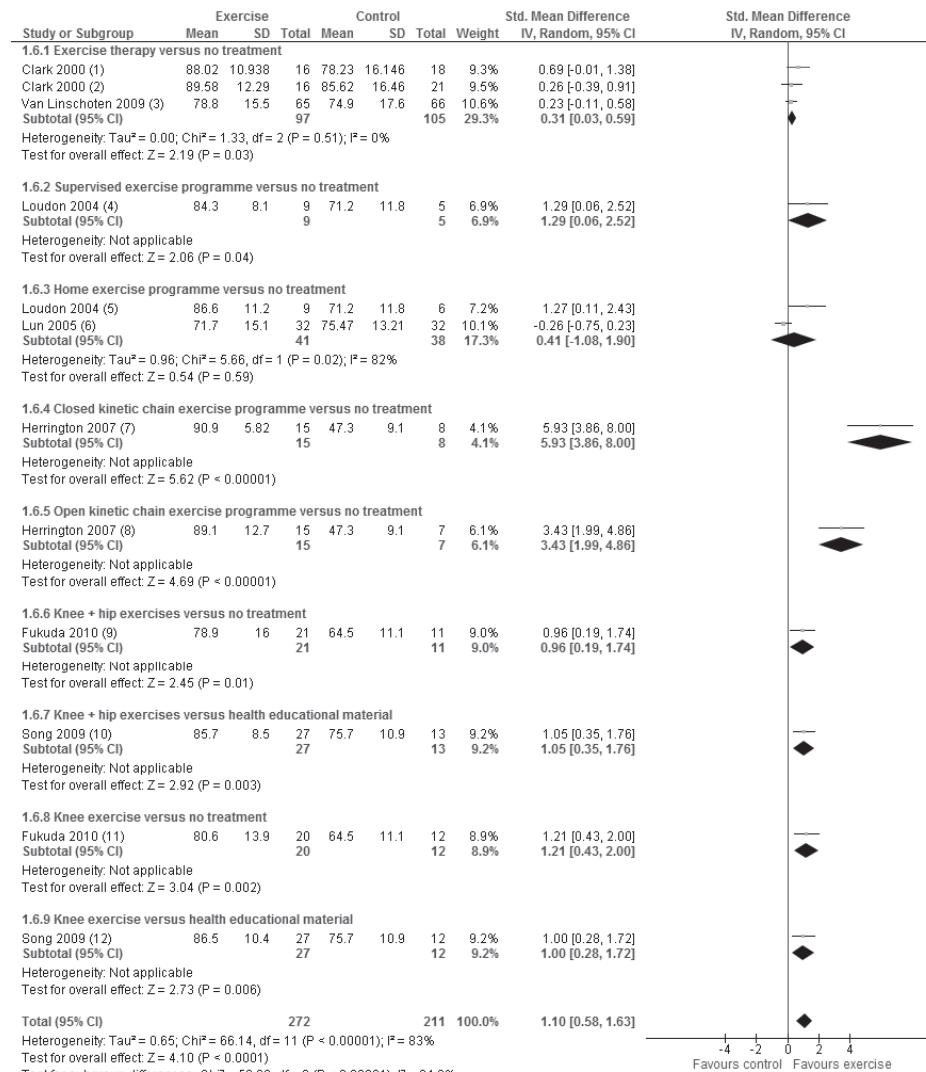
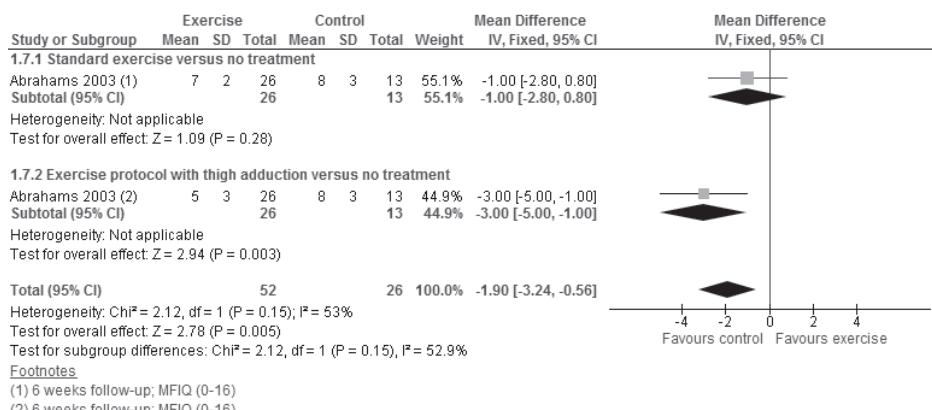


Figure 5 Forest plot Exercise therapy versus control, outcome: 1.5 Sum: functional ability continuous short-term

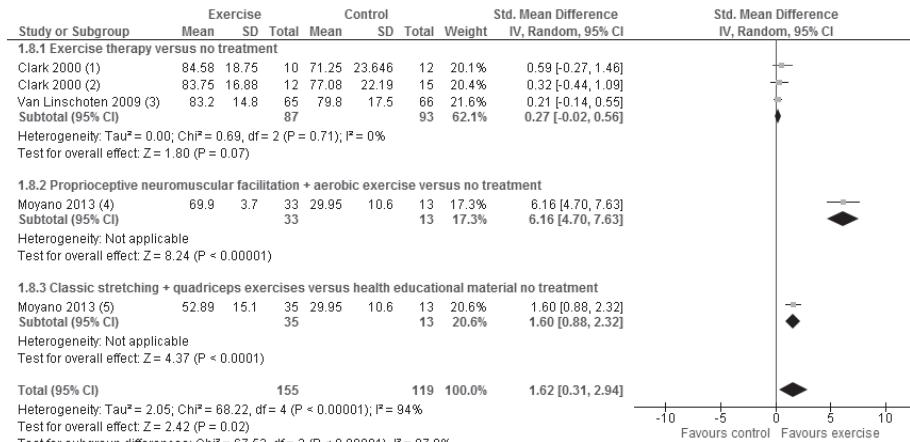
Based on the MFIQ (0 to 16), Abrahams et al.³⁹ (78 participants) reported a MD of -1.90, favouring a control strategy, 95% CI -3.24 to -0.56, P value = 0.005; very low quality evidence due to risk of bias and serious imprecision; see Analysis 1.7.



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)

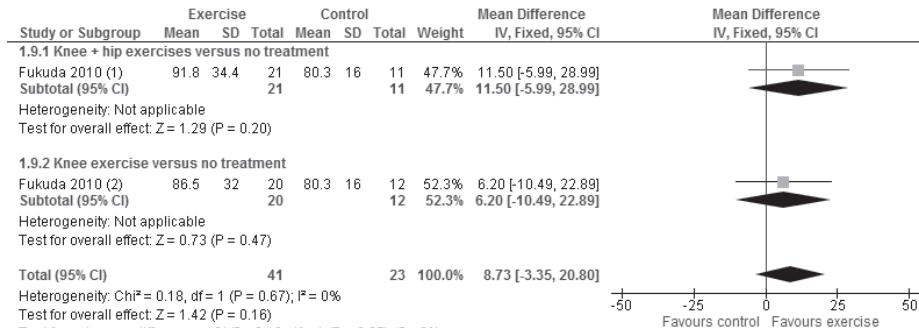
Pooled data from three studies^{27 43 53} (274 participants) resulted in a SMD of 1.62, favouring exercise therapy, 95% CI 0.31 to 2.94, P value = 0.02; random-effects model used due to statistical heterogeneity (heterogeneity P value < 0.00001, $I^2 = 94\%$); very low quality evidence due to risk of 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 (SMD 0.27, 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)

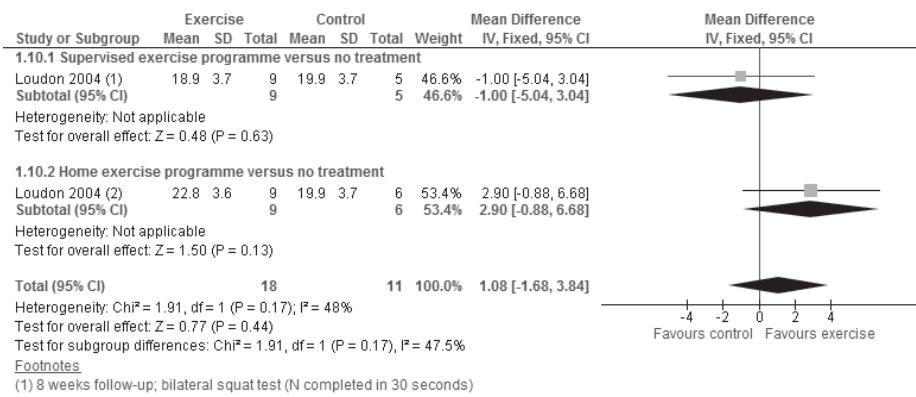
Functional performance in the short term (single-limb hop test; bilateral squat)

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.

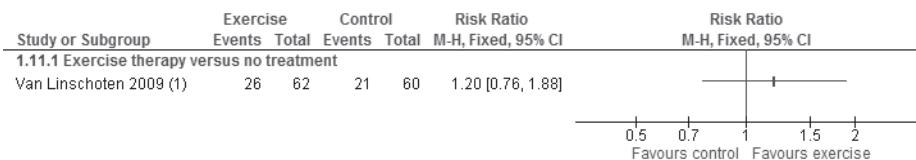


Analysis 1.10 Comparison I Exercise therapy versus control, outcome 10 Functional performance (short term), bilateral squat test

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.

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.



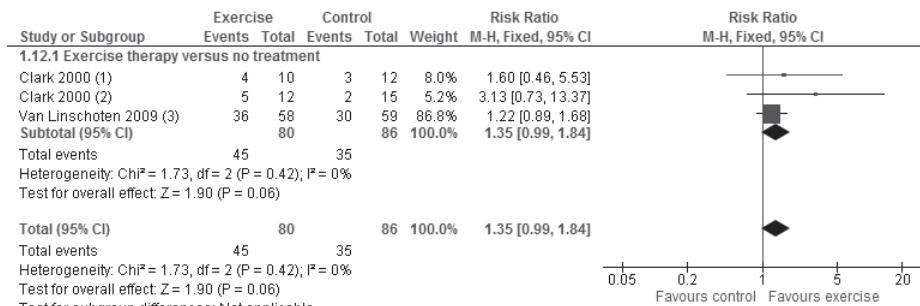
Footnotes

(1) 3 months follow-up; Number of patients recovered

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 12 months; RR 1.35 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 serious 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.

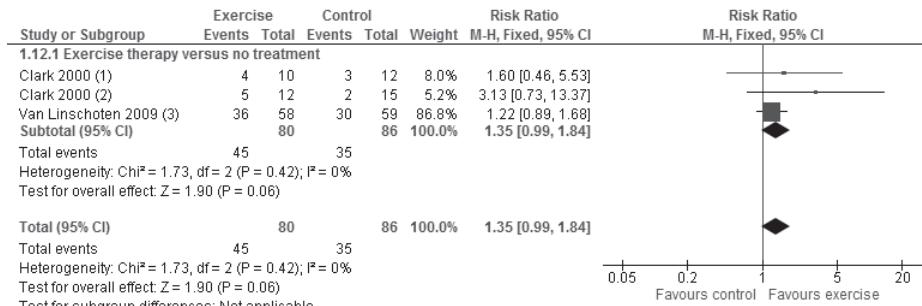
Exercise therapy versus tape

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.

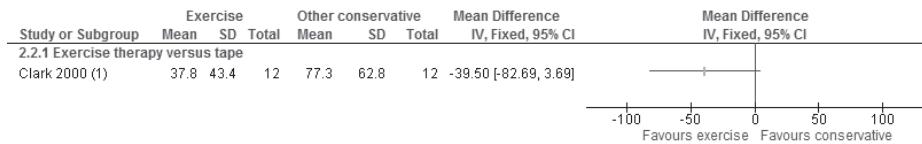


Analysis 2.1 Comparison 2 Exercise therapy versus unimodal conservative interventions, Outcome 1 pain during activity (short term)

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.



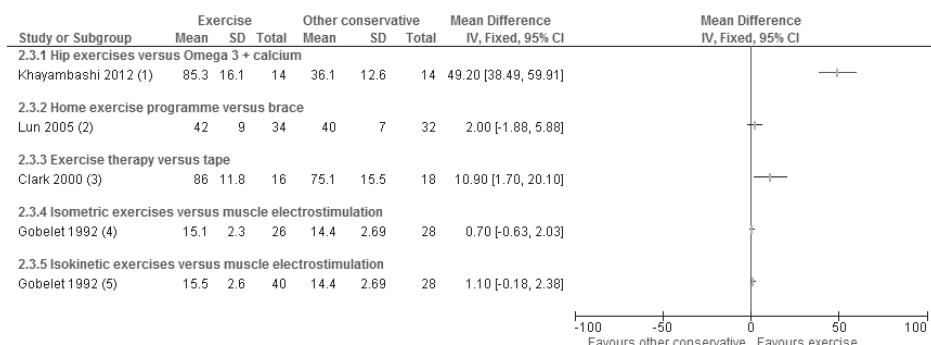
Footnotes

(1) 12 months follow-up; VAS (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.

**Footnotes**

(1) 8 weeks follow-up; WOMAC (0-96) (Inverted scores: 96 - actual score)

(2) 3 months follow-up; Function Scale (0-53)

(3) 3 months follow-up; WOMAC (0-96) (inverted score: 96 - actual score)

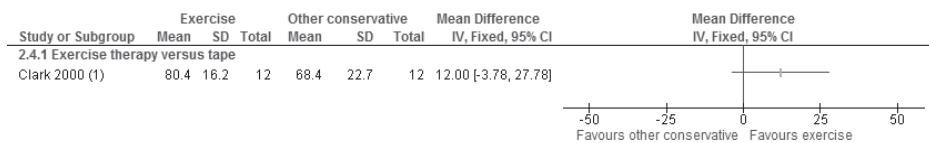
(4) 4 weeks follow-up; Arpege function scale (0-18)

(5) 4 weeks follow-up; Arpege function scale (0-18)

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.

**Footnotes**

(1) 12 months follow-up; WOMAC (0-96) (Inverted scores: 96 - actual score)

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 Bannister⁶² 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

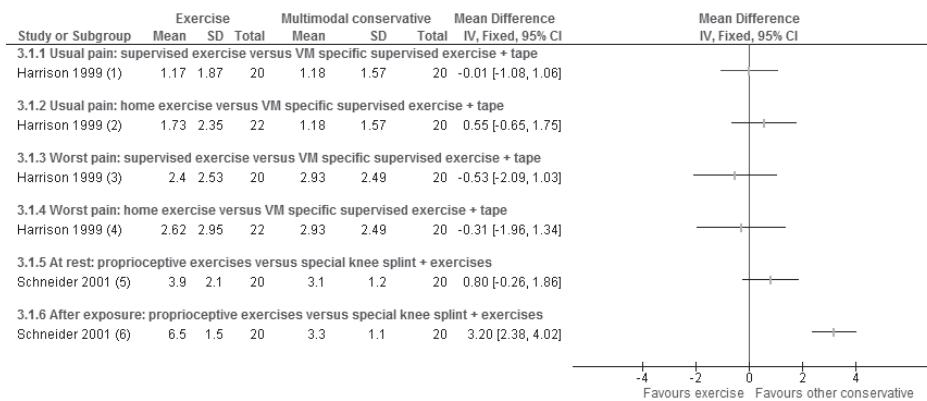
Knee pain in the short term

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.

Footnotes

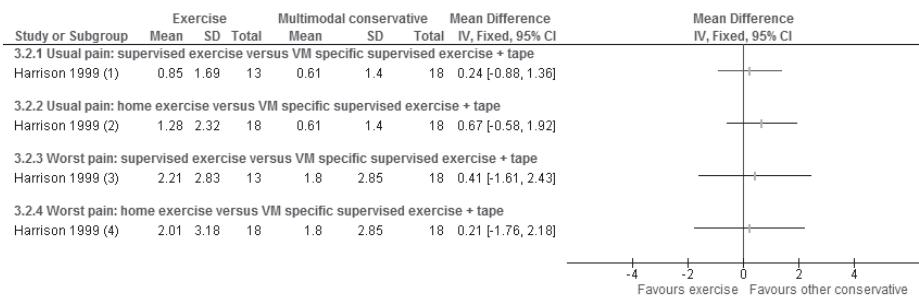
- (1) 3 months follow-up; VAS (0-10)
- (2) 3 months follow-up; VAS (0-10)
- (3) 3 months follow-up; VAS (0-10)
- (4) 3 months follow-up; VAS (0-10)
- (5) 8 weeks follow-up; VAS (1-10)
- (6) 8 weeks; VAS (0-10)

Analysis 3.1 Comparison 3 Exercise therapy versus multimodal conservative interventions, Outcome 1 Pain (short term)Knee pain in the long termUsual 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.

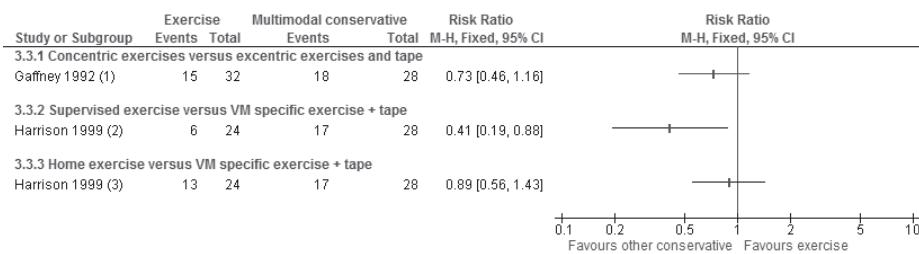
**Footnotes**

- (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**

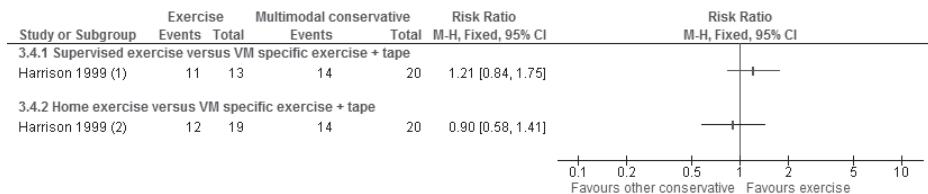
- (1) 8 weeks follow-up; Number of patients improved
- (2) 1 month follow-up; high modified FIQ scores (best function)
- (3) 1 month follow-up; high modified FIQ scores (best function)

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.



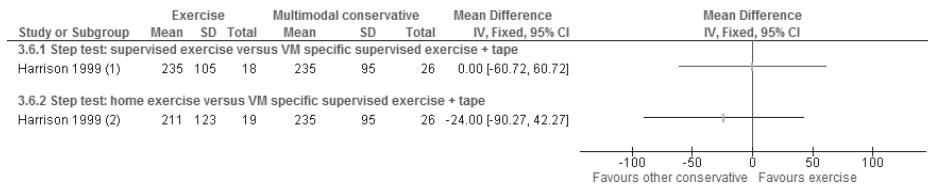
Footnotes

(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)

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.



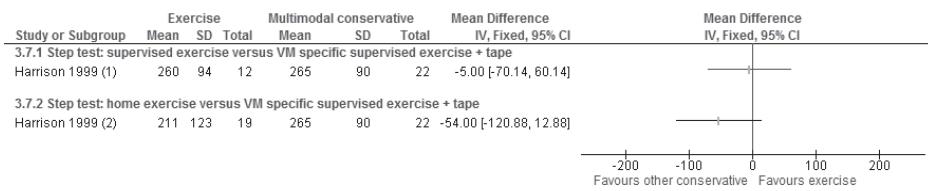
Footnotes

(1) 3 months follow-up; step test (seconds until pain)
 (2) 3 months follow-up; step test (seconds until pain)

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)

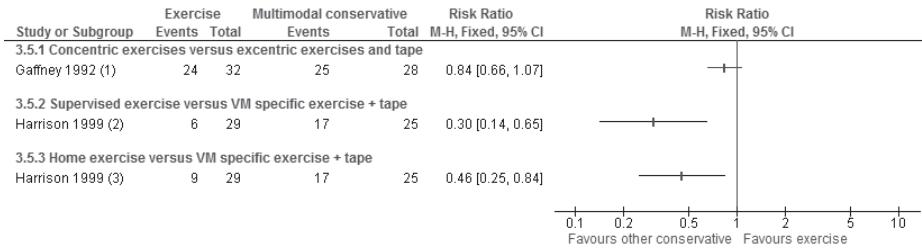
Harrison et al.⁵⁰ (34 participants) performed a step test (time until pain) and reported a MD of -5.00 seconds favouring a vastus medius specific exercise programme plus taping, 95% CI -70.14 to 60.14, P value = 0.88; very low quality evidence due to risk of bias and serious imprecision; see Analysis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



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

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 favouring 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 from 53 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

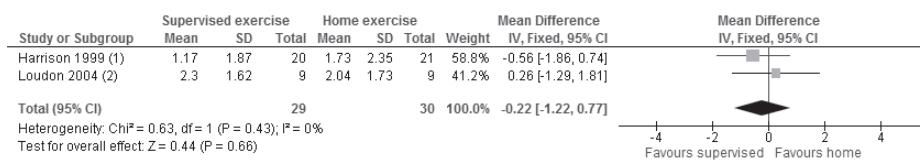
Two studies compared supervised with home exercise programmes.^{50 65} Harrison et al.⁵⁰ reported functional ability using a modified FIQ and a non-validated patellofemoral scale; only the modified FIQ is presented below. Neither study reported on adverse

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.



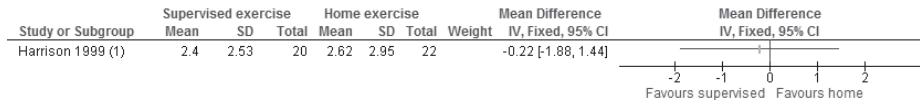
Footnotes

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

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.



Footnotes

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

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

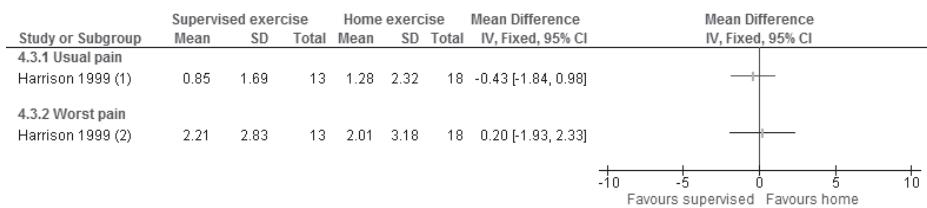
Knee pain in the long term

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.

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*.

**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)

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**

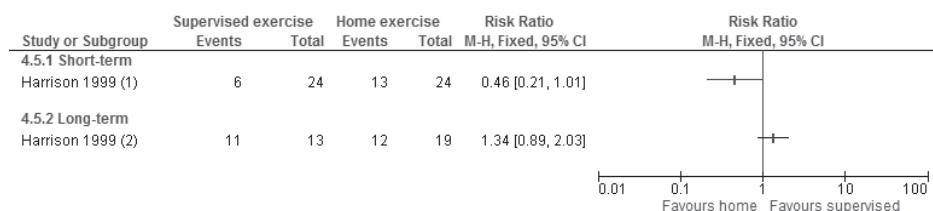
(1) 8 weeks follow-up; AKPS (0-100)

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*.

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.

**Footnotes**

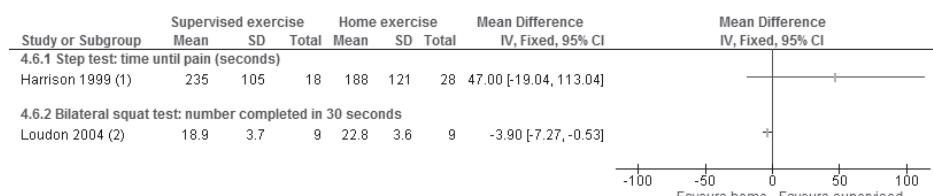
(1) 1 month follow-up; high modified FIQ scores (best function)

(2) 12 months follow-up; high modified FIQ scores (best function)

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

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.

**Footnotes**

(1) 3 months follow-up

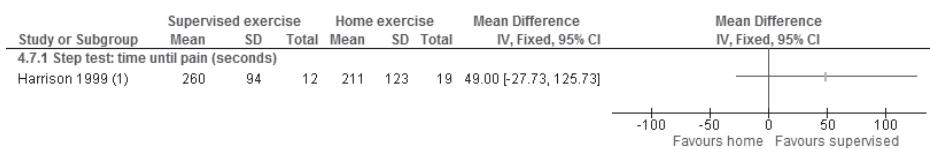
(2) 8 weeks follow-up

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

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.



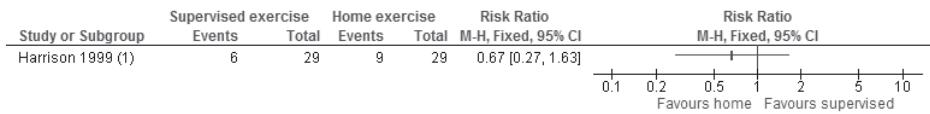
Footnotes

(1) 12 months follow-up; step test (seconds until pain)

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.



Footnotes

(1) 1 month follow-up: participants' rating of significant improvement

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.

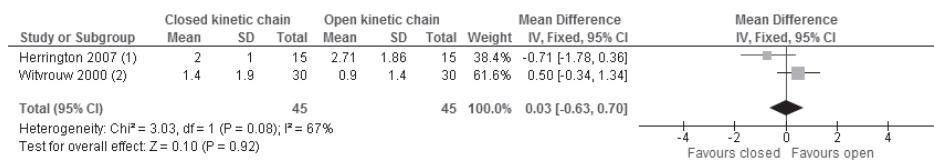
Closed kinetic chain exercises versus open kinetic chain exercises

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 function⁵¹ and function¹⁷ 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.



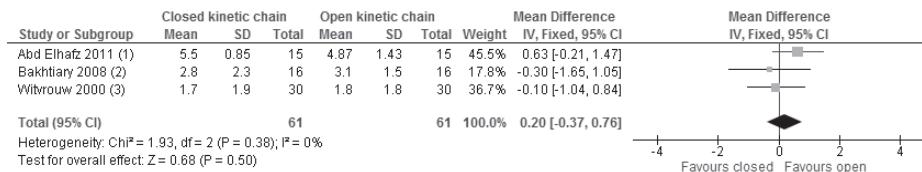
Footnotes

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

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.

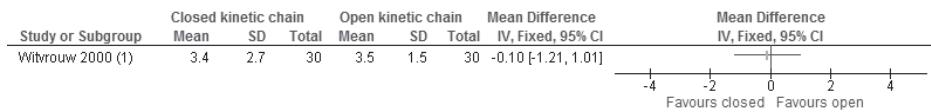
**Footnotes**

- (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)**

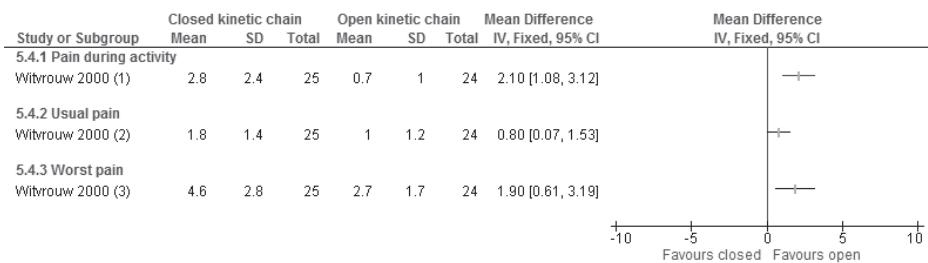
Witvrouw et al.¹⁷ (49 participants) showed a MD of 2.10 favouring open kinetic chain exercises, 95% CI 1.08 to 3.12, P value <0.0001; very low quality evidence due to risk of bias and serious imprecision; see Analysis 5.4.

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.

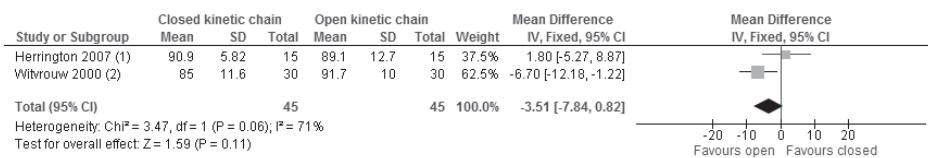
**Footnotes**

(1) 5 years follow-up; VAS (0-10)
 (2) 5 years follow-up; VAS (0-10)
 (3) 5 years follow-up; VAS (0-10)

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

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.

**Footnotes**

(1) 6 weeks follow-up; AKPS (0-100)
 (2) 3 months follow-up; AKPS (0-100)

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.

**Footnotes**

(1) 5 years follow-up; AKPS (0-100)

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

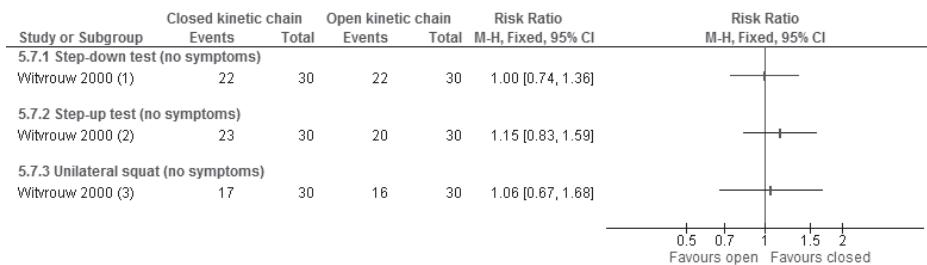
Functional performance in the short term (step-up, stepdown, unilateral squat)

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)

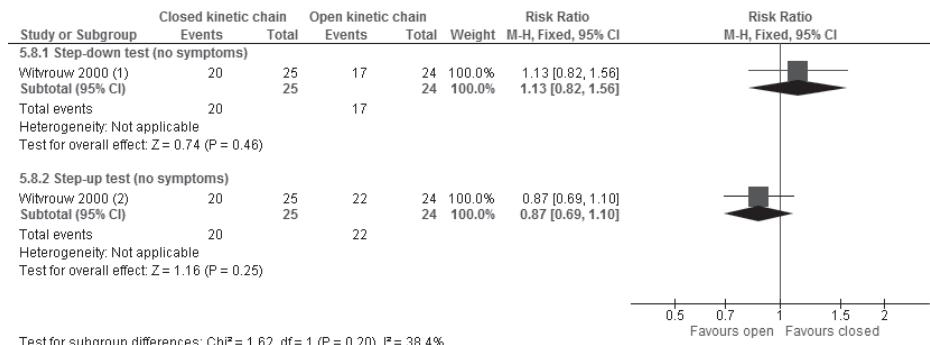
Analysis 5.7 Comparison 5 Types of exercise: closed kinetic chain exercises versus open kinetic chain exercises, Outcome 7 Functional performance (short term)

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

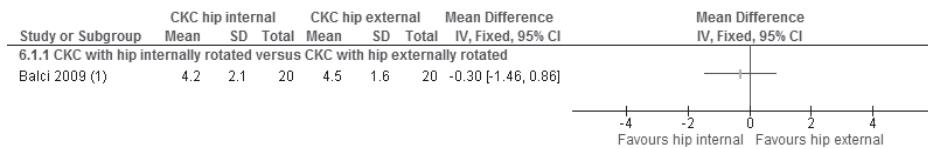
Two studies tested variants of closed kinetic chain exercises. Abrahams et al.³⁹ compared an exercise protocol with thigh adduction and tibiamedial rotation during eccentric squat versus a traditional exercise protocol. Balci et al.⁴² compared closed kinetic chain exercises with internally rotated hip 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.

**Footnotes**

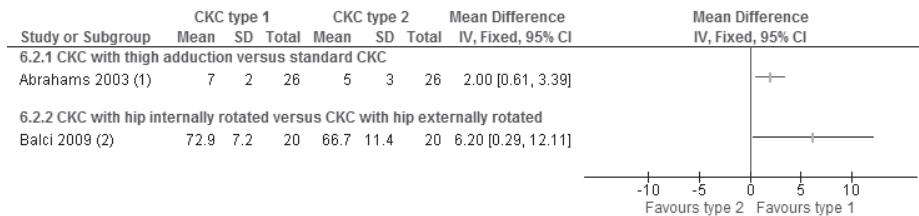
(1) 4 weeks follow-up; VAS (0-10)

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

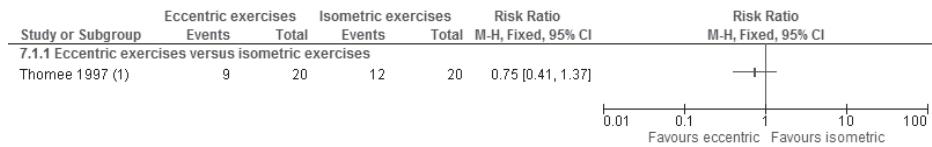
The comparisons undertaken by four studies fell into this category. One study compared eccentric exercises versus concentric exercises.⁴⁹ One study compared eccentric exercises versus isometric exercises.⁶⁶ One study compared isokinetic exercises versus isometric exercises.²⁹ One study compared combined 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.

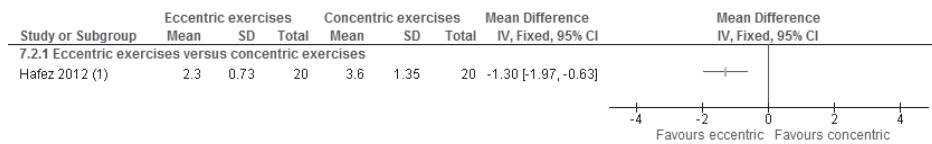
**Footnotes**

(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**

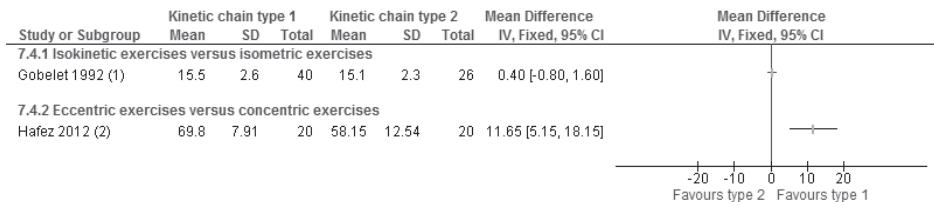
(1) 12 months follow-up; Number of patients with pain during jogging

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.

**Footnotes**

(1) 4 weeks follow-up: Arpège function scale (0-18)

(2) 12 weeks follow-up: WOMAC (0-96) (inverted score: 96 - actual score)

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)

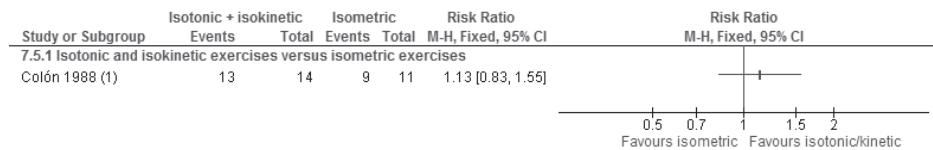
Only Thomee et al.⁶⁶ reported on functional performance, using the vertical jump test; however, only the overall data for the trial population were provided.

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.

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.



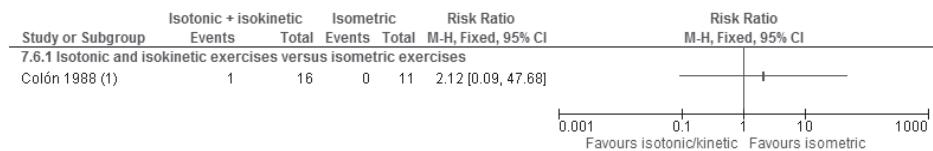
Footnotes

(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)

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

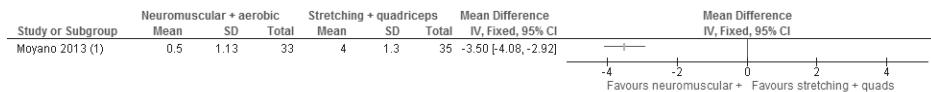
Proprioceptive neuromuscular facilitation stretching and aerobic exercise versus classic stretching and quadriceps exercises

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.



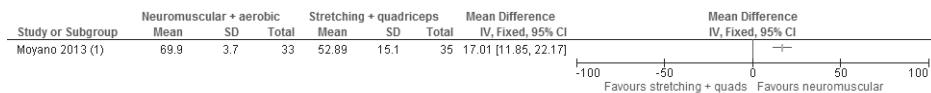
Footnotes

(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

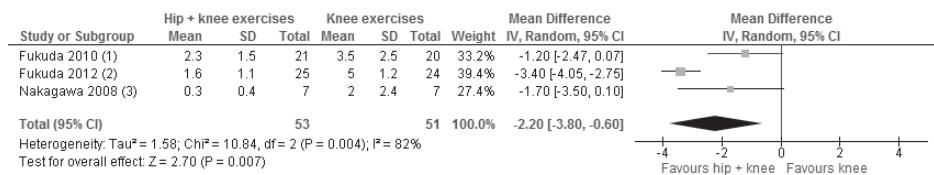
Knee and hip exercises versus knee exercises alone

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

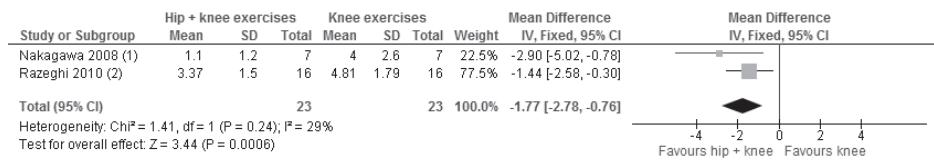
- (1) 4 weeks follow-up; NPRS (0-10)
- (2) 3 months follow-up; NPRS (0-10)
- (3) 6 weeks follow-up; VAS (0-10)

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.

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).



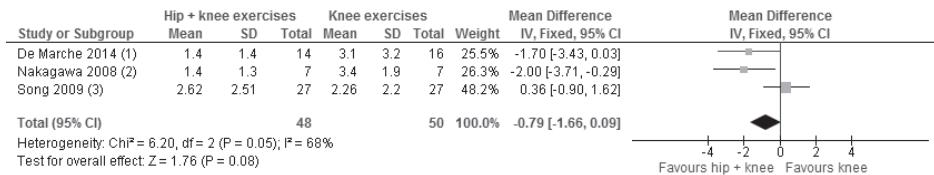
Footnotes

- (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)

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

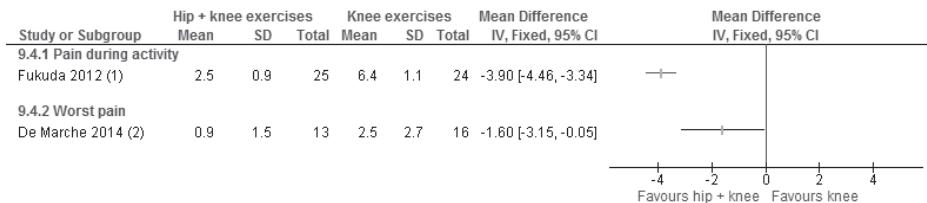
Analysis 9.3 Comparison 9 Target of exercise: hip + knee versus knee exercises, Outcome 3 Worst pain (short term)

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.

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.

**Footnotes**

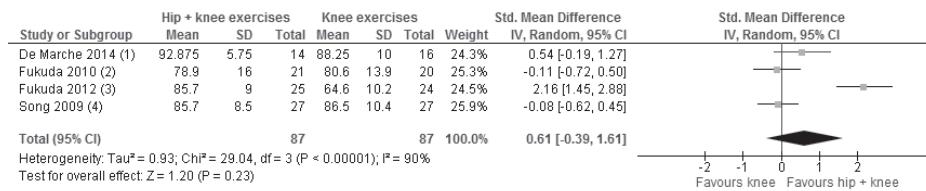
(1) 12 months follow-up; NPRS (0-10)
 (2) 5 months follow-up; VAS (0-10)

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

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 I² = 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).



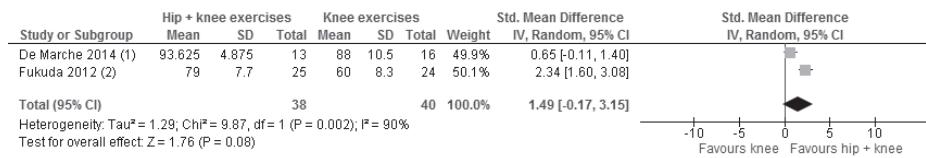
Footnotes

- (1) 8 weeks follow-up; LEFS (0-80) scaled to 0-100
- (2) 4 weeks follow-up; AKPS (0-100)
- (3) 3 months follow-up; AKPS (0-100)
- (4) 8 weeks follow-up; Lysholm (0-100)

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, I² = 90%); see Analysis 9.6.



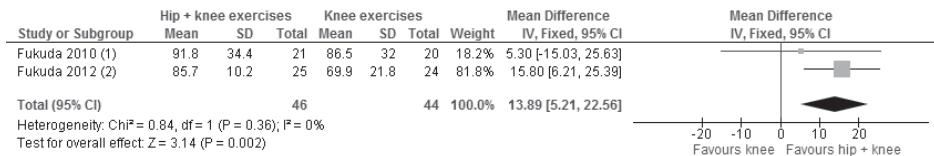
Footnotes

- (1) 5 months follow-up; LEFS (0-80) scaled to 0-100
- (2) 12 months follow-up; AKPS (0-100)

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.

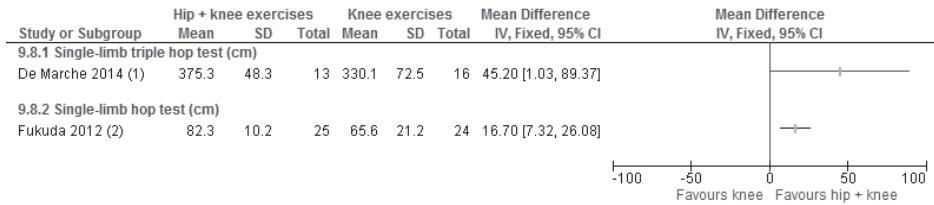
Footnotes

(1) 4 weeks follow-up; single limb hop test (cm)
(2) 3 months follow-up; single limb hop test (cm)

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.

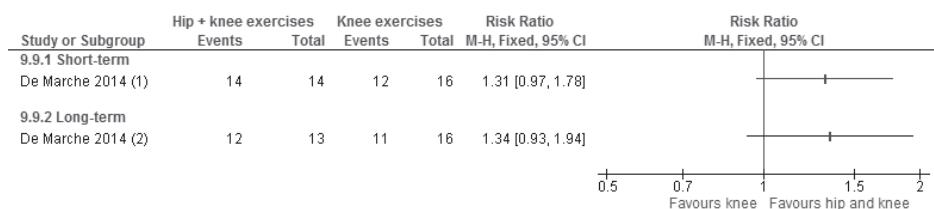
Footnotes

(1) 5 months follow-up
(2) 12 months follow-up

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 favour-

ing 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.

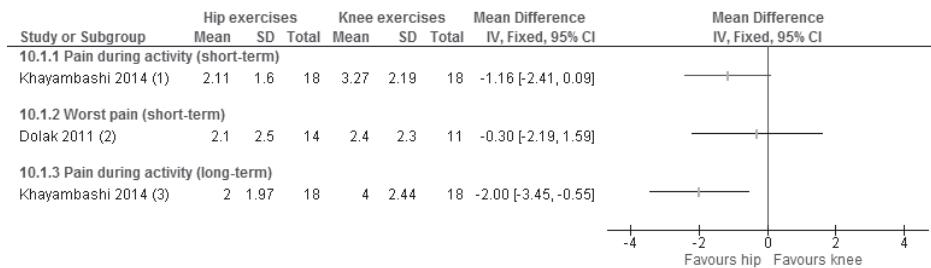
Worst pain (VAS 0 to 10; higher scores mean worse pain)

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.

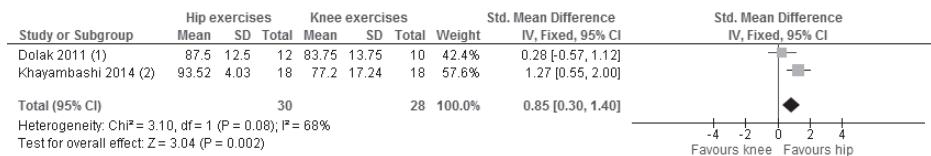
**Footnotes**

- (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)

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.

**Footnotes**

- (1) 3 months follow-up; LEFS (0-80) scaled to 0-100
- (2) 8 weeks follow-up; WOMAC (0-96) inverted and scaled to 0-100

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.

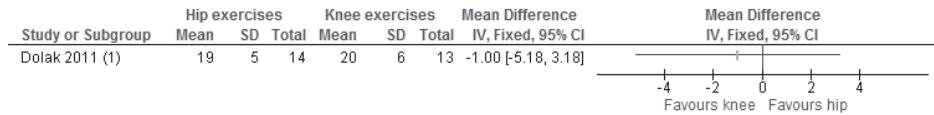
**Footnotes**

- (1) 6 months follow-up; WOMAC (0-96) (inverted score: 96 - actual score)

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.

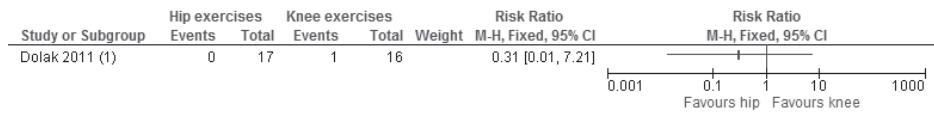
**Footnotes**

(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**

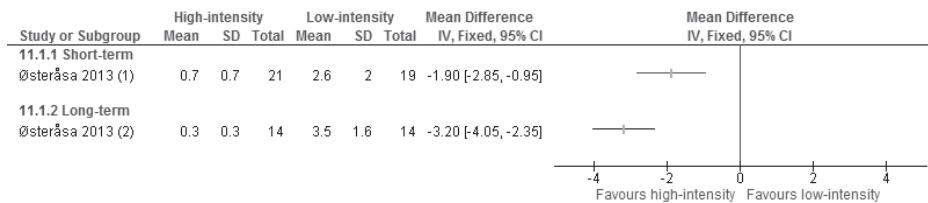
One study compared high-dose, high-repetition medical exercise therapy (MET) with low-dose, low-repetition exercises.⁶⁰ Østerås et al.⁶⁰ did not report on aspects of recovery or adverse events.

*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

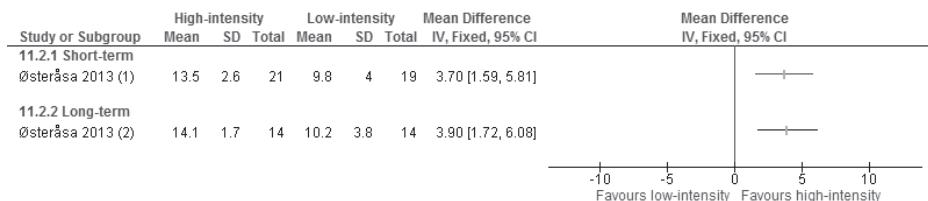
(1) 3 months follow-up; VAS (0-10)

(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) 6 months follow-up; WOMAC (0-96) (inverted score: 96 - actual score)

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 (online available).

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 Summary of findings for the main comparison (online available)).

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 12 months; 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 electro-stimulation 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 eccentric 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 2 (online available)). 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 3 (online available)). 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 4 (online available)). 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 (12 months) 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 5 (online available)). 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 Summary of findings 6 (online available)). 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 malignancy. 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/week⁶⁵ 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 injuries²⁶ 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 not⁹⁰, 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 answers. 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 duration⁶⁰, 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. Al-

though 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, Bolglia and Boling⁹¹ 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 Bolglia and Boling⁹¹ 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 popula-

tions. 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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Chapter V

Can we predict which patients with patellofemoral pain are more likely to benefit from exercise therapy? A secondary exploratory analysis of a randomized controlled trial

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Abstract

Study design

Secondary exploratory analysis of a randomized controlled trial comparing supervised exercise therapy to usual care in patients with patellofemoral pain (PFP).

Objective

To explore which patients with PFP are more likely to benefit from exercise therapy.

Background

Patellofemoral pain is a common condition for which exercise therapy is effective in reducing pain and improving function. However, not all patients benefit from exercise therapy.

Methods

The present study explored patient characteristics that might interact with treatment effects of PFP in 131 patients treated with usual care or exercise therapy. These characteristics were tested for interaction with treatment in a regression analysis. The primary outcomes were function and pain on activity at a 3-month follow-up.

Results

None of the tested variables had a significant interaction with treatment. A positive trend was seen for females with PFP: they were more likely to report higher function scores with exercise therapy than with usual care compared to males with PFP ($\beta = 12.1$; 95% confidence interval: 0.23, 24.0; $P = .05$). A positive trend was seen for patients with a longer duration of complaints (greater than 6 months); they were more likely to report higher function scores and to have less pain on activity with exercise therapy than with usual care compared to those with a shorter duration of complaints ($\beta = 12.3$; 95% confidence interval: -0.08, 24.7; $P = .05$ and $\beta = -1.74$; 95% confidence interval: -3.90, 0.43; $P = .12$, respectively).

Conclusion

Two factors, sex and duration of complaints, may have a predictive value for response to exercise therapy at 3-month follow-up. Due to the exploratory design of the study, future research should confirm this tendency.

Introduction

Until now, the evidence on the effectiveness of different conservative therapies (eg, exercise, tape, orthoses) to reduce pain and improve function in those with patellofemoral pain (PFP) has been limited.¹⁻⁵ There is consensus that a multimodal physical therapy program that includes exercise therapy is the preferred treatment for PFP.⁶

In the short term, exercise therapy seems to be more effective than a “wait and see” approach.³ However, not all patients seem to benefit from exercise therapy, which is evident in the percentage of patients with persistent complaints. Earlier studies have reported 1-year recovery rates after exercise therapy that range from 40% to 60%.⁷⁻⁹ So, although exercise therapy is more effective compared to a “wait and see” approach, a relatively large percentage of patients who continue to have complaints for up to 1 year after receiving exercise therapy.

Some patient characteristics are known to be related to the prognosis in those with PFP. It has been suggested that a longer duration of knee complaints, older age, lower function, bilateral symptoms, and greater difference in side-to-side knee extension strength are associated with poorer long-term outcomes.¹⁰⁻¹³ However, these prognostic factors are not necessarily treatment effect modifiers.¹⁴ Establishing effect modifiers is important, because it helps clinicians to determine which patients are likely to benefit from exercise therapy and which patients are not.¹⁵ This was highlighted by a recent review that emphasized the need for identification of such effect modifiers in patients with PFP, given the absence of randomized controlled trials (RCTs) that investigate effect modifiers.¹⁶ Study of these effect modifiers would enable clinicians to provide better information on the expected effect of treatment for patients with PFP.

Therefore, the present study explores patient characteristics that might interact with the treatment effect of exercise therapy in patients with PFP. To our knowledge, this is the first study to explore the clinical predictors for response to treatment in patients with PFP. The setting of this study is exploratory, and the aim is to provide directions for future research.^{17,18}

Methods

Design

For this post hoc exploratory study, we used data from an RCT that compared the effectiveness of supervised exercise therapy to that of usual care in patients with PFP.⁹ In this earlier trial, patients who consulted a general practitioner (38 HONEUR practices, a research network of general practitioners allied with the Department of General Practice of Erasmus University Medical Center, Rotterdam, the Netherlands) or a sport physician

(sport medical advice centers in Rotterdam, Leidschendam, Breda, and Gorinchem, the Netherlands) and had symptoms of PFP were recruited and randomized by an independent researcher to exercise therapy or usual care. The researcher used a computer-generated list in which patients were stratified by clinical setting and age. Enrollment commenced in August 2005 and finished in May 2007. The follow-up period was 1 year. The protocol for the original RTC was approved by the Erasmus Medical Center (trial registration ISRCTN83938749).

Participants

Patients with PFP, aged 14 to 40 years, who had no history of previous active treatment with exercises within the last 6 months were eligible for the study. The complaint of PFP had to be more than 2 months but no more than 2 years in duration. At least 3 of the following symptoms had to be present: pain when squatting, pain when walking up or down stairs, pain when running, pain when cycling, pain when sitting with knees flexed for a prolonged period, grinding of the patella, and a positive clinical patellar test (such as Clarke's test or the patellofemoral grinding test).^{19,20} Patients with knee osteoarthritis, patellar tendinopathy, Osgood-Schlatter disease, or other defined pathological conditions of the knee were excluded from this study. Patients were also excluded if they had previous knee injuries or surgery.

After informed consent and baseline information was gathered using a self-reported questionnaire and clinical examination, each person was randomly assigned to a group that received supervised exercise therapy or a group that received usual care. An independent researcher performed the randomization using a computer-generated list in which patients were stratified by age and setting. All rights of the included participants were protected.

Interventions

Both groups received advice and information on the background of PFP from a physician, similar to the advice given by general practitioners and sport physicians in a normal-care situation. The intervention group also followed a standardized exercise program supervised by a physical therapist (9 sessions during 6 weeks). The program comprised static and dynamic exercises for the quadriceps muscles, flexibility exercises, and balance exercises. The patients in the exercise group also received instructions to continue the exercise program for 6 weeks (25 minutes a day). A detailed description of the intervention is published elsewhere.²¹

Data Collection

Self-report questionnaires were completed by participants at baseline; at 6 weeks; and at 3-, 6-, 9-, and 12-month follow-ups. For the purpose of the present study, items

from the baseline questionnaire and from the 3-month follow-up questionnaire were used. At baseline and follow-up (unless otherwise stated), the following domains were assessed by questionnaires: (1) demographics: date of birth, sex, height, and weight (only assessed at baseline); (2) knee symptoms: duration of complaints (only assessed at baseline), knee pain during rest and knee pain during activity (both measured on an 11-point numeric pain-rating scale), intensity of activity measured with the Functional Index Questionnaire,²² anterior knee symptoms and functional limitations measured with the Kujala patellofemoral scale²³; and (3) experienced recovery (not assessed at baseline) measured on a 7-point Likert scale.

Primary Outcomes

For this study, the outcome measures of function, as assessed by the Kujala patellofemoral scale, and pain with activity, as assessed with an 11-point numeric pain-rating scale, were regarded as the primary outcomes.

Candidate Variables

Participant characteristics that might interact with treatment were selected from the baseline questionnaire (based on the literature and clinical relevance).²⁴⁻²⁸ The selection of the candidate variables was limited to 5 variables to reduce the chance of type I error.²⁹

The selected variables were sex, age, body mass index (kg/m²), duration of complaints, and sports intensity. Participants were asked to report how long the complaints were present before consulting the physician (1 to 2 months, 2 to 6 months, greater than 6 months to 1 year, or greater than 1 year to 2 years). The duration of knee complaints was dichotomized into 1 to 6 months and greater than 6 to 24 months. Sport intensity was expressed as the mean total hours of sports participation per week. To calculate sport intensity, subjects were asked to report their type of sport activities; then, for the sport that was performed the most, the mean total hours per day and mean days per week of participation were registered. We chose to refrain from categorizing the continuous variables into 2 or more categories to ensure optimal statistical strength.³⁰

Data Analysis

Linear regression analysis was carried out separately for each of the 5 candidate variables (selected a priori). The dependent variable was pain on activity measured at 3-month follow-up, and the other regression model included function measured at 3-month follow-up as the dependent variable. Each regression model included the candidate variable, the treatment allocation, and the interaction between the candidate variable and treatment.

All candidate variables were tested for interaction with treatment. Significance was set at $P < .01$ (Bonferroni correction for 5 variables).^{31 32} Analyses were performed with SPSS Version 21.0 (SPSS Inc, Chicago, IL).

Results

A patient flow chart is provided in the figure. The baseline characteristics of the candidate variables and the primary outcomes of the study are presented in Table 1.

At baseline, no significant differences were found for the candidate variables between the exercise group ($n = 65$) and control group ($n = 66$). The entire sample comprised nearly twice as many women as men, and the mean age of the participants was 24.0 years. At 3-month follow-up, 40% of the participants in the exercise group had recovered versus 32% in the usual care group; at the 12-month follow-up, 55% of the participants

Table 1 Baseline characteristics and primary outcomes of the study participants after short- and long-term follow-ups*

Variable	Exercise therapy	Usual Care	Total
	n=65	n=66	n=131
Age in years (mean (SD))	24.7 (8.6%)	23.4 (7.8)	24.0 (8.2)
Female gender (N(%))	42 (65%)	42 (64%)	84 (64%)
BMI (mean (SD))	23.5 (3.4)	22.7 (3.9)	23.1 (6.7)
Duration of symptoms			
2-6 months (N(%))	45 (69%)	44 (67%)	89 (68%)
6-24 months (N(%))	20 (31%)	22 (33%)	42 (32%)
Sport intensity (mean (SD))	3.02 (3.34)	3.33 (3.71)	3.17 (3.52)
Function score (0-100)			
baseline (mean (SD))	64.4 (13.9)	65.9 (15.2)	65.1 (14.5)
3 months (mean (SD))	78.8 (15.6)	74.9 (17.6)	77.0 (16.6)
12 months (mean (SD))	83.2 (14.8)	79.8 (17.5)	81.5 (16.2)
Pain on activity (0-10)			
baseline (mean (SD))	6.32 (2.22)	5.97 (2.27)	6.15 (2.21)
3 months (mean (SD))	3.81 (2.91)	4.60 (2.96)	4.20 (2.95)
12 months (mean (SD))	2.57 (2.85)	3.54 (3.38)	3.06 (3.16)
Perceived recovery			
3 months (yes n, (%))	26 (40%)	21 (32%)	47 (36%)
12 months (yes n, (%))	36 (55%)	30 (46%)	66 (50%)

*Values are mean (SD) unless otherwise indicated.

†Mean total hours of sports participation per week.

‡Assessed with the Kujala patellofemoral scale.

§Assessed with an 11-point numeric pain-rating scale.

in the complaints exercise group had recovered versus 46% in the usual care group. The interaction effects between exercise therapy and the candidate variables are presented in Tables 2 and 3.

Function

None of the candidate variables had a significant interaction with treatment on the outcome of function, as assessed with the Kujala patellofemoral scale. However, for sex, a positive trend was seen for female patients with PFP, who were more likely than male patients with PFP to report better function scores with exercise therapy than with usual care ($\beta = 12.1$; 95% confidence interval [CI]: 0.23, 24.0) (Table 2). A positive trend was also seen for patients with a longer duration of complaints (greater than 6 months) compared with patients with a shorter duration of complaints: they were more likely to report higher function scores with exercise therapy than with usual care ($\beta = 12.3$; 95% CI: -0.08, 24.7) (Table 2).

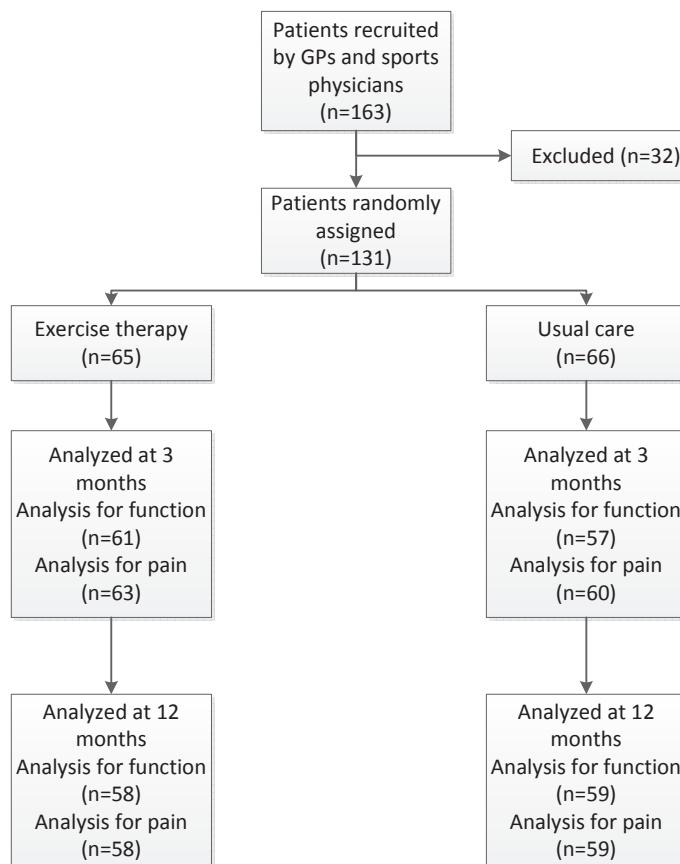


Figure Patients flow chart

Table 2 Interaction between candidate variables and treatment for the outcome 'function' at 3-months follow-up.

Interaction terms	Standardized coefficients (β)	95% CI for B	p-value
Age†	0.01	-0.70 – 0.72	0.98
Gender† (female)	12.1	0.23 – 24.0	0.05
Body mass index†	-0.08	-1.78 – 1.62	0.93
Sport intensity†	0.31	-1.35 – 1.97	0.71
Duration of knee complaints† (6-24 months)	12.3	-0.08 – 24.7	0.05

†Variable was multiplied with treatment.

Table 3 Interaction between candidate variables and treatment for the outcome 'pain on activity' at 3-months follow-up.

Interaction terms	Standardized coefficients (β)	95% CI for B	p-value
Age†	-0.03	-0.16 – 0.09	0.60
Gender† (female)	-0.18	-2.26 – 1.91	0.87
Body mass index†	0.02	-0.27 – 0.31	0.88
Sport intensity†	0.07	-0.23 – 0.36	0.66
Duration of knee complaints† (6-24 months)	-1.74	-3.90 – 0.43	0.12

†Variable was multiplied with treatment.

Pain Intensity

No significant interaction was found between the candidate variables and treatment for the outcome of pain on activity (Table 3).

Discussion

This study was conducted because earlier research showed that there was a relatively large percentage of patients who did not benefit from the often-advocated exercise therapy. Although none of the tested variables had a significant interaction with treatment, 2 factors (duration of complaints and sex) appeared to have a predictive value for response to exercise therapy at 3-month follow-up.

The findings of this study are particularly important for clinicians in primary care (eg, general practitioners and physical therapists). With the identification of characteristics of patients who are more likely to respond to exercise therapy, a clinician can give more information about the expected effect of that therapy. Furthermore, the identification of effect modifiers for response to treatment can also contribute to the decision to refer

or start a different or additional therapy in patients who are less likely to respond to exercise therapy.

The analysis in the present study shows a positive, non-significant interaction for female patients, who were more likely to report better function with exercise therapy compared to usual care. Earlier studies on gender differences in PFP patients have reported that females are more likely to suffer from PFP compared to males,²⁴ and Willson and Davis³³ reported gender differences in the lower extremity kinematics between males and females with PFP.²⁷ However, gender was not associated with a poorer prognosis for PFP.¹¹ Furthermore, the interaction between sex and treatment was not seen for the outcome of pain on activity. Additionally, the associated CI was wide, and exploratory analyses of long-term outcomes (12 months) did not show an interaction between sex and treatment for both function and pain intensity. Therefore, it seems rather implausible that there would be an interaction effect of sex on exercise therapy.

For complaints of longer duration, a trend toward greater effectiveness of exercise therapy compared to usual care was found for the outcome of function. Furthermore, although not significant, the interaction between treatment and pain intensity on activity showed a clinically relevant reduction in pain. Despite the fact that the CIs were wide, especially for the outcome of function, this trend was also seen in additional analyses of 12-month follow-up outcomes for both function and pain intensity ($\beta = 17.0$; 95% CI: 4.95, 29.0; $P = .01$ and $\beta = -2.31$; 95% CI: -4.70, 0.07; $P = .06$, respectively). A possible explanation for this interaction may be that patients with a longer duration of symptoms have decreased lower extremity muscle strength (eg, knee extension, hip abduction) and therefore benefit more from exercise therapy than from usual care. Because the trend of the interaction between treatment and duration of complaint was found at both short-term and long-term follow-ups, we expect this interaction to be replicated in future research. This could imply that patients with a shorter duration of complaints should not receive exercise therapy in the first place, but may benefit more from other types of therapy (eg, taping or foot or knee orthoses). However, more research is needed to test this hypothesis, especially because a large proportion of the patients who visit general practitioners and physical therapists for knee complaints have a relatively short duration of complaints (less than 6 months).^{34 35}

Although in the RCT by van Linschoten et al⁹ a positive effect of supervised exercise therapy for pain and function was evident in the patients recruited by a general practitioner, there was no significant difference between exercise therapy and usual care in the patients recruited by a sport physician. The mechanism of the differences in outcomes between patients recruited by a general practitioner and those recruited by a sport physician is not well understood. In the current study, we included sport intensity as a possible variable that might explain the differences found in types of recruiting physician. We did not include the variable of setting in our model because the health care

system in the Netherlands differs from that of other countries, thus the results would not have been generalizable to other countries. However, we did not find a significant interaction between sport intensity and treatment in the present study. Nevertheless, it could be hypothesized that patients with high sport intensity levels, indicating greater strength,²⁸ would interact with treatment and show a better response to a “wait and see” approach versus a supervised exercise therapy program. In the present study, we did not measure quadriceps strength, and this might explain why we did not find an interaction between sport intensity and treatment.

Strength and Limitations of the Study

One limitation of this study was the small sample size, which limited the number of variables that could be tested for interaction. Because the exact mechanism of the effect of exercise therapy on PFP is not well understood, the choice of the selected potential effect modifiers (sex, age, body mass index, sport intensity, and duration of complaints) was merely based on the literature and the clinical interpretability. However, other variables that may modify the effect of treatment would have been interesting to explore, such as occupation (eg, sedentary occupations), bilateral complaints due to possible differences in posture, baseline pain and function scores, and coping strategies.⁶ Because we used data from a completed RCT, we were limited to the type of baseline variables measured in that trial. For example, the duration of complaints was measured by means of a multiple-choice question and was dichotomized, which consequently reduced the statistical strength. Nevertheless, dichotomizing the data can be desirable because it may help clinicians in their decision making.

Moreover, we were also limited to the type of primary outcomes measured in the study by van Linschoten et al.⁹ In that study, it was shown that at 3-month follow-up, supervised exercise therapy resulted in less pain and better function compared with usual care in patients with PFP. At 12-month follow-up, the intervention group still showed better outcomes than the control group with regard to pain, but not to function. Exercise therapy did not produce a significant difference in the rate of self-reported recovery at 3- and 12-month follow-ups.⁹ For this reason, pain and function at 3-month follow-up were selected as the primary outcomes in the present study.

There are more ways to identify clinical predictors of response to treatment. We chose to include interaction terms in an unadjusted regression analysis instead of subgroup analyses. Including interaction terms is the most appropriate way to overcome the concerns of a false-positive conclusion, and is currently seen as the gold standard in subgroup analyses.¹⁴⁻¹⁸ A positive interaction between the candidate variables and treatment is only seen when the trial is sufficiently powered to show such an interaction or when the interaction is very strong.¹⁴ To detect an interaction effect, the sample size had to be quadrupled¹⁴⁻¹⁸; therefore, to ensure sufficient power, 40 participants were re-

quired per variable tested for the interaction of each variable with treatment. However, to reduce the risk of an exaggerated false-positive outcome, we corrected the *P* value to the numbers of comparisons that we made.^{31 32} Due to our small sample size, we might have been underpowered to find significant interactions between different patient characteristics and exercise therapy. However, the setting of this study was exploratory, and we aimed to give directions for future research.

Implications for Future Research

To identify clinical predictors of response to treatment is an important way to interpret the results of RCTs, especially for clinicians. However, such identification is not easy, and it is important to use the correct methodology to identify such predictors.¹⁴ Although the present RCT is one of the largest to study the effectiveness of exercise therapy for PFP, we still could not perform an adjusted multivariate analysis because of the sample size. This is a common problem among subgroup analyses in trials, because most RCTs are only powered to detect the overall main effect between treatment groups.³⁶ One solution to this problem may be the use of individual patient data (IPD) from multiple trials to perform a meta-analysis.^{14 37} For future studies, IPD could be an ideal solution to increase power. However, heterogeneity in terms of type of exercise program applied for the treatment of PFP and outcome measures used could raise a problem in analyzing IPD.³⁸ Nonetheless, as established in the consensus statement of the Third International Patellofemoral Pain Research Retreat, researchers are currently using a standard series of outcome measures in trials, which should enable the use of IPD in future analyses.⁶ Moreover, future research should also aim at identification of possible beneficial effect modifiers in other treatment options for PFP.¹⁶

Conclusion

This is the first study to examine the interaction between patient characteristics and treatment for the outcomes of function and pain intensity on activity. This study shows a positive trend for patients with a longer duration of complaints: they seem to be more likely to benefit from exercise therapy, compared with usual care, than patients with a shorter duration of complaints. Future research could use IPD to confirm the trend of the findings in this study.

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Chapter VI

Five to eight year course and prognosis of patellofemoral pain: A multicentre observational analysis

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Abstract

Background/aim

This study describes the proportion of people with patellofemoral pain (PFP) who report unfavourable recovery and have radiographic signs of knee osteoarthritis (OA); and determines prognostic indicators of poor outcome after 5-8 years.

Methods

Long-term follow-up data were derived from two randomised controlled trials (n=179, n=131). Patient-reported measures were obtained at baseline. Pain severity (100mm visual analogue scale [VAS]), function (anterior knee pain scale [AKPS]) and self-reported recovery were measured 5-8 years later, along with knee radiographs. Prognostic ability for baseline variables (PFP duration, pain, AKPS) to predict primary outcomes of pain VAS and AKPS were evaluated, using multivariate backward stepwise linear regression analyses.

Results

60 participants completed the questionnaires at 5-8 year follow-up (45 women, mean age at baseline 26 years). No baseline differences were observed between responders and non-responders. 34 (57%) reported unfavourable recovery at 5-8 years. 49 out of 50 participants (98%) had no signs of radiographic knee OA. PFP duration (>12 months; R^2 0.22) and lower AKPS at baseline (R^2 0.196) were significant baseline predictors of poor prognosis at 5-8 years on measures of worst pain VAS and AKPS, respectively.

Conclusion

Of those who responded a large proportion of people with PFP still had notable symptoms at 5-8 years post-recruitment, but did not have radiographic knee OA. Longer PFP duration and worse AKPS score at baseline remain predictors of poor PFP prognosis over longer-term follow-up. Education of health practitioners and general public is recommended, to change the long-held belief that PFP is self-limiting.

Introduction

Patellofemoral pain (PFP) that is aggravated by activities such as squatting, stair walking and running is a common condition affecting a large proportion of adolescents and young adults.¹⁻⁴ Although PFP has traditionally been viewed as self-limiting,⁵ the proportion of those reporting chronic knee problems varies widely, from 20% after one-year follow up, to 91% after 18 years.²⁻⁶⁻¹¹

It is important for clinicians to gain a better insight into the natural course of PFP, so that they can identify patients at risk of chronicity, and better inform patients regarding prognosis. Previous studies have identified baseline factors that are associated with poor PFP prognosis, including longer duration of symptoms, greater pain severity, lower self-reported function, greater height, positive patella apprehension test, and crepitus during physical examination.⁷⁻¹²⁻¹⁵ However, most of these studies were short term, varying from three to 12 month follow-up. Only one study had a seven-year follow-up,¹³ but a substantial proportion of the cohort had undergone surgery (22%), and 35% underwent pre-enrolment diagnostic arthroscopy. Surgery may have altered the natural history of PFP and knee osteoarthritis (OA), and does not represent current practice for PFP.

It has been proposed that PFP may be a precursor to patellofemoral osteoarthritis (PFOA).¹⁶⁻¹⁹ PFP and PFOA share common characteristics in terms of symptoms and biomechanics, such as lower limb malalignment (patella and knee), hamstring tightness, and reduced quadriceps strength.²⁰⁻²³ Furthermore, a history of PFP symptoms and the presence of knee crepitus are associated with MRI features of PFOA.²⁴ However, longitudinal evidence for a temporal relationship between PFP and PFOA is lacking, particularly with respect to high-quality cohort studies of adequate sample size.¹⁷

The aim of this study was to conduct a long-term, five- to eight-year follow-up of two international randomised clinical trials (RCT), in order to: i) describe the proportion of people with PFP who report unfavourable recovery; ii) identify whether people with a history of PFP have radiological signs of PFOA; and iii) determine prognostic indicators of poor outcome on self-reported measures of pain, symptoms and function.

Methods

Long-term follow-up data were derived from two RCTs performed in Australia (n=179) and the Netherlands (n=131).^{6,8} Both RCTs investigated the effectiveness of physical therapies for PFP, with detailed methodologies published previously.^{25,26} Ethical approval was obtained prior to commencement of each study (The University of Queensland's Medical Research Ethics Committee⁶; The Erasmus Medical University, Rotterdam⁸).

Participants

All participants from the original RCTs were invited by letter (Netherlands) or email and letter (Australia) to participate in the long-term follow-up study, five to eight years after baseline testing. Participants were originally recruited into the RCTs via primary care referral (general practitioners and sport physicians)⁸ and self-referral (local advertising).⁶ Inclusion criteria for both RCTs were insidious onset peri- or retropatellar knee pain present for more than 6 weeks, provoked by at least three of the following activities that load the patellofemoral joint (PFJ) (e.g. stair ambulation, squatting, running, cycling, prolonged sitting with knees flexed). The Dutch RCT included participants from 14 years of age, while the minimum age for the Australian RCT was 18 years. Exclusion criteria for both studies were: i) age > 40 years; ii) other defined knee pathology (e.g. osteoarthritis, patellar tendinopathy, Osgood-Schlatter's disease); iii) previous knee surgery; and iv) physiotherapy intervention within the preceding year. The Australian RCT also excluded volunteers if they rated their worst pain severity in the previous week to be less than 30 mm on a 100 mm visual analogue scale (VAS); had used foot orthoses in the previous year; had foot conditions precluding foot orthoses use; or had concomitant pain in the hip or lumbar spine. Both RCTs randomly allocated participants via concealed allocation. Participants in the Australian RCT were assigned to one of four groups: prefabricated foot orthoses (n=46); flat shoe inserts (n=44); physiotherapy (n=45); and foot orthoses with physiotherapy (n=44).⁶ The Dutch RCT allocated participants to supervised exercise therapy (n=65) or usual care (n=66).⁸ Participants who volunteered for the five to eight year follow-up provided written informed consent additional to that obtained at baseline.

Outcome measures

Baseline, three- and 12-month outcomes were collected via paper format for both studies. The same outcome measures were collected at five to eight years after randomisation across both cohorts, with the Australian cohort completing paper versions, and the Dutch cohort completing online versions.²⁷

(i) Recovery

Perceived recovery was assessed at five to eight years for both cohorts. The Australian trial used a five-point Likert scale ('marked improvement' to 'marked worsening'), while the Dutch trial used a seven-point Likert scale ('fully recovered' to 'worse than ever').

(ii) Five to eight year patient reported outcomes

Participants rated their usual knee pain severity (pain on average, or pain at rest) and worst knee pain severity (worse pain or pain during activity). This was completed using 100 mm VAS (Australian cohort) or 11-point numerical rating scales (NRS) (Dutch cohort). The Anterior Knee Pain Scale (AKPS) was used to measure anterior knee pain

symptoms and function, ranging from zero (maximal disability) to 100 (no disability).^{28 29} The Knee Injury and Osteoarthritis Outcome Score (KOOS) was only measured at long-term follow-up.³⁰ This includes five subscales, with a normalised score for each subscale calculated separately, from zero (extreme knee problems) to 100 (no knee problems).³⁰ Functional limitations were measured with the Functional Index Questionnaire (FIQ), which has eight items relating to activities that are commonly aggravating for PFP.³¹ An overall score from zero (maximal disability) to 16 (no disability) was calculated.^{28 31}

(iii) Radiographic features

At five to eight years follow-up, weight-bearing anterior-posterior (AP) and lateral radiographs, as well as skyline view radiographs (Hughston view, with knee in 45° flexion) were taken of the study knee (nominated as most painful knee at baseline). AP radiographs were analysed for tibiofemoral joint space narrowing (none [0], doubtful [1], mild [2] or moderate [3]), medial and lateral tibial and femoral osteophytes (none to moderate [1-3]), tibial attrition (present [0] or absent [1]), tibial and femoral sclerosis, and tibial spiking (present [0] or absent [1]). All features on AP radiographs were scored according to Altman et al,³² with the exception of tibial spiking.³³ Kellgren & Lawrence (K&L) criteria were used to score tibiofemoral joint osteoarthritis (OA).³⁴ For lateral views, only osteophytes were scored (none to moderate [1-3]).³³ On the skyline views, osteophytes, patellofemoral joint space narrowing and patellofemoral sclerosis (none [1] to moderate [3]) were scored.³³ All radiographs were scored by one trained medical student, who has established substantial reliability (inter-observer with trained GP reader prevalence bias adjusted kappa score: 0.61 to 0.75).^{35 36}

(iv) Predictor variables

Baseline variables were evaluated for their prognostic ability for primary outcomes of VAS pain (worst or activity-related) and AKPS score at five to eight years. All prognostic indicators that were identified in the analyses for the 3 and 12 months follow-up⁷ were investigated in the long-term follow-up. These were duration of pain (categorised as 1–2 months, 2–6 months, 6–12 months and ≥12 months), recruitment method (health care professional, self-referral), baseline pain VAS (usual/resting, worst/activity-related), and baseline AKPS score.

Statistical analyses

To establish whether there was selective loss to follow-up, characteristics of long-term participants (n=60) and non-responders (n=290), measured at baseline, three months and 12 months, were compared using t-tests for continuous data and Mann-Whitney U tests for non-normally distributed variables (if n<30) (p<0.05). For normally and non-normally distributed categorical data, Pearson χ^2 tests or Fisher's exact test were

used, respectively. Descriptive statistics were applied to describe long-term outcomes. Scores for recovery were dichotomised into favourable recovery ('completely recovered', 'strongly recovered' or 'marked improvement') and unfavourable recovery ('moderate improvement' to 'worse than ever'). Potential predictor variables were entered into multivariate backward stepwise linear regression analyses ($p(\text{in}) 0.05$, $p(\text{out}) 0.10$). In case of selective follow-up ($p < 0.1$ in both cohorts), those variables were also included in the multivariate analyses. Because more women than men participated in the follow-up study, multivariate analyses also included sex. All analyses were performed based on complete case analysis, using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA). Significance was set at 0.05.

Results

Of the initial 310 participants from the two RCTs, 60 participants (20 (11.1%) from the Australian RCT, and 40 (30.5%) from the Dutch RCT) completed the patient-reported outcomes at five to eight years, while knee radiographs were obtained for 50/60 (83%) participants. Time since baseline ranged from 5 years and 9 months to 8 years and 6 months. Baseline characteristics and three- and 12-month outcomes for long-term follow-up participants and non-responders are presented in Table 1. The long-term cohort ($n=60$) contained significantly more women (Pearson χ^2 test 7.549, df 1, $p = 0.006$). Australian participants who completed the long-term follow-up had a significantly higher baseline FIQ score compared to non-responders (mean difference [95% confidence interval]: 0.403 [-1.72 to -0.70]), but this was not clinically relevant²⁸ and there were no significant differences at three and 12 months.

Outcomes

On the dichotomised measure of global recovery, 26 out of 60 participants (43.3%) reported a favourable outcome, while 56.7% reported an unfavourable outcome (Figure 1).

Five- to eight-year outcomes are presented in Table 2. The mean (SD) pain severity score (worst or activity-related pain) among the responding participants was 29.9 (27.7) at the long-term follow-up, while the AKPS was 81 (14.5).

Radiographic features

Frequencies of radiographic features for knee OA at five to eight years are presented in Table 3. A K&L score of 0 or 1 was scored in 98% of the participants. Tibial osteophytes ≥ 2 on the AP view were present in two participants. Out of the 50 participants, two had patellofemoral osteophytes ≥ 2 on the lateral view. Only one participant had osteophytes ≥ 2 on the skyline view (lateral).

Table 1 Participant characteristics at baseline, 3 months and 12 months (split by responders [participated in follow-up] and non-responders).

Variables*	Australia			The Netherlands			Total	
	Responders (n=20)	Non responders (n=159)	p-value	Responders (n=40)	Non responders (n=91)	p-value	Responders (n=60)	Non responders (n=250)
Age (years)	28.5 (5.63)	28.5 (6.75)	0.485	25.1 (8.56)	23.6 (8.08)	0.352	26.2 (8.10)	27.3 (7.18)
Gender (female) (%)	15 (75.0%)	85 (54.0%)	0.094	30 (75.0%)	54 (59.3%)	0.085	45 (75.0%)	139 (55.6%)
BMI (kg/m ²)	24.3 (4.42)	24.8 (5.22)	0.668	22.4 (3.51)	23.3 (3.78)	0.673	23.0 (3.91)	24.3 (4.78)
Sport participant (%)	14 (70.0%)	104 (65.4%)	0.805	34 (85.0%)	68 (74.7%)	0.192	48 (80.0%)	172 (68.8%)
Work status			0.482			0.601		
Not employed	5 (25.0%)	23 (14.5%)		17 (42.5%)	35 (38.5%)		22 (33.7%)	58 (23.2%)
Sedentary	10 (50.0%)	90 (56.6%)		10 (25.0%)	18 (19.8%)		20 (33.3%)	108 (43.3%)
Active	5 (25.0%)	45 (28.3%)		12 (30.0%)	35 (26.1%)		17 (28.3%)	80 (32.0%)
Unknown	0	1 (0.63%)		1 (2.50%)	3 (2.29%)		1 (1.67%)	4 (1.60%)
Duration of knee pain (%)			0.564			0.713		
1-2 months	0	8 (5.03%)		18 (45.0%)	32 (35.2%)		18 (30.0%)	40 (16.3%)
2-6 months	1 (5.0%)	16 (10.1%)		10 (25.0%)	29 (31.9%)		11 (18.3%)	45 (18.3%)
6-12 months	3 (15.0%)	27 (17.0%)		6 (15.0%)	13 (14.3%)		9 (15.0%)	40 (16.3%)
> 12 months	16 (80.0%)	104 (65.4%)		6 (15.0%)	17 (18.7%)		22 (36.7%)	121 (49.2%)
Unknown	0	4 (2.52%)		0	0			
Bilateral pain (%)	13 (65.0%)	89 (56.0%)	0.483	23 (57.5%)	56 (61.5%)	0.663	36 (60.0%)	145 (58.0%)
Allocated preferred treatment			0.592			0.253		
Not allocated	7 (35%)	59 (37.1%)		13 (32.5%)	39 (42.8%)		20 (33.3%)	98 (39.2%)
Allocated	8 (40.0%)	47 (29.8%)		15 (37.5%)	35 (38.5%)		23 (38.3%)	82 (32.8%)
No treatment preference	3 (15.0%)	35 (22.0%)		12 (30.0%)	16 (17.5%)		15 (25.0%)	51 (20.4%)
Unknown	2 (10.0%)	18 (11.3%)		0	1 (1.1%)		2 (3.33%)	19 (7.60%)

Table 1 Participant characteristics at baseline, 3 months and 12 months (split by responders [participated in follow-up] and non-responders). (continued)

Variables*	Australia			The Netherlands			Total	
	Responders (n=20)	Non responders (n=159)	p-value	Responders (n=40)	Non responders (n=91)	p-value	Responders (n=60)	Non responders (n=250)
Recruitment (health professional) (%)	0	2 (1.26%)	1.000	40 (100%)	91 (100%)	n.a.	20 (33.3%)	154 (62.3%)
Global recovery (% recovered):								
3 months	10 (50.0%)	56	0.468	14 (35.0%)	33 (40.2%)	0.576	24 (40.0%)	89 (39.9%)
12 months	9 (45.9%)	87	0.341	23 (59.0%)	43 (55.1%)	0.692	32 (54.2%)	130 (56.8%)
Usual or resting pain (VAS/100):								
Baseline	36.1 (17.1)	36.4 (16.6)	0.952	39.8 (22.0)	41.3 (23.2)	0.895	38.5 (20.4)	38.2 (19.4)
3 months	17.8 (15.2)	21.2 (18.7)	0.447	29.5 (27.8)	26.5 (26.4)	0.935	25.6 (24.8)	23.1 (22.0)
12 months	12.1 (17.0)	16.0 (19.1)	0.388	19.7 (25.1)	20.5 (26.9)	0.445	17.2 (22.8)	17.6 (22.2)
Worst or activity-related pain (VAS/100):								
Baseline	58.6 (14.3)	60.8 (16.1)	0.555	63.0 (19.6)	60.8 (23.2)	0.597	61.5 (18.0)	60.8 (18.9)
3 months	32.3 (23.7)	30.1 (23.2)	0.696	42.3 (29.6)	40.4 (29.5)	0.969	40.9 (28.3)	33.9 (26.1)
12 months	23.7 (25.2)	23.7 (24.1)	0.993	30.5 (30.1)	30.6 (32.5)	0.215	28.2 (28.5)	26.1 (27.4)
AKPS (/100):								
Baseline	75.2 (8.67)	71.0 (9.87)	0.075	65.8 (13.2)	64.9 (15.1)	0.309	68.9 (12.6)	68.8 (12.4)
3 months	84.3 (10.7)	83.5 (10.7)	0.784	75.2 (16.6)	77.8 (16.7)	0.782	78.3 (15.4)	81.5 (13.6)
12 months	86.7 (9.27)	88.0 (10.9)	0.611	80.9 (18.0)	81.8 (15.4)	0.328	82.9 (15.7)	85.6 (13.1)
FIQ (/16):								
Baseline	10.6 (1.64)	9.70 (2.14)	0.035	9.20 (2.38)	9.60 (2.60)	0.398	9.67 (2.25)	9.67 (2.31)
3 months	13.7 (2.11)	12.8 (2.64)	0.151	11.9 (3.38)	12.0 (3.37)	0.835	12.5 (3.09)	12.5 (2.93)

Table 1 Participant characteristics at baseline, 3 months and 12 months (split by responders [participated in follow-up] and non-responders). (continued)

Variables*	Australia			The Netherlands			Total
	Responders (n=20)	Non responders (n=159)	p-value	Responders (n=40)	Non responders (n=91)	p-value	
12 months	13.7 (2.39)	13.6 (2.82)	0.859	12.8 (3.12)	13.2 (3.36)	0.665	13.1 (2.90)
Treatment:							
<i>Usual care</i>	n.a.	n.a.	0.491	19 (47.5%)	47 (51.6%)	0.662	19 (31.7%)
<i>Supervised exercise therapy</i>	n.a.	n.a.		21 (52.5%)	44 (48.4%)		21 (35.0%)
<i>Physiotherapy</i>	4 (20.0%)	41 (25.8%)		n.a.	n.a.		4 (6.70%)
<i>Foot orthoses</i>	8 (40.0%)	38 (23.8%)		n.a.	n.a.		8 (13.3%)
<i>Flat inserts</i>	4 (20.0%)	40 (25.2%)		n.a.	n.a.		4 (6.70%)
<i>Physiotherapy + foot orthoses</i>	4 (20.0%)	40 (25.2%)		n.a.	n.a.		4 (6.70%)

* Variables measured at baseline unless otherwise stated

^ significant at p<0.05 VAS; visual analogue scale; AKPS: Anterior Knee Pain Scale; FIQ: Functional Index Questionnaire; n.a.: not applicable

Table 2 Five- to eight-year outcomes (n=60). Values are mean (SD) unless otherwise stated.

Usual or resting pain (VAS,/100)	13.7 (20.0)
Worst or activity-related (VAS,/100)	29.9 (27.7)
Anterior Knee Pain Scale (/100)	81.0 (14.5)
Functional Index Questionnaire (/16) (mean (SD))	12.2 (3.77)
KOOS pain (/100)	81.1 (18.7)
KOOS symptoms (/100)	59.5 (15.4)
KOOS ADL (/100)	86.8 (19.2)
KOOS sport/rec (/100)	68.5 (30.3)
KOOS quality of life (/100)	58.8 (18.2)

Favourable recovery; 'completely recovered', 'strongly recovered' or 'marked improvement'

Un favourable recovery; 'moderate improvement' to 'worse than ever'

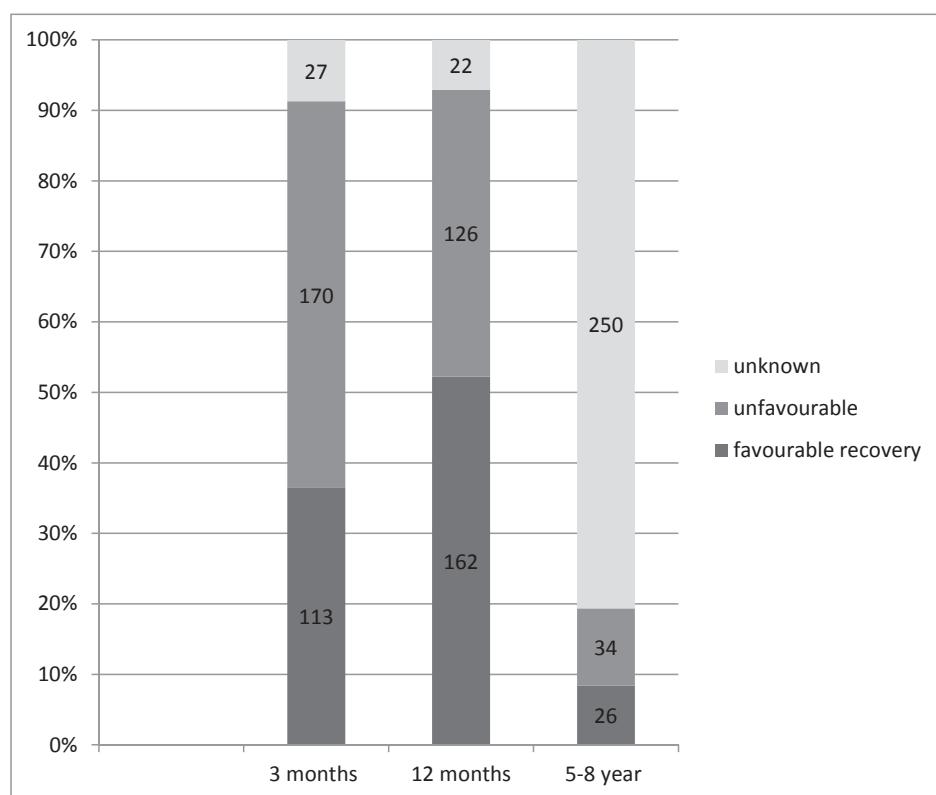


Figure 1 Distribution of favourable and unfavourable outcome scores at three months, 12 months and 5-8 years (total n=310 for each time point).

Table 3 Frequencies of radiographic features for knee osteoarthritis at 5-8 year follow-up (n=50)

	Grades	0	1	>=2
Anterior-Posterior view; K&L score (Grades), n	36	13	1	
Anterior-Posterior view; features, n				
<i>Joint-space narrowing</i>	38	11	1	
<i>Femoral osteophytes</i>	47	3	0	
<i>Tibial osteophytes</i>	38	10	2	
<i>Tibial sclerosis</i>	48	2	0	
<i>Femoral sclerosis</i>	49	1	0	
<i>Tibial attrition</i>	50	0		n.a.
<i>Tibial spiking</i>	16	34		n.a.
Lateral view; features, n				
<i>Patellofemoral osteophytes</i>	36	12	2	
Skyline view; features, n				
<i>Patellofemoral osteophytes</i>	33	16	1	
<i>Patellofemoral joint space narrowing</i>	45	4	1	
<i>Patellar Sclerosis</i>	50	0	0	

Abbreviations: K&L: Kellgren & Lawrence, N: number of participants, Tibiofemoral joint: Anterior-Posterior view, Patellofemoral joint: Lateral and skyline view

Prognostic indicators

The multivariate analysis for worst or activity-related pain VAS at five to eight years revealed that baseline symptom duration longer than 12 months was significantly associated with greater pain severity at long-term follow-up (β 2.90 95% CI 1.14 to 4.65) (Table 4). The model, including symptom duration, recruitment source and AKPS, explained 21.6% of the total variance.

The multivariate model for AKPS at five to eight years revealed that a lower (worse) AKPS score at baseline was significantly associated with a lower AKPS score at long-term follow-up (β 0.48 95% CI 0.21 to 0.76) (Table 4), with the model explaining 19.6% of the total variance.

Discussion

Consistent with our previous findings at three and 12 months,⁷ we found that a large proportion of people with PFP who responded to our survey experienced symptoms up to eight years later, and more than half of these reported an unfavourable recovery. However, only two participants demonstrated radiographic signs of knee OA. We also identified that a longer duration of PFP (>12 months) and lower AKPS score at baseline

Table 4 Prognostic factors for pain severity (worst/activity) and Anterior Knee Pain Scale at 5-8 year follow-up.

Variables*	Pain severity (worst)			Anterior Knee Pain Scale		
	β	(95% CI)	p-value	β	(95% CI)	p-value
Duration of complaints (ref = 1-2 months)						
<i>2-6 months</i>						
<i>6-12 months</i>						
<i>>12 months</i>	29.0	(11.4; 46.5)	0.002	-6.91	(-14.1; 0.31)	0.06
Recruitment (self-referral)	-16.7	(-35.6; 2.20)	0.082			
Baseline usual/rest pain						
Baseline worse/on activity pain						
Anterior Knee Pain Scale	-0.52	(-1.07; 0.04)	0.069	0.484	(0.21; 0.76)	0.001
Sex						
R ²	0.216			0.196		

abbreviations: 95% CI; 95% confidence interval, R²: coefficient of determination

were associated with worse pain and symptom severity, respectively, five to eight years later.

The proportion of people with PFP who reported an unfavourable recovery increased from 40% (126/310) at one-year follow-up,⁷ to 57% (34/60) after five to eight years. This provides further evidence that PFP is not self-limiting, even over a prolonged time period, and in a cohort who were seen by primary care practitioners (e.g. general practitioners, physiotherapists) at baseline. While previous studies have reported long-term PFP symptoms, the generalisability of their findings to the greater PFP population is questionable, as they were attending orthopaedic clinics or half of the cohort had received an arthroscopy or surgery to the knee.^{2 5 9 10} In comparison, the interventions received by participants in our two trials reflect more recent practice, whereby at least 50% of participants received a short term efficacious intervention (e.g. exercise therapy, physiotherapy, foot orthoses).^{6 8} The finding that a high proportion of PFP patients who receive treatment reflecting current practice report unfavourable recovery, highlights the need to educate first contact health practitioners, as well as the general public, to change the long-held belief that PFP is self-limiting. Unfortunately, it would appear that the information regarding the self-limiting nature of PFP remains in current usual care provided by physicians and physiotherapists. For example, in the United Kingdom and the Netherlands, primary care for PFP consists of an information leaflet advising participants that PFP has a good prognosis.^{37 38} Our findings challenge this information, and should be integrated into educational material to provide PFP participants with more realistic expectations.

Our finding that longer symptom duration (>12 months) at baseline predicts worse pain at follow-up is consistent with our previous findings. Collins et al.⁷ reported that duration of PFP >2 months predicted poor outcomes for pain, symptoms and function after one year. This consistent finding highlights the importance of early recognition and management of PFP, using effective interventions. Our findings suggest that future RCTs evaluating PFP interventions should consider stratifying participants based on symptom duration and worse pain and function scores at baseline. Targeting of interventions has the potential to enhance long-term outcomes. It is also likely that a short period of intervention, as used in our RCTs, is insufficient to manage a chronic condition such as PFP. Indeed, systematic reviews have highlighted that non-surgical interventions were effective in reducing pain and improving function in the short term, but long term (>12 months) effects are largely unknown.³⁹⁻⁴¹ Therefore, there is a need for studies to evaluate longer interventions with regular top-up sessions, which could potentially maximise long-term outcomes.

Contrary to the results of Kannus et al.², whereby 35% of the young PFP participants had signs of OA on magnetic resonance imaging (MRI), the majority of participants in the current study did not demonstrate signs of knee OA on x-ray. While our findings do not support the proposition that long term PFP is necessarily PFOA,^{16 17 19} it is plausible that the radiographic criteria used was inappropriate for this population. In this relatively young PFP cohort (age range at baseline 14-40 years), x-ray is unlikely to be sufficiently sensitive to detect early OA changes, such as those detectable on MRI.⁴² This may have led to an underestimation of the percentage of participants with early signs of PFOA with radiography.⁴³⁻⁴⁵ Furthermore, 13 (26%) participants were scored as K&L grade 1, which suggests as a subgroup of early disease, and the strongest predictor for future definite OA.⁴⁶⁻⁴⁸ Taken with the findings of Kannus et al.², it appears that future studies evaluating long-term PFP outcomes in younger adults, and the proposed relationship with PFOA, should utilise MRI techniques or longer follow-up periods.

There are strengths and limitations of this study that should be considered. This prospective, longitudinal study evaluated two of the largest PFP cohorts to date. While the proportion of responders to the five to eight year follow-up was small (approximately 20%), findings that baseline, three-month and 12-month characteristics largely did not differ between responders and non-responders reduces the likelihood of responder bias. We observed a significantly greater proportion of women in the long-term follow-up (75%) than the non-responders (55.6%), a phenomenon common in epidemiological studies. We therefore included sex in the multivariate analyses. However, due to the high percentage of loss to follow-up, the results of the present study should be interpreted with caution as we analysed the results based on complete case analysis, which could introduce bias.⁴⁹ Furthermore, despite the smaller sample size, prognostic factors identified for one-year outcomes⁷ (duration of PFP, worse AKPS score) remain significant pre-

dictors of outcome at five to eight years, increasing confidence in our findings. However, the smaller sample size at five to eight years (n=60) limited the number of potential predictor variables that could be included in the multivariate regression analyses. For this reason, we chose to include the same prognostic factors that were found in the 12-month follow-up study.⁷ The relatively small adjusted R² values observed indicate that other factors are important in determining PFP prognosis. Factors such as coping strategies and pain sensitivity have been suggested as possible prognostic factors in other musculoskeletal diseases, and are worth investigating in future PFP prognostic studies.⁵⁰⁻⁵²

Conclusion

A substantial proportion of young adults with PFP who responded at follow-up still report notable symptoms after five to eight years, despite initially receiving treatment and education. This supports previous findings that PFP is not a self-limiting condition, and suggests that efficacious interventions may be required on an ongoing basis to maximise longer-term outcomes. The majority of participants did not have signs of radiographic knee OA at five to eight year follow-up, which does not support the proposition that long term PFP is associated with radiographic PFOA. Longer duration of pain and worse symptoms and function, measured at baseline, remain predictors of poor PFP prognosis up to eight years later. Education of health practitioners and the general public is recommended, to change the long-held belief that PFP is self-limiting.

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Chapter VII

Incidence, prevalence, natural course and prognosis of patellofemoral osteoarthritis; data of Cohort Hip and Cohort Knee study

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Submitted

Abstract

Background/aim

This study examines the proportion of isolated patellofemoral osteoarthritis (PFOA) compared to tibiofemoral OA (TFOA) in middle-aged participants with early OA symptoms of the knee. The natural course of the diseases was assessed at 2 and 5 years follow-up with the aim to identify whether participants with PFOA have a different phenotype compared to participants with TFOA, or with combined PFOA and TFOA (COA).

Method

Participants with early OA symptoms of the knee were selected, completed questionnaires, underwent physical examination, and had knee radiographs at baseline, and 2 and 5 years follow-up. Based on the radiographs, participants were classified as having isolated TFOA, isolated PFOA, COA, or no radiographic OA. Multivariate logistic regression was used to identify participant characteristics associated with a specific group of OA at 2 years follow-up.

Results

The cohort comprised 845 participants (mean age 55.9 years). At baseline, 116 had PFOA, none had TFOA or COA. Of these 116 participants, 66.3% had developed COA at 5 years follow-up. At 2 years follow-up, PFOA, TFOA and COA were present in 77 (10.8%), 39 (5.5%) and 83 (11.6%) participants, respectively. Multivariate regression analyses showed that participants with radiographic PFOA or TFOA were not significantly different from each other with respect to signs and symptoms.

Conclusion

Results suggest that OA is more likely to start in the patellofemoral joint and then progress to COA in individuals with symptoms of early knee OA. No differences in TFOA and PFOA phenotypes were determined with respect to signs and symptoms.

Introduction

The most common condition to affect the knee joint is osteoarthritis (OA).¹⁻² The knee joint consists of two compartments the tibiofemoral (TF) and the patellofemoral (PF) compartment. OA in the knee can occur solely in the TF joint [isolated tibiofemoral osteoarthritis (TFOA)] or in the PF joint [isolated patellofemoral osteoarthritis (PFOA)] or can be present in both joints [combined TFOA and PFOA (COA)]. Most research on OA has focused on the TF joint, although the prevalence of isolated PFOA might be higher than isolated TFOA.³⁻⁶ Furthermore, radiographic signs of PFOA might be associated with symptoms such as pain and disability.⁷⁻¹⁰

Although the main goal of treatment for OA is pain relief, not every participant responds equally well to treatment.¹¹⁻¹² One possible explanation for this difference is that the heterogeneous OA population consists of persons with different phenotypes of OA.¹²⁻¹⁴ Identification of the distinct phenotypes in OA may help classify which preventive measures are suitable for an individual.¹⁴ Therefore, it is suggested to study participants phenotypes in knee OA.¹⁵⁻¹⁸ However, Mills and Hunter stated: '*due to the inclusion of homogenous study groups based on TFOA in clinical trials, the phenotype specific effects of OA can be masked*'.¹⁹ Therefore, large cohort studies that include participants with COA and isolated TFOA and PFOA are needed to determine whether participants with PFOA have a different phenotype compared to those with TFOA or COA.

Additionally, evidence from a study including participants aged ≥ 50 years with knee complaints suggests that OA in the knee starts in the PF joint and subsequently progresses to the TF joint.²⁰ Therefore, more insight is required in the natural course of PFOA and in differences compared with the natural course of TFOA. The few studies describing the prevalence and natural course of TFOA and PFOA included participants with severe signs of OA on radiographs²¹ or studied a general population which also included individuals without knee complaints.^{9,22} Other studies focusing on TFOA and PFOA included participants with a relatively high age (mean age 68.4 and 65.2 years, respectively).^{20,23,24} Although two studies evaluated the prevalence of PFOA in a younger population (aged 34-55 years), these participants had chronic knee complaints²⁵ or no baseline X-ray data of the PF joint were available so that progression could not be evaluated.²⁶ Thus, most research has focused on older participants with a longer symptom duration of knee pain, or on the general population. Currently no data are available that address the incidence and prevalence rates, as well as the natural course of PFOA and TFOA, in younger individuals with a recent onset of knee complaints.

Therefore, the aim of this study is to 1) determine the proportion of PFOA compared to TFOA in individuals with early knee OA symptoms; 2) describe the natural course of PFOA at 2 and 5 years follow-up compared with that of TFOA; and 3) identify whether

participants with PFOA have a different phenotype of signs and symptoms compared to those with TFOA, and those with COA.

Methods

Study population

The present study used baseline data, and data from 2 and 5 years follow-up of the Cohort Hip and Cohort Knee study (CHECK). A detailed description of this cohort is published elsewhere.^{27 28} In brief, the cohort included 1002 participants recruited between October 2002 and September 2005. Inclusion criteria were: participants aged 45-65 years with hip and/or knee complaints (pain or stiffness) who had never visited a general practitioner (GP) for their complaints, or had visited a GP no longer than 6 months previously.

Participants were excluded if they had a pathologic disorder (based on medical history and physical examination) that also could explain the symptoms (e.g. for the knee; other rheumatic disease, ligament or meniscus injury, knee joint replacement, plica syndrome, Baker's cyst); had a serious comorbidity that did not allow physical evaluation/follow-up for up to 10 years; and did not have adequate understanding of the Dutch language.²⁷

For the current study only those participants that reported knee pain or knee stiffness at baseline were included (n=845). Ethical approval was obtained and participants provided informed consent prior to commencement of the study.²⁷

Questionnaires

Self-reported questionnaires were filled in yearly by all participants. At baseline and at follow-up the following domains were assessed by questionnaires: 1) Socio-demographic characteristics: age (in years), sex (male/female), body height (m) and weight (kg), 2) Knee symptoms: duration of complaints (only assessed at baseline), side of knee pain, number of participants with hip and knee symptoms, and the Western Ontario and McMaster Universities Index (WOMAC)²⁹ for knee function (higher scores indicating worse function). Moreover, information on pain when going up/down upstairs and when walking on a flat surface was obtained by means of a five-point Likert scale ('none', 'slight', 'moderate', 'severe', 'extreme').²⁹

Physical examination

All participants underwent a standardised physical examination at baseline, and at 2 and 5 years follow-up. For the present study, we used data of the physical examination at baseline and data of the 2-year follow-up of the index knee (i.e. the most affected knee).³⁰ Range of joint motion was measured with a goniometer (in degrees). To assess knee effusion the refill test was used (present or absent), palpable warmth was determined

by comparing both knees with each other (present or absent), and bony enlargement, joint line tenderness, crepitus (during squatting) and patellofemoral grinding test were all scored for presence or absence.

Radiographs

At baseline and at 2 and 5 years follow-up, weight-bearing posterior-anterior (PA), with 7-10° knee flexion; lateral weight-bearing radiographs with 30° of knee flexion; and skyline view with the knees in 30° flexion were made of both knees separately. Individual features of OA were scored according to the atlas of Altman et al.³¹ for the PA radiographs: joint space narrowing (none, doubtful, mild or moderate), femoral medial and lateral osteophytes, and tibial medial and lateral osteophytes (none to moderate). The original Kellgren & Lawrence (K&L) criteria were used to score the severity of TFOA of the involved knee on the PA radiographs.³² On the lateral views osteophytes (grade 0 to grade 3) were scored and on the skyline view osteophytes (none to moderate) and joint space narrowing (0 to 3) were scored according to Burnett et al.³³ All the above-mentioned features were scored by five observers independently, according to a paired reading procedure (inter-reader reliability: 0.62).³⁴

Definition of radiographic OA per compartment

The type of OA was defined for the index knee of the individual. Isolated PFOA was defined as a K&L score <2 on PA radiographs and osteophytes grade ≥2 on both skyline and lateral radiographs (or narrowing grade ≥2 and osteophytes grade ≥1 for skyline radiographs). Isolated TFOA was defined as a K&L score ≥2 on PA radiographs and osteophytes grade <2 on both skyline and lateral radiographs (or narrowing grade <2 and osteophytes grade <1 for skyline radiographs). COA was defined as a K&L score ≥2 on PA radiographs and skyline or lateral osteophytes grade ≥2 (or narrowing grade ≥2 and osteophytes grade ≥1 for skyline radiographs). No radiographic OA was defined if none of the above-mentioned definitions was fulfilled. Incident cases at 2 or 5 years follow-up were defined as participants with radiographic signs of any type of OA at follow-up who did not have signs of OA at baseline or at 2 years follow-up.^{4,22}

Statistical analyses

Descriptive statistics (mean, standard deviations [SD] and proportions) were applied to describe the participants characteristics at baseline and at 2 years follow-up, and to describe the proportions of OA in the knees at baseline and follow-up. Clinical signs and symptoms of the index knee were used for the radiographic and physical examinations. Differences in characteristics at baseline and at 2 years follow-up were analysed with independent t-tests and with ANOVA tests. Multivariate binary logistic regression (based on complete case analyses) ($p<0.01$) was used to identify which participant character-

istics, and characteristics from physical examination, were associated with a specific group of OA participants, at 2 years follow-up. The data at 2 years follow-up were used because none of the participants had TFOA or COA at baseline so that we were unable to test for differences in phenotypes at baseline. The following variables were included in the regression analyses: gender, age, body mass index (BMI), pain when walking up/down stairs and when walking on a flat surface [both dichotomised into no pain ('none' and 'slight') and painful ('moderate', 'severe' and 'extreme')], function score (WOMAC), bony tenderness during palpation, joint line tenderness, crepitus in the knee duration flexion, degrees of knee flexion and extension, and the patellar grinding test. This selection of characteristics was based on the literature and their practicability in general practice.^{20 24 35} Significance level was set at $p < 0.01$, and a significant trend was defined as a p-value >0.01 and <0.05 . Analyses were performed using the Statistical Package for the Social Sciences version 21.0 (SPSS Inc., Chicago IL, USA).

Results

Study population

At baseline, the total cohort comprised 845 participants (80% females) who reported knee pain or stiffness. The mean age was 55.9 (5.18) years and mean BMI was 26.3 (4.15) kg/m². Due to missing data, the type of OA could not be determined for 139 (16.4%), 129 (15.3%) and 150 (17.8%) participants at baseline and at 2 and 5 years follow-up, respectively.

Incidence and prevalence of different types of OA

Baseline

Of the 706 participants available at baseline, 116 (16.4%) had isolated PFOA and none had TFOA or COA; 590 participants had no radiographic signs of OA at baseline. The presence of isolated PFOA in those with knee pain at baseline was associated with higher age, higher BMI, hip pain at baseline, crepitus, positive patellofemoral grinding test, palpable bony enlargement and lower knee flexion range of motion (Table 1).

Two-year follow-up

Table 1 presents the characteristics of the 716 available participants at the 2-year follow-up. Isolated PFOA, isolated TFOA and COA were found in 77 (10.8%), 39 (5.5%) and 83 (11.6%) participants, respectively. Of the 590 participants without radiographic OA at baseline, 27 (4.6%) had developed PFOA, 39 (6.6%) had developed TFOA and 18 (3.1%) had developed COA (Figure 1).

Table 1 Participant characteristics and symptoms at baseline and at 2-year follow-up per group: variables are n [%] unless stated otherwise

Characteristics at baseline	isolated TFOA n=116	isolated PFOA n=116	combined TFOA and PFOA n=590	no radiographic OA n=590	total n=845	p-value (between groups)
age (years), mean [SD]	57.8 [4.82]	55.5 [5.16]	55.9 [5.18]	55.9 [5.18]	55.9 [5.18]	<0.01
sex (female)	89 [76.7]	473 [80.2]	672 [79.5]	672 [79.5]	672 [79.5]	0.40
BMI (kg/m ²), mean [SD]	28.1 [4.55]	26.1 [4.00]	26.3 [4.15]	26.3 [4.15]	26.3 [4.15]	<0.01
bilateral complaints (yes)	61 [52.6]	324 [54.9]	461 [54.6]	461 [54.6]	461 [54.6]	0.17
hip and knee pain at baseline (yes)	42 [36.2]	324 [54.9]	431 [51.0]	431 [51.0]	431 [51.0]	<0.01
pain when walking on flat surface (yes)	21 [18.1]	96 [16.3]	143 [16.9]	143 [16.9]	143 [16.9]	0.67
pain when going up or down stairs (yes)	61 [52.6]	258 [43.7]	387 [45.8]	387 [45.8]	387 [45.8]	0.10
baseline WOMAC function (0-68), mean [SD]	25.9 [17.2]	22.7 [16.9]	23.9 [17.3]	23.9 [17.3]	23.9 [17.3]	0.06
crepitus (yes)	72 [62.1]	271 [45.9]	398 [47.1]	398 [47.1]	398 [47.1]	<0.01
bony enlargement (yes)	12 [10.3]	21 [3.6]	37 [4.4]	37 [4.4]	37 [4.4]	<0.01
patellofemoral grinding test (pos)	46 [39.7] *	159 [26.9] *	237 [28.0] *	237 [28.0] *	237 [28.0] *	<0.01
knee flexion ROM (degrees), mean [SD]	130.8 [10.6]	135.1 [8.88]	134.2 [9.92]	134.2 [9.92]	134.2 [9.92]	<0.01
knee extension ROM (degrees), mean [SD]	2.63 [2.68]	2.73 [2.77]	2.64 [2.74]	2.64 [2.74]	2.64 [2.74]	0.73
knee effusion (yes)	15 [12.9]	43 [7.3]	63 [7.5]	63 [7.5]	63 [7.5]	0.04
morning stiffness knee < 30 minutes (yes)	85 [73.3]	356 [60.3]	533 [63.1]	533 [63.1]	533 [63.1]	0.01
joint line tenderness (yes)	49 [42.2]	273 [46.3]	375 [44.4]	375 [44.4]	375 [44.4]	0.41
Characteristics at T2	n=39	n=77	n=83	n=517	n=845	
age (years), mean [SD]	58.5 [5.54]	59.3 [5.39]	59.7 [4.16]	57.5 [5.21] ^	58.1 [5.17]	<0.01
sex (female)	33 [84.6]	58 [75.3]	68 [81.9]	407 [78.7]	672 [79.5]	0.61
BMI (kg/m ²), mean [SD]	26.7 [3.81]	26.4 [4.27]	28.4 [4.67] ^	25.7 [3.75]	26.2 [4.06]	<0.01
bilateral complaints (yes)	17 [43.6]	38 [49.4]	51 [61.4]	217 [42.0]	367 [43.4]	0.03
pain when walking on flat surface (yes)	18 [46.2]	12 [15.6]	21 [25.3]	75 [14.5]	143 [16.9]	0.22
pain when going up or down stairs (yes)	6 [15.4]	37 [48.1]	56 [67.5]	214 [21.4]	387 [45.8]	0.03

Table 1 Participant characteristics and symptoms at baseline and at 2-year follow-up per group: variables are n [%] unless stated otherwise (continued)

Characteristics at baseline	isolated TFOA n=116	isolated PFOA n=116	combined TFOA and PFOA n=390	no radiographic OA n=845	total n=845	p-value (between groups)
WOMAC function (0-68), mean [SD]	19.5 [16.2]	24.9 [20.1]	27.8 [17.7]	21.2 [17.1]	22.9 [17.8]	<0.01
crepitus (yes)	18 [46.2]	40 [51.9]	49 [59.0]	201 [38.9]	339 [40.1]	<0.01
bony enlargement (yes)	1 [2.6]	8 [10.4]	6 [7.2]	24 [4.6]	43 [5.1]	0.15
patellofemoral grinding test (pos)	4 [10.3] **	17 [22.1]*	20 [24.1]*	88 [17.0]*	142 [16.8]**	0.18
knee flexion ROM (degrees), mean [SD]	134.6 [8.02]	136.9 [9.07]	130.0 [10.4]	136.1 [8.50]	135.3 [9.09]	<0.01
knee extension ROM (degrees), mean [SD]	2.19 [2.23]	2.52 [3.27]	2.84 [2.99]	2.69 [2.63]	2.64 [2.74]	<0.01
knee effusion (yes)	4 [10.3]	2 [2.6]	11 [13.3] ^	27 [5.2]	50 [5.9]	0.01
morning stiffness knee < 30 minutes (yes)	22 [56.4]	49 [63.3]	56 [67.5]	288 [55.7]	464 [54.9]	0.14
joint line tenderness (yes)	6 [15.4]	15 [19.5]	28 [33.7]	164 [31.7]	242 [28.6]	0.02

SD: standard deviation, n: number, BMI: body mass index, m: meter, kg: kilogram, WOMAC: Western Ontario and McMaster Universities Arthritis Index, pos: positive, ROM: range of motion, OR: odds ratio, PFOA: patellofemoral osteoarthritis, TFOA: Tibiofemoral osteoarthritis, COA: combined osteoarthritis, OA: osteoarthritis

Bold indicates: p-value <0.01 between groups

^ Posthoc analysis: significant different compared to PFOA

Missing:

At baseline: type OA was missing for 139 persons

At 2-year follow-up: type of OA was missing for 129 persons

*>10% <20%

** >20%

Five-year follow-up

At the 5-year follow-up, 100 participants were diagnosed with isolated PFOA, 54 with TFOA and 102 with COA. Of the 488 participants without radiographic OA at baseline and at 2-year follow-up, 30 (6.1%) had developed PFOA, 17 (4.5%) had developed TFOA and 7 (1.4%) had developed COA.

Natural course of PFOA and TFOA

Of the 116 participants with isolated PFOA at baseline, 63 (54.3%) had developed COA at the 2-year follow-up and 77 (66.4%) had developed COA at the 5-year follow-up.

Of the 39 participants with isolated TFOA at the 2-year follow-up, 8 (20.5%) had developed COA at the 5-year follow-up (Figure 1).

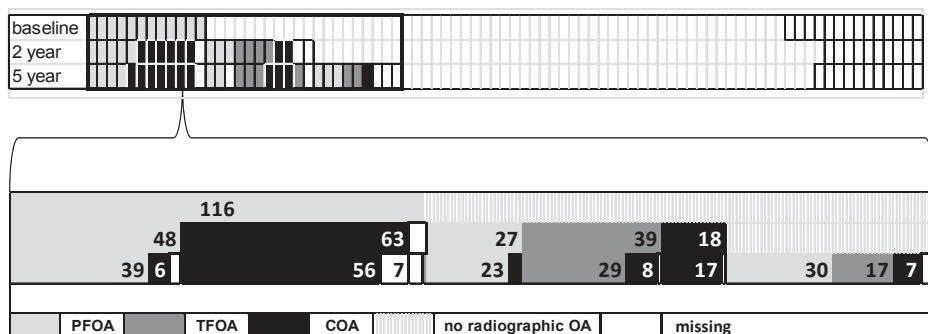


Figure 1 Natural course of different subgroups of OA

The colored blocks indicate the number of patients with OA. At follow-up the colored blocks below the different blocks at the previous time point indicate the number of patients that remained the same type of OA or developed another type of OA. In the upper graphic one block is indicating 10 subjects, whereas in the enlargement one block is indicating 1 subject

Multivariate regression analysis for different types of OA at 2-year follow-up

No significant differences in clinical signs and symptoms were found between participants with radiographic PFOA or TFOA.

Compared with participants with PFOA, those with COA were more likely to have a lower knee flexion range of motion (OR 0.94, 95% CI 0.89-0.98).

Participants without radiographic knee OA had better knee function (lower WOMAC scores) compared with those with isolated PFOA (OR 0.97, 95% CI 0.95-0.99) and reported more joint line tenderness compared with those with isolated PFOA (OR 3.13, 95% CI 1.47-6.69). Participants without radiographic OA tended to be younger, were less likely to have palpable bony enlargement and were less likely to have crepitus during knee flexion compared to those with isolated PFOA (Table 2).

Table 2 Multivariate regression analysis for different types of osteoarthritis at 2-year follow-up

	TFOA vs PFOA				COA vs PFOA				NOA vs PFOA			
	n=39 vs n=77		n=83 vs n=77		n=83 vs n=77		p-value		n=517 vs n=77		p-value	
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	OR	95% CI	p-value	
sex (female)	2.69	0.71-10.1	0.15	1.01	0.38-2.69	0.99	1.03	0.52-2.03	0.94			
BMI (kg/m ²)	0.95	0.84-1.08	0.45	1.07	0.98-1.18	0.14	0.95	0.88-1.02	0.17			
age (years)	0.98	0.89-1.08	0.70	1.02	0.93-1.12	0.68	0.93	0.88-0.99	0.02			
pain when walking on flat surface (yes)	0.42	0.07-2.58	0.35	1.91	0.53-6.83	0.32	1.13	0.44-2.90	0.81			
pain when going up or down stairs (yes)	0.58	0.14-2.52	0.47	1.33	0.46-3.85	0.60	1.20	0.55-2.59	0.65			
WOMAC function (0-68)	1.01	0.97-1.05	0.70	0.97	0.94-1.00	0.08	0.97	0.95-0.99	<0.01			
crepitus (yes)	0.47	0.16-1.38	0.17	1.04	0.45-2.41	0.92	0.54	0.30-0.97	0.04			
bony enlargement (yes)	0.18	0.02-1.78	0.14	0.25	0.05-1.12	0.07	0.36	0.13-0.96	0.04			
knee extension ROM (degrees)	0.96	0.74-1.25	0.77	0.85	0.68-1.07	0.17	1.09	0.96-1.25	0.20			
knee flexion ROM (degrees)	0.94	0.88-1.00	0.04	0.94	0.89-0.98	<0.01	0.98	0.94-1.01	0.16			
joint line tenderness (yes)	0.56	0.14-2.33	0.43	2.18	0.83-5.73	0.11	3.13	1.47-6.69	<0.01			
patellofemoral grinding test (pos)	0.62	0.15-2.48	0.50	1.23	0.46-3.30	0.69	0.85	0.42-1.73	0.65			
R ²			0.19		0.24		0.15					

Dependent variable PFOA

Abbreviations:

BMI: body mass index, m: meter, kg: kilogram, WOMAC: Western Ontario and McMaster Universities Arthritis Index, pos: positive, ROM: range of motion, OR: odds ratio, PFOA: patellofemoral osteoarthritis, TFOA: Tibiofemoral osteoarthritis, COA: combined osteoarthritis, OA: osteoarthritis, R²: coefficient of determination**Bold** indicates: p-value <0.01*Italics* indicates: p-value >.01 and <.05

Discussion

The results of this study suggest that OA may start in the PF joint because, at baseline, 16.4% of our participants with symptoms of early knee OA were diagnosed with radiographic isolated PFOA and none with isolated TFOA. At the 2-year follow-up, half of the participants with PFOA at baseline had developed COA, and at 5-year follow-up two thirds of the participants with isolated PFOA at baseline had developed COA. The incidence of COA and TFOA in patients that presented with symptoms of knee OA was low, i.e. 3.1-6.6%, respectively at the 2-year follow-up and 1.4-4.5%, respectively, at the 5-year follow-up.

Compared to the CAS(K) studies^{20 24 36 37}, in the present study the prevalence of PFOA at baseline was lower (23.9% versus 16.4%, respectively) and this difference remained at follow-up (28.8% at 3 years follow-up in the CAS(K) study versus 4.6% at 2 years follow-up in the present study).²⁰ These differences in prevalence and incidence are probably explained by the different populations in the studies. The CAS(K) studies^{20 24} comprised older participants with a higher BMI compared to our CHECK population. However, it was notable that, compared to Thorstensson et al.²⁶ who included younger individuals (age range 35-54 years) with chronic knee complaints (>3 months), we found a lower prevalence of TFOA at baseline (47% versus 0%, respectively). Therefore, the differences in prevalence and incidence might not only be due to different populations but might also be attributed to the use of inconsistent definitions for knee OA.³⁸ The inconsistency in definitions of radiological OA in studies evaluating different OA types may have led to misclassification into the different OA groups.³⁹ This emphasises the need for consensus on the radiographic classification system used for OA.³⁸

In the literature, three main signs of OA that were determined on physical examination (i.e. crepitus, restricted movement, and bony enlargement) were found to be associated with the development of radiographic OA.² These positive physical examination findings increase the risk of radiographic OA.² However, the present results indicate the difficulty of discriminating between the different types of OA using the measures from clinical history and physical examination. However, the results do indicate that participants with COA had a lower knee flexion ROM compared to those with isolated PFOA, and a trend was seen in participants with TFOA; i.e. they also had a lower knee flexion ROM compared to those with isolated PFOA. Consistent results were reported in another cross-sectional study on clinical features of symptomatic OA, showing that lower knee flexion ROM was an indicator for radiographic COA and not for radiographic PFOA.²⁴ Furthermore, this latter study also reported that lower knee flexion ROM was an indicator for TFOA.²⁴ It is proposed that knee flexion ROM is an important clinical finding in (especially) participants with severe radiological signs of OA.⁴⁰ In the present cohort, the majority of participants with knee symptoms had PFOA at baseline and this

was already associated with reduced knee flexion ROM. Therefore, reduced knee flexion ROM seems to be an early sign of knee OA. However, it is questionable whether the ROM can distinguish between those with isolated PFOA, and those with TFOA and COA, in young persons with knee symptoms.

It is noteworthy that participants without radiographic signs of OA were more likely to have joint line tenderness compared to those with PFOA. It could be hypothesised that joint line tenderness might be associated with other intra-articular pathologies (e.g. meniscus) that are not seen on radiographs. This hypothesis is strengthened by the fact that, when the K&L grade ≥ 1 variable was added to the multivariate regression model to test differences in phenotype between participants without radiographic signs of OA and those with PFOA, the significant association between joint line tenderness remained (data not shown).

The strength of the present study is that we were able to analyse a large cohort of relatively young subjects with early knee symptoms so that the natural course of OA could be evaluated. However, the study also has some limitations. In this relatively young cohort of participants with symptoms of knee OA, X-rays may not be sufficiently sensitive to detect early OA features and changes that are detectable on MRI.⁴¹ On the other hand, these participants were followed over five years, a period in which radiographic signs are expected to progress.⁴²

Due to the small number of participants with TFOA we were unable to test for differences in phenotype based on baseline characteristics; therefore, we performed a cross-sectional analysis with the 2-year follow-up data. Furthermore, a limited number of variables were included in the regression analysis. Additional variables measured in the CHECK study (including clinical hand OA, profession, and physical activity) and reported to be risk factors for knee OA, might also differ between persons with PFOA and TFOA.⁴²

The explained variance in the regression model was low, indicating that other factors not included in the present study (e.g. quadriceps strength, malalignment) might be able to differentiate between the different types of OA.^{19 24 42} These biomechanical variables could be potential targets for specific treatments for PFOA.⁴³

Implications for future research

Two-thirds of the participants that had PFOA at baseline had progressed to COA at the 5-year follow-up, whereas only 20% of the participants that had TFOA at the 2-year follow-up progressed to COA at the 5-year follow-up. This indicates that, in participants with a recent onset of knee complaints, not only is OA more likely to start in the PF joint, but also that those who have their first signs of radiographic OA in the PF joint are more likely to progress to COA compared to those with isolated radiographic signs of OA in the TF joint. This is in agreement with earlier studies.^{20 37} However, a longer follow-up period is needed to determine whether all participants with PFOA at baseline

will develop COA, or whether there are more subgroups within the PFOA population (e.g. stable PFOA, progression to COA, and progressive PFOA).

Conclusion

The results of this study suggest that OA is likely to start in the PF joint and then progress to COA. Differences in TFOA and PFOA phenotypes could not be determined with respect to signs and symptoms. A longer follow-up is necessary to determine whether all participants with PFOA will eventually develop COA.

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Chapter VIII

Physical therapy for knee and/or ankle symptoms: Self-referral compared to a general practitioner's referral

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Submitted

Abstract

Background

Since 2006 patients in the Netherlands no longer need a referral from a physician to visit a physical therapist. However, differences in patient characteristics between self-referred and GP-referred patients with knee or ankle symptoms are still unknown.

Objective

To determine patient characteristics, frequency of use, type of symptoms and treatment outcomes in patients with knee or ankle symptoms, separately, for patients referred by their GP and self-referred patients.

Design

Longitudinal study.

Setting

Dutch primary care physical therapy practices

Method

Data were collected from the NIVEL Primary Care Database. The mode of access (self-referral or referral) was determined in all patients. For analyses, descriptive statistics, unpaired t-tests, chi-square test and logistic regression analyses were applied.

Results

The study included 6794 patients with knee or ankle symptoms. The use of self-referral increased from 26% in 2006 to 57% in 2012 and stabilized in 2010-2012. Self-referred patients were younger, had a higher education level and a shorter duration of symptoms compared to GP-referred patients. Self-referred patients had less treatment sessions compared to GP-referred patients.

Limitations

Treatment characteristics could not be included in the multivariate regression analyses due to the high percentage of missing data.

Conclusion

Patients with knee or ankle symptoms of younger age, a higher education level, a shorter duration of symptoms, and recurrent symptoms more frequently used self-referral. Self-referred patients had fewer treatment sessions. After 2009, the frequency of use of self-referrals to a physical therapist stabilized. Future studies should examine the effectiveness of physical therapy via self-referral in acute knee and ankle symptoms.

Introduction

Musculoskeletal symptoms (e.g. back shoulder, knee and ankle) are common in primary care and, in the Netherlands, account for about 12% of all consultations in general practice.^{1,2} Knee and ankle symptoms are common types of musculoskeletal symptoms with an incidence of 10.9-13.7 per 1000 persons and 3.3 per 1000 persons, respectively.^{2,3}

Various non-surgical treatment options are available for knee and ankle symptoms and mainly comprise advice to rest and pain relief for acute traumatic symptoms.^{4,5} For both non-traumatic and chronic knee/ankle symptoms (including chronic symptoms due to trauma), physical therapy is also considered.^{4,6,7} In the Netherlands, although physical therapy is not strongly recommended in the guidelines for general practitioners (GPs), there is evidence that supervised exercise therapy can result in pain reduction and functional improvement compared to usual care in patients with non-traumatic knee symptoms, traumatic knee injury and ankle injury.^{4,8-10}

One result of the new healthcare system introduced in the Netherlands in 2006, is that patients no longer need a formal referral by a GP (or other physician) to consult a physical therapist (PT). This change led to an increase in the number of patients with musculoskeletal complaints consulting the PT through self-referral, with rates increasing from 31.9% to 46.9% between 2006 and 2012, respectively.¹¹

Three earlier studies in the Netherlands comparing characteristics of patients who visited a PT via referral from a GP or by referring themselves, found that self-referred patients had a higher education level and a shorter duration of symptoms.¹²⁻¹⁴ The first study was conducted immediately after implementation of self-referral and had a shorter duration of follow-up,¹² whereas the other two studies evaluated patient characteristics in the period 2006-2009¹³ and 2006-2010.¹⁴ However, the studies included back pain patients only¹³ or patients with diverse types of musculoskeletal disease (e.g. back, neck, shoulder)¹⁴ and patients with knee and ankle symptoms may differ from these patients. Patients with knee and ankle symptoms are more likely to be distributed between different age groups (including young and older patients) and will probably include a percentage of traumatic symptoms which could impact the choice of care.^{4,5}

To date, no studies have examined the association between patient characteristics and the mode of access to physical therapy among patients with knee or ankle symptoms. Therefore, the primary aims of this study are: i) to establish the distribution in mode of access of patients with knee or ankle symptoms during 2006-2012, and ii) to investigate the differences in patient and treatment characteristics between patients referred for

physical therapy versus self-referred patients, and to identify the characteristics associated with self-referral.

Methods

Data were collected from the NIVEL Primary Care Database (NPCD) formerly known as National Information Service for Allied Health Care (LiPZ). The NPCD consists of longitudinal data, collected by extraction of routinely recorded data in the healthcare provider's electronic health record system. For the current study, only data and registrations of patients who visited a PT were used. The PTs were selected from extramurally working (community-based) PTs in the Netherlands and are nationally representative by regional distribution. More detailed information about the NPCD is published previously.¹²⁻¹⁴

Study population

The study population consisted of all patients who visited a PT with knee or ankle symptoms in the period 2006-2012. Knee and ankle symptoms were identified using the International Classification of Primary Care (ICPC).¹⁵ Each treatment episode represented in the NPCD was linked to one or more ICPCs. In case of referral, the written record made by the referring GP was recoded: in case of self-referral, the main health problem was recoded into an ICPC. A research assistant monitored and verified this digitalized recoding process. The following codes were used to select patients with knee symptoms: knee symptoms and complaints (L15), knee sprain/distortion (L78), osteoarthritis of the knee (L90), Osgood-Schlatter /osteochondritis dissecans (L94), acute meniscal or ligamental injury (L96), chronic internal knee trauma (L97), patellofemoral syndrome (L99.07), corpus liberum (L99.10) and pseudarthrosis (L99.11). To select patients with ankle symptoms, the following codes were used: ankle signs and symptoms (L16) and ankle sprain/distortion (L77). The types of symptoms were divided into traumatic and non-traumatic symptoms. Knee sprain/distortion (L78) and meniscal or ligamental injury (L96) were used to describe traumatic knee symptoms. Ankle sprain/distortion (L77) was used to define traumatic ankle symptoms.

In the NPCD, each episode of knee or ankle symptoms was registered separately. An episode was defined as an occurrence of knee or ankle symptoms from the start of a first consultation to the end of treatment in 2006-2012; therefore, one patient could be included for multiple episodes. Patients were excluded if the mode of access was not reported, if they had both knee and ankle symptoms the same episode, or if they had a referral from a physician other than a GP.

Ethical approval was not obligatory because the NPCD does not fall within the scope of the Medical Research Involving Human Subjects Act. Data were collected anonymously

and patients were informed about the research by posters and leaflets in practice waiting rooms. The study was performed in adherence to the tenets of the Declaration of Helsinki.

Measurements

From 2006-2012 the following data were collected for each episode:

Patient characteristics: Age (years), gender, urbanization (urban/rural), patient identification number, and educational level in patients aged >16 years (high/middle/low).

Referral: Diagnosis (based on the ICPC code), and mode of access (self-referral or referral).

Health problem: Recurrence of knee or ankle symptoms (visiting a PT with the same symptoms >3 months after the termination of care for the first episode) (yes/no) and duration of symptoms (≤ 7 days, 1 week-1 month, 1 month-12 months, ≥ 12 months).

Treatment: Number of visits to the PT for current episode, and duration of treatment episode (the total number of days a patient visited a PT)

Evaluation: Self-reported reason for termination of care (goals achieved, no insurance, terminated by patient, terminated by PT, or terminated by referrer) and self-reported results with respect to the treatment goal set at start of treatment (achieved, partially achieved, or not achieved).

Data analyses

Data on knee and ankle symptoms were analyzed separately. Analyses were performed using STATA version 13.0.

Patient characteristics, treatment outcomes and evaluation of treatment were analyzed using descriptive statistics. Differences between referral and self-referral were analyzed using unpaired t-tests in case of normally distributed data; chi-square tests were used in case of non-normally distributed and discrete data.

A multivariate logistic regression model with backward stepwise selection [p (in) 0.05, p (out) 0.10] was used to study the association between mode of access to physical therapy and patient characteristics, in patients with knee or ankle symptoms. Explorative analyses (due to the low number of patients) were performed to examine the association between mode of access and number of treatment sessions. The following characteristics were included in the analysis: gender, age, diagnosis, education level, urbanization, duration of symptoms, and recurrent symptoms. Associations were presented as odd ratios (ORs) with 95% confidence intervals (95% CI). In case of missing values >20%, dummy variables, including the variable 'unknown', were created to check whether missing data biased the results.

Results

Study population

From the initial 76806 patients who visited a PT in the period 2006-2012, 6794 patients with knee or ankle symptoms were selected for the present study (Figure.1).

Of these, the mean age was 40.5 (range 4-101) years, and 3151 (46%) were men. A total of 5160 (76%) patients were diagnosed with a knee complaint and 1634 (24%) with an ankle complaint (Table 1). The majority of patients with knee or ankle symptoms (61%) visited the PT with a GP referral. Of all patients with knee symptoms, 75% were diagnosed with 'knee symptoms/complaints' (L15). Other common knee diagnoses were 'patellofemoral syndrome' (9%) and 'osteoarthritis of the knee' (8%). The most common ankle symptom (61%) was a 'sprained ankle' (L77). The majority of patients with the diagnosis 'knee symptoms/complaints' were self-referrals. Of the patients with ankle complaints who were self-referrals, the most common diagnosis was 'sprained ankle' (55%). However, of all patients with ankle complaints the most common mode of access was a GP referral (Table 2).

Time trends in mode of access

The total number of self-referred patients with knee or ankle symptoms increased from 26% in 2006 to 57% in 2012 (Figure. 2). This increase was mainly observed in the years 2006-2009 and stabilized in the years 2010-2012.

Characteristics of patients with knee symptoms

Compared to referred patients, self-referred patients with knee symptoms more often were male (48% vs. 45%), younger (41.0 vs. 43.8 years, respectively), had a higher education level, lived in more urbanized areas, and had a shorter duration of symptoms (Table 1).

Furthermore, patients with knee symptoms who used self-referral had fewer physical therapy sessions and treatment days compared to patients who were referred: 6.4 vs. 9.2 sessions and 51.3 vs. 61.5 days, respectively (Table 3).

Multivariate regression analyses showed that patients with knee symptoms were more likely to use self-referral if they had a higher education level (OR 2.56; 95% CI 2.13-3.05) (Table 4) and less likely to use self-referral if they were aged 25-44 and 45-64 years: OR 0.73 (95% CI 0.60-0.89) and OR 0.68 (95% CI 0.55-0.82), respectively, and had a longer duration (>1 month) of symptoms (OR range 0.56-0.64) (Table 4).

Explorative multivariate regression analyses showed that male gender, higher education level, patellofemoral symptoms, and use of self-referral were associated with less treatment session (data not shown).

Table 1 Characteristics of the patients visiting a physical therapist due to knee or ankle symptoms, separately, by mode of access.

	Knee symptoms			Ankle symptoms		
	Referral n = 3157	Self-referral n = 2003	p-value	Referral n = 925	Self-referral n = 709	p-value
	n (%)	n (%)		n (%)	n (%)	
Gender: male	1425 (45.2)	965 (48.2)	0.04	417 (45.1)	344 (48.5)	0.17
Age in years, mean (SD)	43.8 (20.8)	41.0 (20.0)	<0.01	34.1 (19.3)	32.6 (17.7)	0.37
Age in categories			<0.01			0.13
<15 years	230 (7.3)	127 (6.3)		151 (16.3)	99 (14.0)	
15-24 years	562 (17.8)	449 (22.4)		237 (25.6)	217 (30.6)	
25-34 years	323 (10.2)	279 (13.9)		126 (13.6)	98 (13.8)	
35-44 years	461 (14.6)	273 (13.6)		122 (13.2)	104 (14.7)	
45-54 years	557 (17.6)	318 (15.9)		127 (13.7)	95 (13.4)	
55-64 years	470 (14.9)	286 (14.3)		83 (9.0)	57 (8.0)	
65-74 years	294 (9.3)	156 (7.8)		58 (6.3)	29 (4.1)	
75+ years	260 (8.2)	115 (5.7)		21 (2.3)	10 (1.4)	
Education level^a			<0.01			<.01
Lower	825 (38.5)	374 (25.2)		204 (35.8)	96 (20.4)	
Middle	785 (36.6)	481 (32.4)		200 (35.1)	163 (34.6)	
Higher	533 (24.9)	628 (42.4)		166 (29.1)	212 (45.0)	
Urbanization^b			<0.01			0.02
Urban	1493 (61.1)	966 (66.4)		398 (55.5)	318 (62.1)	
Rural	949 (38.9)	488 (33.6)		319 (44.5)	194 (37.9)	
Duration of symptoms^c			<0.01			<0.01
< 1 month	1014 (32.9)	888 (45.9)		496 (54.7)	440 (63.6)	
1 month - 3 months	879 (28.5)	471 (24.3)		212 (23.4)	135 (19.5)	
3 months - 12 months	674 (21.9)	322 (16.6)		123 (13.6)	66 (9.5)	
>12 months	517 (16.8)	255 (13.2)		76 (8.4)	51 (7.4)	
Recurrent symptoms: yes	832 (27.0)	570 (29.5)	0.13	219 (24.0)	213 (30.9)	<0.01
Type of symptoms			0.64			<0.01
Traumatic	213 (6.8)	142 (7.1)		600 (64.9)	390 (55.0)	
Non-traumatic	2944 (93.2)	1861 (92.9)		325 (35.1)	319 (45.0)	

Missing data

Knee symptoms

^a referral: 31.1%, self-referral: 26.0%, ^b referral: 22.7%, self-referral: 27.4%, ^c referral: 2.3%, self-referral: 3.3%

Ankle symptoms

^a referral: 39.4%, self-referral: 33.6%, ^b referral: 22.5%, self-referral: 27.8%, ^c referral: 1.9%, self-referral: 2.4%

Table 2 Specification of knee and ankle symptoms, separately, for each mode of access.

Diagnosis (ICPC code)	Total population	Referral	Self-referral	p-value overall
	n (%)	n (%)*	n (%)*	
Knee symptoms	5160	3157 (61.2)	2003 (38.8)	<0.01
Knee symptoms/complaints (L15)	3877 (75.1)	2215 (70.2)	1662 (83.0)	
Sprained knee (L78)	264 (5.1)	157 (5.0)	107 (5.3)	
Osteoarthritis of the knee (L90)	416 (8.1)	314 (10.0)	102 (5.1)	
Osgood-Schlatter (L94.02)	31 (0.6)	24 (0.8)	7 (0.4)	
Acute meniscal injury (L96)	91 (1.8)	56 (1.8)	35 (1.8)	
Chronic internal trauma knee (L97)	17 (0.3)	15 (0.5)	2 (0.1)	
Patellofemoral syndrome (L99.07)	464 (9.0)	376 (11.9)	88 (4.4)	
Ankle symptoms	1634	925 (56.6)	709 (43.4)	<0.01
Ankle symptoms/complaints (L16)	644 (39.4)	325 (35.1)	319 (45.0)	
Sprained ankle (L77)	990 (60.6)	600 (64.9)	390 (55.0)	

P-values show a significant difference in distribution of diagnoses between the referral and the self-referral group

Characteristics of patients with ankle symptoms

Patients with ankle symptoms who used self-referral were higher educated, lived in more urbanized areas, reported shorter duration of symptoms, and had more recurrent symptoms compared to referred patients. Referred patients had more traumatic symptoms compared to patients who used self-referral (Table 1).

Moreover, patients with ankle symptoms who used self-referral had fewer treatment sessions compared to patients who were referred (5.5 vs. 6.7 sessions and 41.6 vs. 44.7 days, respectively) (Table 3)

Similar to patients with knee symptoms, multivariate analyses showed that patients with ankle symptoms were more likely to use self-referral if they had a higher education level (OR 2.69; 95% CI 1.92, 3.75), whereas they were less likely to use self-referral if they were aged 25-44 years (reference category), had traumatic ankle symptoms (sprained ankle) (OR 0.53; 95% CI 0.40-0.71) and had a longer duration (>1 months) of symptoms (OR range 0.53-0.70) (Table 4).

Explorative multivariate analyses showed that patients with ankle symptoms with shorter duration (1-3 months) of symptoms and use of self-referral were associated with fewer treatment sessions (data not shown).

Table 3 Treatment characteristics of patients visiting a physical therapist due to knee or ankle symptoms, separately, by mode of access.

	Knee symptoms			Ankle symptoms		
	Referral n = 3157	Self-referral n= 2003	p-value	Referral n= 925	Self-referral n= 709	p-value
	n (%)	n (%)		n (%)	n (%)	
Treatment sessions^a						
Number of sessions, mean (SD)	9.2 (11.3)	6.4 (7.4)	<0.01	6.7 (7.2)	5.5 (5.9)	<0.01
Duration of treatment episode in days, mean (SD)	61.5 (99.4)	51.3 (81.4)	<0.01	44.7 (60.0)	41.6 (57.1)	<0.01
Goals accomplished?^b						
Goals accomplished	1040 (67.0)	623 (69.1)		417 (82)	247 (78)	0.32
Goals partially accomplished	385 (24.8)	221 (24.5)		70 (14)	55 (17)	
Goals not accomplished	128 (8.2)	58 (6.4)		19 (4)	14 (4)	
Reason termination of care^c						
Goals accomplished	1216 (83.0)	726 (88.5)	<0.01	461 (92.4)	299 (92.9)	
No compensation insurance	29 (2.0)	9 (1.1)		5 (1.0)	2 (0.6)	
Terminated by patient	99 (6.8)	28 (3.4)		14 (2.8)	9 (2.8)	
Terminated by therapist	111 (7.6)	55 (6.7)		14 (2.8)	11 (3.4)	
Terminated by referrer	10 (0.7)	2 (0.2)		5 (1.0)	1 (0.3)	

Missing data

Knee symptoms

^a Referral: 10.2%, self-referral: 16.1%, ^b Referral: 50.8%, self-referral: 55.0%, ^c Referral: 53.6%, self-referral: 59.1%

Ankle symptoms

^a Referral: 8.5%, self-referral: 16.9%, ^b Referral: 45.3%, self-referral: 55.4%, ^c Referral: 46.1%, self-referral: 54.6%

Discussion

This study examined differences in patient characteristics between patients with knee or ankle symptoms who visited a PT after referral by a GP compared with patients using self-referral. In 2006 26% of all patients visiting a PT were self-referred, increasing to 57% of all patients in 2012; this growth stabilized in the period 2010-2012. Furthermore, patients were more likely to use self-referral when they had a higher education level, were of younger of age and had a shorter duration of symptoms.

It is reported that patients of older age and with a longer duration of symptoms are at higher risk of comorbidity and more complex and chronic symptoms, resulting in more visits to a GP.¹⁶⁻¹⁸ This is supported by our study showing that patients were less likely to use self-referral if they suffered from a diagnosis with a higher prevalence in older patients and of a more chronic nature (e.g. osteoarthritis).

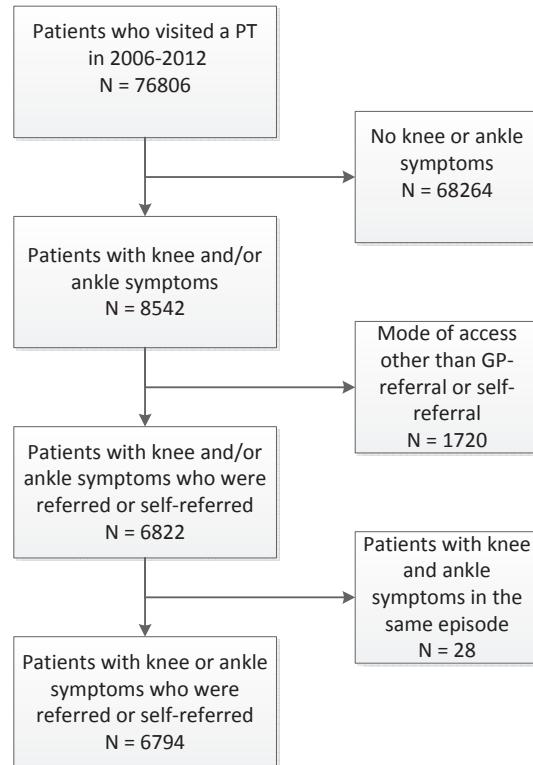


Figure 1 Flowchart of patients selected for the present study

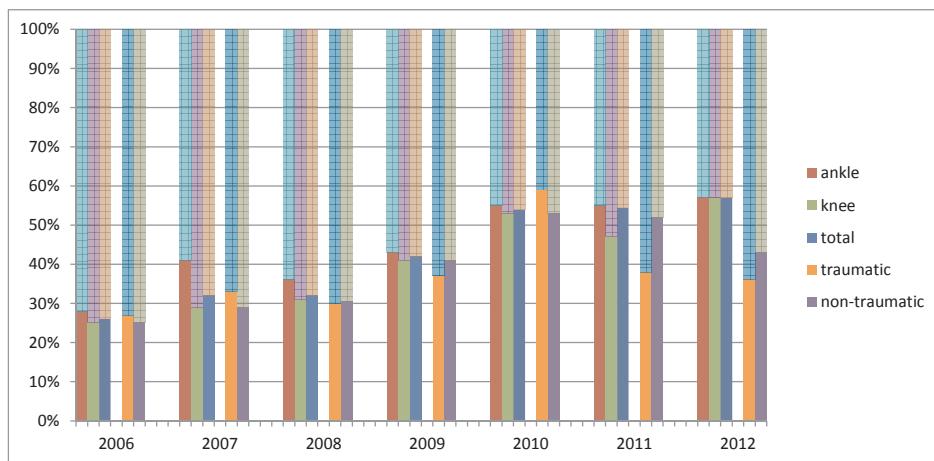


Figure 2 Distribution in the mode of access in patients with knee or ankle symptoms in the period 2006-2012

The darker bars represent the percentage of patients using self-referral and the lighter ones patients using a referral by a GP

Table 4 Multivariate logistic regression for factors associated with the use of self-referral in patients with knee or ankle symptoms.

	Knee symptoms		Ankle symptoms	
	Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value
Gender: male				
Age in categories				
<25 years	Reference category		Reference category	
25-44 years	0.73 (0.60-0.89)	<0.01	0.70 (0.51-0.97)	0.03
45-64 years	0.68 (0.55-0.82)	<0.01	0.80 (0.57-1.12)	0.19
>65 years	0.81 (0.62-1.05)	0.11	0.61 (0.35-1.08)	0.09
Disorder				
Knee symptoms/complaints (L15)	Ref.cat.			
Sprained knee (L78)	0.65 (0.48-0.90)	<0.01		
Osteoarthritis of the knee (L90)	0.63 (0.46-0.85)	<0.01		
Osgood-Schlatter (L94.02)	0.43 (0.04-4.28)	0.48		
Acute meniscal injury (L96)	0.72 (0.44-1.18)	0.19		
Chronic internal trauma knee (L97)	0.22 (0.05-1.01)	0.05		
Patellofemoral syndrome (L99.07)	0.30 (0.22-0.41)	<0.01		
Ankle symptoms/complaints (L16)			Ref. cat.	
Sprained ankle (L77)			0.53 (0.40-0.71)	<0.01
Education level				
Lower	Ref. cat		Ref. cat.	
Middle	1.32 (1.10-1.57)	<0.01	1.79 (1.28-2.51)	<0.01
Higher	2.56 (2.13-3.05)	<0.01	2.69 (1.92-3.75)	<001
Urbanization				
Urban				
Rural				
Duration of symptoms				
< 1 month	Ref. cat.		Ref. cat.	
1 month - 3 months	0.64 (0.54-0.77)	<0.01	0.62 (0.45-0.87)	<0.01
3 months - 12 months	0.54 (0.44-0.66)	<0.01	0.44 (0.28-0.69)	<0.01
>12 months	0.56 (0.44-0.70)	<0.01	0.53 (0.31-0.92)	0.02
Recurrent symptoms: yes	1.29 (1.10-1.52)	<0.01	1.40 (1.04-1.88)	0.03

Similar to other studies, the patients in our study with a shorter duration (<1 month) of symptoms were more likely to use self-referral to a PT.^{12 13} It is questionable whether these latter patients actually need physical therapy at this stage of the disease (although PTs perform a standardized intake for all new patients to determine the need for physical therapy). An earlier study on self-referral showed that 87% of the self-referred patients with musculoskeletal symptoms who visited a PT were in fact treated by a PT after the

initial intake.¹⁴ Thus, it seems that a large percentage of the self-referred patients who seek help for their musculoskeletal symptoms (including knee and ankle symptoms) are treated by their PT. However, evidence on the effectiveness of physical therapy for acute knee and ankle symptoms (duration of symptoms < 1 months) is lacking. Also, in the present study, the patient characteristics associated with the use of self-referral are comparable to the prognostic factors for better recovery rates in both knee and ankle symptoms reported by others (e.g. younger age, shorter duration of symptoms, higher level of education).^{19 20} This indicates that these patients are probably more likely to recover with or without treatment from a PT. Furthermore, in the guidelines for GPs for non-traumatic or traumatic knee symptoms and ankle symptoms, physical therapy is not advised for acute knee or ankle symptoms.⁴⁻⁷ Although PTs also have guidelines for the treatment of specific complaints (e.g. ankle symptoms, osteoarthritis of the knee)²¹⁻²³ adherence to these guidelines varies between PTs for patients with ankle symptoms.²⁴ Furthermore, information on prognostic factors for recovery and, therefore, possible indicators that treatment after the first intake is (or is not necessary), is lacking in these guidelines. This information is essential for PTs' decision-making process at first intake, e.g. to treat, refer, or wait and see. Therefore, future studies should examine the (cost-) effectiveness of physical therapy via self-referral in acute knee and ankle symptoms.

Patients with knee or ankle symptoms who visited a PT on their own initiative had fewer treatment sessions and days of treatment compared to patients who used a GP referral. These results are consistent with other studies evaluating differences in treatment characteristics among patients who seek help with a PT with or without a referral.^{12 25-28}

Moreover, we performed additional explorative multivariate regression analyses with the number of treatment sessions as the dependent variable, to identify whether the relation between the mode of access and the number of treatment session between those with and without a referral was influenced by any other factors. This analysis showed that, besides the mode of access, other characteristics (e.g. duration of symptoms) were also associated with fewer treatment sessions. Thus, although patients who visited a PT without a referral had fewer treatment sessions compared to patients with a referral, the difference in the number of treatment sessions was merely influenced by these other patient characteristics. Therefore, it remains unclear whether the differences in treatment sessions seen between patients with and without a GP referral is caused by the mode of access or by other patient characteristics. Therefore, based on the data from this study, no conclusions can be drawn about the cost-effectiveness of the implementation of self-referral.

Strengths and limitations

The differences found in patient characteristics between patients using self-referral and referred patients are in agreement with two earlier studies conducted in the Netherlands.^{12 13} In these latter studies, patient characteristics associated with self-referral were similar to ours (e.g. education level and duration of the complaint). However, we also analyzed the effects of the availability of self-referral over a longer period of time in specific musculoskeletal symptoms (i.e. knee and ankle). Therefore, the present study provides information on differences between patients with traumatic and non-traumatic knee and ankle symptoms, as well as more insight into the effects of the implementation of self-referral six years after its implementation in this specific patient group.

All diagnoses in the present study were based on ICPC codes.¹⁵ These codes were allocated by a computer program developed by NIVEL. Although all diagnoses were provided by the same computer program, some methodological differences might exist in the allocation of the diagnosis between patients with and without a referral. In patients using self-referral, all details on the diagnosis came from the PT's record, whereas for the referred patients the exact wording of the GP's referral was recoded. Due to this methodological difference, the prevalence rates presented here should be interpreted with caution.

For the variables 'education level' and 'urbanization' data was missing >20%. To check whether these missing data biased the results we performed a regression analyses including the variables 'unknown education level' and 'unknown urbanization'. Only 'unknown education level' was significantly associated with self-referral in the final model for patients with ankle complaints. This did however not influence the odds ratios of the other variables included in the model. The high percentage of missing data for education level can be explained by the fact this variable was only created in patients >16 years. Another limitation is that the severity of complaints was not measured and that the variables 'goals accomplished' and 'reasons for termination of care' had a high percentage of missing data (missing >50.0%). Due to the high percentage of missing data, these variables were not included in the multivariate regression analyses. Moreover, 'severity of symptoms' has been suggested as a possible explanatory factor for the lower number of treatment sessions in patients that used self-referral.^{12 25 28}

Future research should aim to identify differences in the reasons for termination of care, and differences in the severity of symptoms (e.g. pain and function scores) between patients with knee or ankle disorders who use self-referral compared to patients who use a referral. The severity of symptoms (e.g. based on the International Classification of Functioning, Disability and Health)²⁹ could be assessed at the beginning and at end of

a treatment session. The predefined treatment goal could be based on the magnitude of the difference in symptoms before and after the treatment session. By standardizing these treatment goals, differences in treatment outcomes between patients who used a referral and those who used self-referral can be determined.

In countries where self-referral is already implemented³⁰ researchers should be aware of the differences in patient characteristics between patients who visit a PT with or without a referral. This could influence the results of studies due to possible selection bias; therefore, researchers should consider including patients visiting GPs and PTs to reduce this risk. Finally, the results of the present study are important for PTs and GPs as they need to be fully aware of their responsibilities since the implementation of self-referral.

Conclusion

Since 2006 patients have increasingly use self-referral to visit a PT, whereas after 2009 the frequency of use of this mode of access stabilized. The use of self-referral among patients with knee/ankle symptoms is associated with younger age, higher education level and a shorter duration of symptoms. Furthermore, treatment outcomes (e.g. number of treatment sessions, duration of treatment) differed between GP-referred and self-referred patients. Future studies should examine the effectiveness of physical therapy via self-referral in acute knee and ankle symptoms.

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Chapter IX

General Discussion

General Discussion

The aim of this thesis was to outline and summarize the risk factors and factors associated with patellofemoral pain (PFP) and the effects (benefits and harms) of exercise therapy aimed at reducing knee pain and improving knee function in patients with PFP. Furthermore, we aimed to identify effect modifiers to response to treatment, to determine the natural course of PFP and explore its proposed continuum to patellofemoral osteoarthritis (PFOA).

Aetiology of PFP

Although the cause of PFP is reported to be multifactorial, an overview of all the risk factors for PFP and factors associated with PFP is lacking.^{1,2} The identification of possible risk factors for PFP and factors associated with the presence of PFP is important, as this may help to identify which factors are important with regard to prevention, prognosis and possible treatment targeting. Therefore, Chapters II and III outline and summarize the risk factors and factors associated with the presence of PFP. For these two systematic reviews, we decided to report - separately - the factors which could contribute to the *development* of PFP (risk factors) and those related to the *presence* of PFP.

These two reviews included a total of 54 studies (7 prospective and 47 cross-sectional), a total of 658 variables (135 risk factors, 523 factors associated) for PFP were evaluated, and 21 variables were pooled in a meta-analysis. Only one clear risk factor for PFP was identified, i.e. having lower knee extension strength. Other risk factors were either based on single studies, or presented conflicting evidence. A larger Q-angle, larger sulcus angle, larger patellar tilt angle, less hip abduction strength conveyed as a percentage of body weight, and lower knee extension strength expressed by peak torque, were factors that could be pooled and were associated with PFP. Conflicting findings were described in studies that could not be pooled due to various methodological issues.

This means that a large number of factors that might contribute to the development of PFP, and factors that are associated with PFP, were examined. However, there was considerable lack of agreement between the different studies as to which (risk) factors are associated with PFP. This lack of agreement might be attributed to differences in study populations, differences in the methods used to measure the possible (risk) factors, differences in the variables examined, and/or the lack of a clear and consistent definition of PFP.

It is noteworthy that most of the studies included in our reviews focused on mechanical, static and neuromuscular factors only, rather than on pathophysiological factors related to intra-articular and peri-articular tissue. Despite the large number of included studies and included variables, the aetiology of PFP remains unclear. Dye^{3,4} highlighted the need for studies evaluating parameters other than mechanical factors as potential

factors in the aetiology of PFP, such as pathophysiologic factors (e.g. increase of osseous metabolic activity of patellar bone or inflamed peripatellar synovial lining and fat pad tissues). A possible method to detect loss of tissue homeostasis is bone scintigraphy, as earlier studies have reported that patients suffering from PFP have a diffuse uptake on bone scintigraphy.³⁵ Earlier studies hypothesized that this diffuse uptake may indicate regions of ischaemic stress.³⁵ However, these studies were excluded from our systematic review (Chapter II) because they only included patients with PFP and did not compare their results with assessments made in individuals without pain. Therefore, our department is currently investigating differences in blood flow around the patellofemoral joint in patients with PFP compared to non-symptomatic controls.⁶ In this ongoing study, the presence of subchondral bone marrow oedema and other structural abnormalities (e.g. micro-fractures or stress fractures, aseptic bone necrosis) in the patellofemoral joint in PFP patients will also be evaluated and compared to non-symptomatic controls. One hypothesis of this study is that subchondral bone marrow oedema might contribute to the pain in patients with PFP.⁷

Another reason PFP could be an increase in hyperalgesia. Although longitudinal studies on causal relations are lacking, a study among adolescent female PFP patients reported a lower pain pressure threshold in patients with PFP compared to controls. This indicates that localized hyperalgesia may be present in (a subgroup) PFP patients.⁸

In knee osteoarthritis, although lower pain pressure thresholds are associated with different coping strategies,^{9 10} this association has not yet been examined in patients with PFP. In this perspective it was apparent that only nine of the 658 variables that were evaluated for their association with PFP focused on psychological factors.^{11 12} One prospective study that examined seven psychological factors as possible *risk factors* for PFP, found that those who sought less social support were more likely to develop PFP in the future.¹² Furthermore, higher mental distress and lower self-perceived health status were associated with the *presence* of PFP, and were correlated with knee pain and knee function in patients with PFP.¹¹ Knee pain is the most important symptom of PFP; mechanisms to deal with pain are important in pain management, especially in the presence of chronic pain syndromes.¹³⁻¹⁵ Therefore, it is noteworthy that very few psychological factors have been studied in relation to the *presence* of PFP,¹¹ moreover, in the latter study, patients were recruited from an orthopaedic outpatient department of a hospital, from private physiotherapy clinics, and via advertisements in the local newspaper¹¹ To improve the generalisability for clinical practice in the Netherlands, it is recommended to recruit patients from healthcare providers in primary care (e.g. general practices and/or physiotherapist practices) because the majority of PFP patients will be seen in such a setting. Moreover, large cohort studies are needed to identify whether psychological variables are potential *risk factors* for the development of PFP, as well as the development of chronicity of PFP. Identification of these potential subgroups

at risk for PFP, might result in different and more effective treatment options, such as behavioural interventions in those who have developed PFP. These new cohort studies should include children, adolescents and young adults (aged < 40 years), as the pathology may be different in patients that developed PFP in adolescence compared to those who developed PFP later in life.¹⁶

Exercise for PFP

In Chapter IV, our Cochrane review showed there is very low 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. No differences were found between the different types of exercise (e.g. closed versus open) or the delivery of exercise (e.g. supervised versus home). However, there is very low evidence that targeting of the hip and knee muscles is more effective than targeting the knee muscles alone for reducing pain. This is noteworthy as, in contrast to reduced knee extension strength found as a risk factor for developing PFP, none of the hip variables (strength and angles) included in our review were identified as risk factors for PFP (Chapter II). However, less hip abduction strength was associated with the presence of PFP in our second review

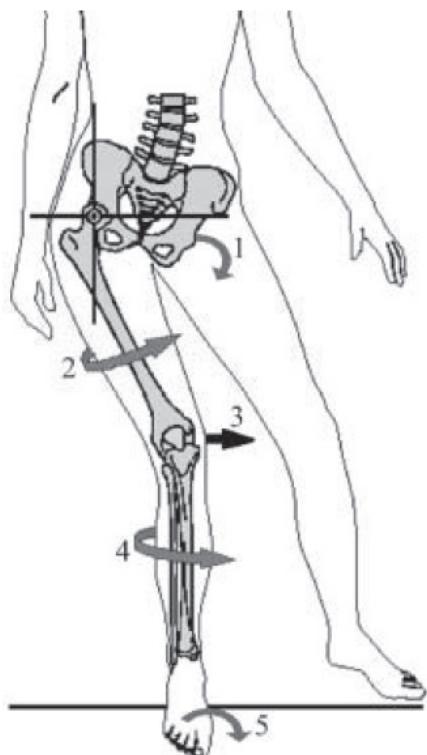


Figure 1 Schematic showing the potential contributors of the various lower extremity segments to abnormal alignment. (Reproduced from: Powers CM. The influence of altered lower-extremity kinematics on patellofemoral joint dysfunction: a theoretical perspective. *J Orthop Sports Phys Ther* 2003; 33: 639-46.) 1) contralateral pelvic drop, 2) femoral internal rotation, 3) knee valgus, 4) tibia internal rotation, and 5) foot pronation.

(Chapter III); also, according to Dolak et al.¹⁷ training of the quadriceps in weight-bearing position involves a contribution of both hip and quadriceps muscles. This is also highlighted by Powers¹⁸, who reported that patients with PFP have abnormal motion of the tibia and femur in the transverse and frontal planes. The interaction of these different segmental motions of the lower extremity (e.g. pelvic drop, femoral internal rotation, knee varus) may have an effect on patellofemoral joint mechanics; therefore, interventions targeting both hip and knee exercises could be more effective than interventions that include knee exercises alone (Figure 1).¹⁸ Because we only found a trend toward very low evidence for more beneficial outcomes when targeting both hip and knee muscles compared to knee muscles alone, this needs to be further investigated in high-quality randomised controlled trials (RCTs).

Who benefits from exercise therapy for PFP?

In Chapter IV, although we found that exercise therapy was effective for both short and long-term outcomes, not all patients benefited from exercise therapy (expressed as the percentage of patients with persistent symptoms). Other studies reported one-year recovery ratios after exercise therapy ranging from 40-60%.¹⁹⁻²¹ Thus, although exercise therapy is more effective compared to a 'wait and see' policy, a relatively large percentage of patients still have symptoms after one year despite having received exercise therapy.

In addition to exercise treatment for PFP, other conservative treatment options have been described.²²⁻²⁴ However, the evidence for the effectiveness of these conservative therapies (e.g. tape and orthoses) compared to exercise or a control strategy for PFP, with regard to pain reduction and improving function is limited.²²⁻²⁴

Several authors highlighted the need to identify subgroups for specific treatment of PFP.¹²⁵⁻²⁸ However, until now there is no consensus as to which subgroups should be targeted to improve outcomes in treatment for PFP. Selfe et al.²⁷ published a research protocol on the possible identification of clinically important subgroups of patients, mainly based on biomechanical differences (e.g. hip abduction and quadriceps weaknesses, or lower limb biarticular muscle tightness). Lack et al.²⁸ summarized the available literature on participant characteristics and structural factors as potential predictors of intervention success, but none of the studies included in their review used an appropriate test (e.g. interaction) for the identification of clinical predictors of response.²⁸⁻²⁹ Therefore, we aimed to identify the characteristics of patients with PFP who were more likely to benefit from exercise therapy, applying a secondary explorative analysis of an RCT comparing supervised exercise therapy to usual care in patients with PFP. We hypothesised that a subgroup of patients might derive more benefit from exercise therapy than from usual care, compared with other patients.

In the original RCT, patients aged 14-40 years with symptoms of PFP persisting for 2-24 months were included and they were randomly allocated to supervised exercise

therapy or to 'usual care'.²¹ From this RCT, patient characteristics were selected that could potentially interact with treatment. Because the exact mechanism of the effect of exercise therapy in PFP is not well understood, we selected potential effect modifiers (e.g. gender, age, BMI, sport intensity and duration of complaints) based on the literature and clinical interpretability (e.g. easy to obtain with anamnesis). However, because the original RCT was not designed to identify effect modifiers, we performed an exploratory secondary analysis. Although none of the selected variables had a significant interaction with treatment, a positive trend was found for patients with a longer duration of symptoms. These patients were more likely to benefit from exercise therapy than from usual care, compared with patients with a shorter duration of symptoms. Patients with a longer duration of PFP symptoms might have decreased strength of the lower extremity muscles and therefore benefit more from exercise therapy than from usual care, compared to those with a shorter duration of symptoms. In patients with knee osteoarthritis, those with weaker upper leg muscle strength benefit more from a supervised exercise program that mainly focused on improving upper leg strength, while patients with stronger muscle strength benefited more from a program that concentrated on stabilising exercises during the first month and, thereafter, added strength exercises.³⁰ However, because in the original RCT no biomechanical data were obtained, we were unable to test the interaction between biomechanical data and treatment.²¹ An earlier study hypothesised that a decrease of muscle strength could be a result of reduced sport activity¹⁶ while others found that patients with a longer duration of symptoms do indeed reduce their sport activities.^{31 32} In the study of Whitelaw et al.³² 92% of the PFP patients that stopped their pain-provoking activities improved after physical therapy compared with 68% of the patients who continued their sport activities.³² An explanation for this is that those who reduced their sport activities before treatment are able to significantly improve their strength with physical therapy, whereas patients who continued their activities are less able to improve their strength and therefore benefit less from physical therapy. This strengthens the rationale that by improving strength in the lower extremity muscles, the load on the patellofemoral joint will decrease and, consequently, normalise the kinematics and thus reduce the pain. However, in Chapter V, sport intensity was not found to be a predictor for treatment outcome; this is probably due to the method we used to express sport intensity. First, we did not ask if patients reduced their sport activity specifically because of their knee symptoms. Second, the mean number of hours of the sport performed most frequently by a participant during the week was used to calculate sport intensity; this may have led to underestimation of the total hours of sport participation if patients practiced more than one sport. Third, because we had a problem with statistical power (the study was not designed to identify effect modifiers), we could not perform multivariate analyses and were therefore unable to test the effect of the duration of symptoms and sport intensity together. The positive

trend for the beneficial effects of supervised exercise therapy over usual care for patients with a longer duration of symptoms, indicates that there are subgroups of patients who respond differently to exercise therapy. However, more studies are needed to confirm our findings and to establish whether other clinically important subgroups of PFP patients exist. Furthermore, because we performed a secondary explorative analysis of an RCT, we were unable to test for other factors that might interact with treatment in patients with PFP. Although Selfe et al.²⁷ aimed to identify subgroups based on biomechanical differences,²⁷ the psychosocial factors should also be taken into account.²⁸⁻³³

Identification of different subgroups of PFP patients for treatment outcomes is not only important to improve outcomes, but might provide more insight into the mechanism of exercise therapy in patients with PFP.

The above-described proposed working mechanism of exercise therapy focuses on patient kinematics. However, it is also reported that patients with chronic PFP symptoms may have coping strategies for pain similar to those of other groups with chronic pain.¹³ In that case, exercise therapy for PFP might have the same mechanism as for other chronic pain syndromes.³⁴ Patients with chronic pain syndromes have increased levels of interleukins and cytokines and these systemic inflammatory responses can be reduced by exercise therapy.³⁵⁻⁴⁰ This might also explain the more beneficial pain outcomes in PFP patients when the hip and knee muscles are trained together, rather than focusing on knee muscles alone (Chapter IV); larger muscles groups might provide a greater anti-inflammatory response. However, the mechanism of exercise is not yet fully clarified and the evidence for more beneficial outcomes when knee and hip muscles are target together in PFP was only limited. Furthermore, it is unknown whether patients with PFP do indeed have an inflammatory response to pain. Therefore, more insight is needed on the aetiology of PFP and the working mechanism of exercise therapy.

Prognosis

Despite that a longer duration of symptoms was found to be a potential predictor of intervention success (Chapter V), this was also found to be a prognostic factor for worse pain scores after long-term follow-up in patients with PFP. The study in Chapter VI was a long-term follow-up of patients participating in two large RCTs (one in the Netherlands²¹ and one in Australia²⁰). Patients were followed for 5-8 years after the initial RCT. Of the 310 patients that participated in both RCTs, 60 participated in the long-term follow-up. The finding that a longer duration of symptoms is a predictor of poor PFP prognosis was consistent with a study by Collins et al.⁴¹ and with studies examining prognostic factors for worse outcomes in other musculoskeletal diseases (e.g. knee osteoarthritis, non-traumatic knee symptoms, and low back pain).⁴²⁻⁴⁴ Various reports show that a longer duration of complaints is a consistent predictor for a poor prognosis in musculoskeletal diseases. This result is often caused by selective inclusion of patients based on disease

duration, in studies evaluating the prognosis for patients with musculoskeletal diseases; those that have already recovered are not included in the study. However, the same type of selection is generally present in patients that visit a clinician for their symptoms and, therefore, we can assume that patients included in the studies examining prognostic factors are representative for the general PFP population.

The results emerging from Chapters V and VI indicate that patients with a longer duration of symptoms have a worse prognosis, but derive more benefit from exercise therapy than from usual care. Therefore, the duration of symptoms is an important aspect to include in the anamnesis of a clinician, as this may provide more insight into the patient's prognosis and help identify the most appropriate treatment option for an individual patient.

In the Netherlands, general practitioners (GPs) are trained to use guidelines during the medical consultation. These guidelines cover information on: the background of the condition, the risk factors, the prognosis, and the therapeutic options. However, in the current guideline for non-traumatic knee complaints (including PFP) information on the aetiology, the risk factors, the prognosis and best treatment options are incomplete and based on a very limited number of studies.⁴⁵ The guideline for non-traumatic knee complaints among children and adolescents includes different conditions of the knee which are prevalent in children and adolescents (e.g. PFP and Osgood-Schlatter) and focuses only on the absence of 'red flags'. In the case of the latter, an explanation about the self-limiting nature of most knee complaints is advised. For PFP patients, although isokinetic exercises for quadriceps muscles can be provided, referral to a physical therapist is not generally recommended.

The findings from Chapter VI challenge the statement in the guideline that PFP is a 'self-limiting' disease⁴⁵, because 57% of the patients that took part in our long-term follow-up reported an unfavourable recovery. This recovery rate is in agreement with earlier studies on the prognosis of PFP, reporting recovery rates ranging from 20% at 1-year follow-up to 91% at 18-years follow-up.^{20 21 41 46-49}

Furthermore, Chapter IV shows that exercise therapy is likely to result in better outcomes in patients with PFP compared to control strategies (including usual care). Therefore, it is recommended to update the guideline for GPs and include supervised exercise therapy as a first treatment option. Information on the course of PFP should also be updated, since its course does not always have a self-limiting nature, especially not for those patients with a longer duration of complaints.

Because of the high percentage of loss to follow-up in the long-term follow-up study (Chapter VI) we were unable to include other prognostic factors that might be associated with a worse recovery in patients with PFP. Factors such as coping strategies and pain sensitivity might be prognostic factors in other musculoskeletal diseases and need to be investigated in future PFP prognostic studies.^{25 50 51} This is important because these

patients might benefit from other treatment strategies, such as behavioural therapy, rather than exercise therapy alone.

Patellofemoral osteoarthritis

PFP to PFOA

Although the guidelines for clinicians emphasise the self-limiting nature of PFP, this disease may be a precursor to patellofemoral osteoarthritis (PFOA).⁵²⁻⁵⁵ However, adequate evidence to support this statement is lacking.²⁵ Therefore, we analysed radiographs (anterior-posterior, lateral and skyline) of 50 of the 60 patients that participated in the long-term follow-up measurement (Chapter VI). The majority of patients had no signs of radiographic knee osteoarthritis (OA) 5-8 years after their diagnosis of PFP. These findings are in contrast to those of Kannus et al., who found that 35% of their young PFP patients had signs of OA on magnetic resonance imaging (MRI).⁴⁷ However, the radiographic criteria used to score the X-rays in our study may have inappropriate for the population studied. In this relatively young PFP cohort (age range at baseline 14-40 years), X-rays might be insufficiently sensitive to detect early OA signs, such as those detectable on MRI.⁵⁶ This may have led to an underestimation of the percentage of patients with early signs of PFOA with radiography.⁵⁷⁻⁵⁹ Furthermore, 13 (26%) patients had a Kellgren & Lawrence (K&L) grade 1 score on the anterior-posterior radiograph. A K&L grade 1 score is suggested to be a subgroup of early OA and the strongest predictor for future (definite) OA.⁶⁰⁻⁶²

Our finding that the majority of PFP patients do not have signs of radiographic knee OA does not support the proposition that long-term PFP is necessarily PFOA.^{53,63,64} Future studies evaluating long-term PFP outcomes in younger adults, and their relationship with PFOA, should use MRI techniques or longer follow-up periods. Because MRI is more sensitive to detect early signs of OA, the use of MRI is recommended.⁵⁶

Natural course of PFOA

In Chapter VII we used the data of the Cohort Hip and Cohort Knee (CHECK) study to determine the prevalence and incidence of PFOA compared to tibiofemoral osteoarthritis (TFOA) in participants with a recent onset of knee pain. The aim of that study was to describe the natural course of PFOA at 2 and 5 years follow-up and the differences compared with the natural course of TFOA. We also aimed to identify whether participants with PFOA have a different phenotype compared to participants with TFOA, or participants with combined PFOA and TFOA, with regard to signs and symptoms. It was found that middle-aged patients with a recent onset of knee pain are more likely to have OA in the patellofemoral joint than in the tibiofemoral joint.

At baseline, the presence of PFOA was associated with signs from physical examination (e.g. crepitus, restricted movement, and bony enlargement). However multivariate analysis at 2-year follow-up showed that these signs could not discriminate between PFOA and TFOA. Given that a large percentage of patients that had PFOA at baseline progressed to combined OA, it seems that PFOA is a precursor to TFOA.

Also, because two thirds of the patients that had PFOA at baseline had developed COA at 5-year follow-up, longer follow-up is necessary to determine whether all patients with PFOA at baseline will eventually develop combined OA, or whether there are more subgroups within the PFOA population; stable PFOA, progressed to combined OA and progressive PFOA.

Although the Dutch guideline for GPs on non-traumatic knee complaints in adults does not recommend the use of posterior-anterior (PA) X-rays to investigate knee pain⁶⁵, radiographs are commonly used in clinical practice.⁶⁶ The recommendation (as described in this guideline) is based on earlier research, in which a discrepancy was found between patient-reported knee pain and findings on PA radiographs.⁶⁷⁻⁶⁹ However, it is unknown whether the combination of lateral and/or skyline radiographs and PA radiographs has additional value in detecting patients with early radiographic knee OA compared to standard PA radiographs. This is being investigated in the Cohort Hip and Cohort Knee (CHECK) study.

Clinical implications

As stated, the guideline for 'non-traumatic knee complaints in children and adolescents'⁷⁰ for GPs needs to be updated and should state that PFP is not self-limiting in all patients. Additionally, the guideline should include the advice to refer patients who have a longer duration of complaints or worse knee function at their first consultation to a physical therapist for exercise therapy. For patients with a shorter duration of complaints, exercise therapy can be recommended for athletes or for those who suffer from pain during their work. For patients with a shorter duration of complaints who are not hindered in their daily activities, exercise therapy may be advised after an initial period of 'wait and see'.

For physical therapists it remains unclear which type of exercises will result in the best outcome in patients with PFP. However, the study in Chapter IV found very low quality evidence that hip *and* knee exercises may be more effective in reducing pain than knee exercise alone. Although this finding needs further validation, it may be advisable to provide exercise therapy targeting quadriceps muscles and hip muscles.

Chapter VIII showed that patients with knee and ankle complaints visiting a physical therapist without a GP referral have different characteristics compared to those who visit the therapist with a referral. The patient characteristics associated with the use of self-referral are comparable to the prognostic factors for better recovery rates in both

knee and ankle symptoms (e.g. shorter duration of complaints, younger age and higher education level).^{43 71} This may indicate that self-referred patients have a better prognosis compared to the GP-referred patients and that these patients are more likely to recover with or without treatment from a physical therapist. Therefore, physical therapists should be informed about the differences in patient characteristics between referred and self-referred patients, and the natural course of PFP.

Implications for future research

In Chapter V the aim was to identify subgroups of patients that might respond differently to exercise therapy using the data from an earlier RCT. A trend was found towards more beneficial outcomes from exercise therapy compared to usual care in patients with a longer duration of complaints. This strengthens (but does not prove) our hypothesis that these clinical predictors of response to treatment do in fact exist. Because RCTs are usually only powered to detect the overall main effect of the intervention, the identification of subgroups in RCTs is difficult and is not the preferred method for future research.⁷² One solution to overcome the power problem in the identification of effect modifiers is to use individual patient data (IPD) from multiple trials to perform a meta-analysis.^{29 73} For future studies, IPD might be an ideal solution to strengthen statistical power. However, heterogeneity in terms of the type of exercise program applied for the treatment of PFP and the outcome measures used could raise a problem in analysing the data with IPD.⁷⁴ Nevertheless, as established in the consensus statement of the third International Patellofemoral Research Retreat²⁵, researchers are currently using a standard series of outcome measurements in trials which should enable the use of IPD in the future.

Unfortunately, our long-term follow-up study (Chapter VI) comprised a large percentage of patients lost to follow-up (80%). This was mainly due to lack of contact with the patients between the first study year and the 5-8 years of follow-up measurements. At baseline, a follow-up study of only one year was discussed⁷⁵, and the idea for a 5-8 year measurement period was conceived later on. Therefore, at baseline, patients only consented to the 1-year follow-up measurement. Without consent from the patients we were unable to use the contact details that they had provided at baseline. Therefore, the patients' GPs were asked to send information on the long-term follow-up measurement; if a patient was willing to participate they were asked to contact us and give their consent again. This resulted in a loss to follow-up of about one third of the 131 patients at baseline, during the 5-8 years follow-up. To strengthen the power we combined our data with a cohort study from Australia, in which the long-term follow-up was also conceived some years after the original consent. In Australia this resulted in 90% loss to follow-up of the patients. Because this loss to follow-up in our long-term follow-up study could introduce responder bias, we tested the differences between baseline characteristics and the 3-month and 12-month characteristics between responders and non-responders.

The characteristics showed no important differences between responders and non-responders and, therefore, reduces the likelihood of responder bias. However, the results from Chapter VI should be interpreted with caution as we analysed the results based on a complete-case analysis, which could introduce bias.⁷⁶ Therefore, more cohort studies are needed to further elucidate the natural course of PFP and its proposed continuum to PFOA. These cohort studies should include MRIs at baseline and follow-up, to evaluate disease progression and its relation to future PFOA.

The aetiology of PFP is still not well understood (Chapters II and III), although it is thought that the aetiology differs for diverse patient populations (e.g. adolescent, military, athletes, and adults from the general population). A study among adolescents with PFP showed that hip and knee strength was not affected in PFP patients.¹⁶ These findings are in contrast to the findings of our review on factors associated with PFP (Chapter III). This might suggest that there are indeed subgroups of patients with a different aetiology. Because six of the seven prospective studies in Chapter II included military recruits, midshipmen or cadets^{12 77-83}, it is recommended that future cohort studies also focus on other patient populations (e.g. adolescents, athletes).

Although the saying '*prevention is better than cure*' also applies to PFP, this does not mean that future research should focus on prevention programs. Prevention programs are usually only implemented when the disease has a high burden, e.g. loss of disability-adjusted years lived (DALYs)⁸⁴ and/or high costs for the community (e.g. cardiovascular diseases, cancer).⁸⁴⁻⁹⁰ If a disease leads to loss of DALYs and the whole community is at risk (e.g. traffic injuries), public preventive programs are implemented (e.g. legislation on the use of seat belts, and campaigns to reduce the use of alcohol in traffic).⁹¹ If the high costs and lost DALYs are only applicable for a subgroup of the population in which the prevalence of a disease is high, preventive programs should be implemented in that subgroup only (e.g. vaccination programs for young children^{92 93}, cardiovascular risk management in Dutch practices for patients at higher risk⁸⁶, or breast cancer screening in women aged 50-75 years⁸⁷). Because the burden of musculoskeletal diseases and complaints in adolescents and young adults is high⁹⁴ preventive programs to reduce the incidence of musculoskeletal complaints in this age range (15-40 years) might be considered. However, for PFP is it questionable whether preventive programs would be cost-effective if they were applied to the whole community. Subgroups of patients at higher risk for the development of PFP (e.g. military recruits⁸⁰) might benefit from preventive programs, which might then be cost-effective. One study examining the effect of a preventive intervention for PFP in military recruits found a significant reduction of the incidence of PFP using an exercise program consisting of stretching and strengthening exercises of the lower limb.⁹⁵ However, the cost-effectiveness of this preventive program is unknown. Furthermore, as discussed in Chapter I, the true incidence and prevalence of PFP is unknown and varies within subgroups of patients.²⁵ The first step towards

prevention is identification of the extent of the problem (incidence and severity of the problem), the next step is establish the aetiology and, then, to introduce preventive programs.⁹⁶ Therefore, PFP research should focus on identification of the aetiology and incidence of PFP (in different subgroups) before the (cost-) effectiveness of preventive programs can be determined.

For physical therapy by self-referral, a cost-effectiveness study is recommended. Chapter VIII shows that patients that seek help from a physical therapist without a referral had characteristics that were comparable to prognostic factors for better recovery, and self-referral was associated with fewer treatment sessions. However, we also found that besides the mode of access (referral or self-referral), other characteristics (e.g. duration of symptoms, and diagnosis) were associated with fewer treatment sessions. Thus, although patients who visited a physical therapist without a referral had fewer treatment sessions compared to patients with a referral, the differences in the number of treatment sessions was influenced by these other patient characteristics only. Therefore, it remains unclear whether the differences in treatment sessions seen between patients with and without a GP-referral are caused by the mode of access or by the 'other' patient characteristics. Based on the data in Chapter VIII, no conclusions can be drawn about the cost-effectiveness of the implementation of self-referral; therefore, the cost-effectiveness of physical therapy based on self-referral needs to be examined in future studies.

Key findings of the work in this thesis

- A large number of possible risk factors and factors associated with the presence of patellofemoral pain (PFP) have been examined in prospective and case-control studies. However, there was a lack of agreement between the studies as to which (risk) factors are associated with PFP, and the aetiology of PFP is still largely unknown (Chapters II and III).
- Exercise therapy is effective in reducing pain and improving function at both short and long-term follow-up for patients with PFP. Results from this thesis show that patients with a longer duration of complaints (> 6 months) might benefit more from exercise therapy than from usual care, compared to patients with a shorter duration of complaints; however, more research on this topic is required. Also, exercise programs that target hip and knee muscles, and programs with a high level of intensity, might be more effective in reducing pain and improving function in patients with PFP compared to exercise programs focusing on knee muscles alone or with a lower level of intensity, respectively (Chapters IV and V).
- Despite that PFP is often described as 'self-limiting', a large percentage of patients (57%) reported unfavourable recovery at 5-8 years follow-up. The prognostic factors

for worse outcomes in patients with PFP are having a longer duration of complaints at baseline and having a lower knee function (Chapter VI).

- Although it is proposed that PFP may be a precursor to patellofemoral osteoarthritis (PFOA), the findings of this thesis do not support this supposed continuum from PFP to PFOA (Chapter VI).
- The findings of this thesis suggest that OA often starts in the patellofemoral joint and then progresses to the tibiofemoral joint in subjects with a recent onset of knee pain (Chapter VII).
- General practitioners and physical therapists should be aware that patients with knee complaints visiting a physical therapist without a referral from a general practitioner have different patient characteristics compared to patients who are referred to a physical therapist (Chapter VIII).

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Summary

Summary

The aim of this thesis was to summarize and outline risk factors and factors associated with patellofemoral pain (PFP) and the effects (benefits and harms) of exercise therapy aimed at reducing knee pain and improving knee function for people with PFP. Furthermore, we aimed to identify effect modifiers to response to treatment, to determine the natural course of PFP, and to explore its proposed continuum to patellofemoral osteoarthritis (PFOA).

In **CHAPTER II** the risk factors for PFP were systematically outlined. Prospective studies that included 20 or more patients with PFP and examined at least 1 possible risk factor for PFP were included. An assessment list was applied to evaluate the quality of the studies. A meta-analysis was conducted using a random-effects model. Significant differences were based on calculated mean differences, with matching 95% confidence intervals (CIs). For dichotomous data, odds ratios or relative risks were calculated. Of the 3845 potentially relevant articles, 7 were included. These studies examined a total of 135 variables, and pooling was possible for 13 potential risk factors. The pooled data showed that knee extension peak torques were significantly lower in the PFP group than in controls. Mean differences in torque, with negative differences reflecting lower means in the PFP group, were as follows: (a) standardized relative to body weight at 60°/s, -0.24 Nm (95% CI: $-0.39, -0.09$); (b) standardized relative to body weight at 240°/s, -0.11 Nm (95% CI: $-0.17, -0.05$); (c) standardized relative to body mass index at 60°/s, -0.84 Nm (95% CI: $-1.23, -0.44$); (d) standardized relative to body mass index at 240°/s, -0.32 Nm (95% CI: $-0.52, -0.12$); (e) non-standardized in a concentric mode at 60°/s, -17.54 Nm (95% CI: $-25.53, -9.54$); (f) non-standardized in a concentric mode at 240°/s, -7.72 Nm (95% CI: $-12.67, -2.77$). We concluded that weaker knee extension strength, expressed by peak torque, appears to be a risk factor for PFP, based on meta-analyses of pooled results from multiple studies.

In **CHAPTER III** we systematically summarised factors associated with PFP. A systematic literature search was conducted. Studies including ≥ 20 patients with PFPS that examined ≥ 1 possible factor associated with PFP were included. A meta-analysis was performed, clinical heterogeneous data were analysed descriptively. The 47 included studies examined 523 variables, eight were pooled. Pooled data showed a larger Q-angle, sulcus angle and patellar tilt angle (weighted mean differences (WMD) 2.08; 95% CI 0.64, 3.63 and 1.66; 95% CI 0.44, 2.77 and 4.34; 95% CI 1.16 to 7.52, respectively), less hip abduction strength, lower knee extension peak torque and less hip external rotation strength (WMD -3.30 ; 95% CI $-5.60, -1.00$ and -37.47 ; 95% CI $-71.75, -3.20$ and -1.43 ; 95% CI -2.71 to -0.16 , respectively) in PFP patients compared to controls. Foot arch height index and congruence angle were not associated with PFP. Six out of eight pooled variables are associated with PFP, other factors associated with PFP were based on single studies.

The objective of **CHAPTER IV** was to assess the effects (benefits and harms) 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 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. 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 patellofemoral pain were 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 were very unsure about the estimates. The evidence for the two largest comparisons is summarised here.

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.

In conclusion, we 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.

To explore which patients with PFP are more likely to benefit from exercise therapy we performed a explorative secondary analysis of a RCT in **CHAPTER V**. We explored patient characteristics that might interact with treatment effects of PFP in 131 patients treated with usual care or exercise therapy. These characteristics were tested for interaction with treatment in a regression analysis. The primary outcomes were function and pain on activity at a 3-month follow-up. We found that none of the tested variables had a significant interaction with treatment. A positive trend was seen for females with PFP: they were more likely to report higher function scores with exercise therapy than with usual care compared to males with PFP ($\beta = 12.1$; 95% confidence interval: 0.23, 24.0; $P = .05$). A positive trend was seen for patients with a longer duration of complaints (greater than 6 months); they were more likely to report higher function scores and to have less

pain on activity with exercise therapy than with usual care compared to those with a shorter duration of complaints ($\beta = 12.3$; 95% confidence interval: -0.08 , 24.7 ; $P = .05$ and $\beta = -1.74$; 95% confidence interval: -3.90 , 0.43 ; $P = .12$, respectively).

Two factors, sex and duration of complaints, may have a predictive value for response to exercise therapy at 3-month follow-up.

CHAPTER VI describes the proportion of people with PFP who report unfavourable recovery and have radiographic signs of knee OA; and determines prognostic indicators of poor outcome after 5-8 years. Long-term follow-up data were derived from two randomised controlled trials ($n=179$, $n=131$). Patient-reported measures were obtained at baseline. Pain severity (100mm visual analogue scale [VAS]), function (anterior knee pain scale [AKPS]) and self-reported recovery were measured 5-8 years later, along with knee radiographs. Prognostic ability for baseline variables (PFP duration, pain, AKPS) to predict primary outcomes of pain VAS and AKPS were evaluated, using multivariate backward stepwise linear regression analyses. 60 participants completed the questionnaires at 5-8 year follow-up (45 women, mean age at baseline 26 years). No baseline differences were observed between responders and non-responders. 34 (57%) reported unfavourable recovery at 5-8 years. 49 out of 50 participants (98%) had no signs of radiographic knee OA. PFP duration (>12 months; $R^2 0.22$) and lower AKPS at baseline ($R^2 0.196$) were significant baseline predictors of poor prognosis at 5-8 years on measures of worst pain VAS and AKPS, respectively. To conclude, of those who responded a large proportion of people with PFP still had notable symptoms at 5-8 years post-recruitment, but did not have radiographic knee OA. Longer PFP duration and worse AKPS score at baseline remain predictors of poor PFP prognosis over longer-term follow-up. Education of health practitioners and general public is recommended, to change the long-held belief that PFP is self-limiting.

In **CHAPTER VII**, the prevalence and incidence of isolated patellofemoral osteoarthritis (PFOA) compared to tibiofemoral OA (TFOA) in middle aged participants with early OA symptoms of the knee is determined. We also described the natural course after 2 and 5 years follow-up and we tried to identify if participants with PFOA have a different phenotype compared to participants with TFOA, or participants with combined PF- and TFOA (COA). For this study data from the cohort hip and knee (CHECK) study were used. In this cohort, participants with early OA symptoms of the knee and hip were included and completed questionnaires, underwent physical examination and had knee radiographs at baseline, 2 and 5 years follow-up. For the current study only patients that reported knee pain or stiffness at baseline were selected. Participants were classified into: isolated TFOA, isolated PFOA, COA or no radiographic OA. Multivariate logistic regression was used to identify participant characteristics associated with a specific group of OA. The cohort comprised 845 participants (mean age 55.9 years). At baseline 116 participants had PFOA and none of the participants had TFOA or COA. Of

these 116 participants, 66.3% had developed COA at five years follow-up. At two years follow-up, PFOA, TFOA and COA were found in 77 (10.9%), 39 (5.5%) and 83 (11.8%) participants, respectively. Multivariate regression analyses showed that participants with radiographic PFOA or TFOA were not significantly different from each other with respect to signs and symptoms. Results of this study suggest that OA is more likely to start in the PF-joint and then progresses to COA in individuals with early OA symptoms of the knee. Differences in TFOA and PFOA phenotypes could not be determined with respect to signs and symptoms.

Since 2006 patients in the Netherlands no longer need a referral from a physician to visit a physical therapist. In patients with low back pain there are differences in patient characteristics between referred and self-referred patients. However, the differences in patient characteristics between self-referred and GP-referred patients with knee or ankle symptoms are still unknown. Therefore, in **CHAPTER VIII**, we determined patient characteristics, frequency of use, type of symptoms and treatment outcomes in patients with knee or ankle symptoms, separately, for patients referred by their GP and self-referred patients. Data were collected from the NIVEL Primary Care Database. This database consists of longitudinal data from primary care physical therapy practices. The mode of access (self-referral or referral) was determined in all patients. For analyses, descriptive statistics, unpaired t-tests, chi-square test and logistic regression analyses were applied. The study included 6794 patients with knee or ankle symptoms. The use of self-referral increased from 26% in 2006 to 57% in 2012 and stabilized in 2010-2012. Self-referred patients were younger, had a higher education level and a shorter duration of symptoms compared to GP-referred patients. Self-referred patients had less treatment sessions compared to GP-referred patients. Unfortunately, treatment characteristics could not be included in the multivariate regression analyses due to the high percentage of missing data. In conclusion, patients with knee or ankle symptoms of younger age, a higher education level, a shorter duration of symptoms, and recurrent symptoms more frequently used self-referral. Self-referred patients had fewer treatment sessions. After 2009, the frequency of use of self-referrals to a physical therapist stabilized.

CHAPTER IX is the general discussion and reflects the main findings and strength and limitations of this thesis and examines the implications for clinical practice and future studies.

Nederlandse samenvatting

Nederlandse samenvatting

De voornaamste doelen van dit proefschrift waren: 1) het samenvatten van alle risicofactoren en factoren die geassocieerd zijn met het patellofemoraal pijn syndroom (PFP), 2) de effecten (voor- en nadelen) van oefentherapie gericht op het verminderen van pijn in de knie en het verbeteren van de knie-functie voor mensen met een PFP te bepalen, 3) identificeren welke patiënten met PFP meer baat zouden hebben bij oefentherapie en 4) bepalen of patiënten die 5-8 jaar geleden klachten van PFP hadden vroege kenmerken van artrose in het patellofemorale gewricht hadden ontwikkeld.

In **Hoofdstuk II** zijn de risicofactoren voor het ontwikkelen van PFP met behulp van een systematisch literatuuronderzoek samengevat. In dit hoofdstuk werden alle prospectieve studies geïncludeerd waarin tenminste 1 mogelijke risicofactor voor het ontstaan van PFP werd onderzocht en waarin tenminste 20 patiënten met PFP waren geïncludeerd. De kwaliteit van elke studie die werd geïncludeerd werd berekend met een scoringslijst. Een meta-analyse werd uitgevoerd en hiervoor werd het random-effect model gebruikt. Significante verschillen waren gebaseerd op de berekende gemiddelde verschillen met daarbij behorende 95% betrouwbaarheidsintervallen (BI). Odds ratio's en relatieve risico's werden voor dichotome data berekend. Van de 3845 potentieel relevante artikelen, werden 7 artikelen geïncludeerd. Deze studies onderzochten samen 135 mogelijke risicofactoren voor PFP en voor 13 mogelijke risicofactoren konden we een meta-analyse uitvoeren. Uit de meta-analyse kwam naar voren dat mensen die later PFP hadden ontwikkeld, aan het begin van de studie een significant zwakkere knie-extensie kracht, uitgedrukt in maximum moment, hadden in vergelijking met de mensen die geen PFP hadden ontwikkeld. De gemiddelde verschillen in maximum momenten, waren als volgt (negatieve waardes betekenen lager gemiddeld in de PFP groep): (a) gestandaardiseerd ten opzichte van het lichaamsgewicht op 60°/s, -0.24 Nm (95% BI: -0.39, -0.09); (b) gestandaardiseerd ten opzichte van het lichaamsgewicht op 240°/s, -0.11 Nm (95% BI: -0.17, -0.05); (c) gestandaardiseerd ten opzichte van de body mass index op 60°/s, -0.84 Nm (95% BI: -1.23, -0.44); (d) gestandaardiseerd ten opzichte van de body mass index op 240°/s, -0.32 Nm (95% BI: -0.52, -0.12); (e) niet gestandaardiseerd op een concentrische modus op 60°/s, -17.54 Nm (95% BI: -25.53, -9.54); (f) niet gestandaardiseerd op een concentrische modus op 240°/s, -7.72 Nm (95% BI: -12.67, -2.77). We concludeerden op basis van meta-analyses van de verzamelde resultaten van de verschillende studies, dat zwakkere maximum knie-extensie kracht, uitgedrukt als maximum moment, een risicofactor voor PFP lijkt te zijn.

In **Hoofdstuk III** hebben we met behulp van een systematisch literatuuronderzoek alle factoren die geassocieerd zijn met PFP samengevat. We hebben op een systematische manier de literatuur doorzocht en includeerden studies waarin tenminste 20 patiënten met PFP werden geïncludeerd en die tenminste 1 mogelijk geassocieerde

factor met PFP onderzochten. Een meta-analyse werd uitgevoerd, en indien de data te klinisch heterogeen was hebben we deze beschrijvend geanalyseerd. De in totaal 47 geïncludeerde studies, onderzochten 523 mogelijke factoren die geassocieerd zijn met PFP, en voor 8 hebben we een meta-analyse uitgevoerd.

De meta-analyse liet zien dat mensen met PFP een grotere Q-hoek, een grotere sulcus hoek (hoek tussen het mediale en laterale facet van de femorale groeve), een grotere patella tilt hoek (hoek tussen de patella en de ventrale begrenzing van de trochlea) (gewogen gemiddelde verschil (GGV) 2.08 (95% BI: 0.64, 3.63) en 1.66 (95% BI: 0.44, 2.77) en 4.34 (95% BI: 1.16, 7.52), respectievelijk), zwakkere kracht van heup abductoren, zwakker maximum moment van knie extensoren en zwakkere kracht van de heup exorotatoren (GGV –3.30 (95% BI: –5.60, –1.00) en –37.47 (95% BI: –71.75, –3.20) en –1.43 (95% BI: –2.71, –0.16), respectievelijk) hadden in vergelijking met mensen die geen PFP hebben. De voetboog index en congruence hoek waren niet geassocieerd met PFP. Van de 8 factoren die we geanalyseerd hebben in een meta-analyse waren er 6 geassocieerd met PFP.

Het doel van **Hoofdstuk IV** was om de effecten (voor- en nadelen) van oefentherapie gericht op het verminderen van pijn in de knie en het verbeteren van de knie-functie voor mensen met PFP te beoordelen door middel van een systematisch literatuuronderzoek. In deze Cochrane-review includeerden we in totaal 31 gerandomiseerde studies met in totaal 1196 patiënten. De meeste vergelijkingen betroffen oefentherapie versus controle (geen behandeling, placebobehandeling of afwachten) en de combinatie van oefeningen voor zowel knie als heup versus oefeningen voor alleen de knie. De belangrijkste uitkomstmaten waren pijn, fysiek functioneren en herstel. De geïncludeerde gerandomiseerde studies verschilden in veel opzichten van elkaar en de kwaliteit van het bewijs was beperkt. Echter we vonden enig bewijs dat oefentherapie resulteert in klinische relevante pijnvermindering en functieverbetering op korte en lange termijn en ervaren herstel. Ook vonden we enig bewijs dat een combinatie van knie- en heupoefeningen effectiever is dan alleen knie-oefeningen. We konden geen conclusies trekken over welke vorm van oefentherapie het meest effectief was. Ondanks dat de bewijskracht beperkt is lijkt het de moeite waard om bij patiënten met PFP oefentherapie te overwegen. De mate van pijnvermindering en functieverbetering zijn onzeker, maar lijken klinische relevant.

Om er achter te komen welke patiënten met PFP het meeste baat hebben bij oefentherapie hebben we een exploratieve secundaire analyse van een gerandomiseerde studie uitgevoerd in **Hoofdstuk V**. We onderzochten patiënt karakteristieken die mogelijk een interactie zouden kunnen hebben met behandelingseffecten van PFP in 131 patiënten die behandeld werden volgens de standaard behandeling of oefentherapie. Deze karakteristieken werden getest op interactie met behandeling via een regressie analyse. De primaire uitkomstmaten waren functie en pijn bij activiteiten na 3 maanden

follow-up. We vonden dat geen enkele van de geteste variabelen een interactie had met behandeling. Een positieve trend werd echter gezien voor vrouwen met PFP: zij hadden een grotere kans op hogere functie scores met oefentherapie dan met normale zorg in vergelijking met mannen met PFP ($\beta = 12.1$; 95% betrouwbaarheidsinterval: 0.23, 24.0; $P = .05$). Er werd tevens een positieve trend gezien voor patiënten waarbij de klachten langer bestonden (langer dan 6 maanden); deze patiënten hadden een grotere kans op hogere functie scores en minder pijn bij activiteiten met oefentherapie dan met normale standaard zorg in vergelijking met patiënten die korter klachten hadden ($\beta = 12.3$; 95% BI: -0.08, 24.7; $P = .05$ en $\beta = -1.74$; 95% BI: -3.90, 0.43; $P = .12$, respectievelijk). Twee factoren, geslacht en duur van de klachten, hebben mogelijk een voorspellende waarde voor het aanslaan van oefentherapie na 3 maanden follow-up.

Hoofdstuk VI beschrijft welk deel van de patiënten met PFP een ongunstig herstel had. Daarnaast werd er ook gekeken of zij tekenen van artrose op de röntgenfoto hadden. Tevens werd onderzocht welke prognostische factoren verantwoordelijk zijn voor een slechte uitkomst na 5-8 jaar. Lange termijn follow-up data werden verzameld uit twee gerandomiseerde onderzoeken ($n=179$, $n=131$). Patiënt gerapporteerde metingen werden op baseline verzameld. De ernst van de pijn (100mm visual analogue scale [VAS]), functie (anterior knee pain scale [AKPS]) en zelf gerapporteerde herstel werden 5-8 jaar later gemeten, tevens werden er röntgenfoto's van de knie gemaakt. Prognostische factoren (duur van klachten, pijn, AKPS) gemeten op baseline die mogelijk geassocieerd zijn met een slechte uitkomst voor pijn en functie op follow-up werden onderzocht met een multivariate lineaire regressie analyse. 60 patiënten vulden de vragenlijsten na 5-8 jaar volledig in (45 vrouwen, gemiddelde leeftijd op baseline 26 jaar). Er werden geen verschillen op baseline gezien tussen patiënten die wel en niet reageerden. 34 (57%) patiënten rapporteerden slecht herstel na 5-8 jaar. 49 van de 50 deelnemers (98%) hadden geen tekenen van artrose op röntgenfoto's van de knie. De duur van de PFP klachten (>12 maanden; $R^2 0.22$) en lagere AKPS score op baseline ($R^2 0.196$) waren significante voorspellers voor een slechte uitkomst na 5-8 jaar, met betrekking tot respectievelijk VAS score en AKPS score. Concluderend, van de patiënten die reageerden, had een groot deel nog steeds symptomen van PFP na 5-8 jaar. De patiënten hadden echter geen tekenen van artrose op de röntgenfoto's van de knie. Langdurige klachten van PFP en een slechte AKPS score op baseline zijn voorspellers voor een slechte prognose van PFP (bij lange termijn follow-up). Scholing van artsen en fysiotherapeuten en algemeen publiek wordt aanbevolen om de lang vastgehouden gedachte dat PFP vanzelf geneest te veranderen.

In **Hoofdstuk VII** werd de prevalentie en incidentie van geïsoleerde patellofemorale artrose (PFOA) vergeleken met geïsoleerde tibiofemorale artrose (TFOA) bij patiënten met recent ontstane knie klachten op middelbare leeftijd. Ook beschreven we het natuurlijk beloop na 2 en 5 jaar follow-up. Bovendien hebben we getracht om te onderzoeken

of patiënten met PFOA een ander fenotype hadden in vergelijking met patiënten met TFOA, of patiënten met zowel PF- als TFOA (COA). Voor dit onderzoek werd data uit de CHECK studie gebruikt. In dit cohort werden patiënten met vroege symptomen van artrose van de knie en heup geïncludeerd en werden vragenlijsten, lichamelijk onderzoek en röntgenfoto's op baseline en na 2 en 5 jaar follow up afgenoem. Voor de huidige studie werden alleen patiënten die kniepijn of stijfheid van de knie hadden op baseline, geïncludeerd. Patiënten werden verdeeld over de volgende groepen: geïsoleerde TFOA, geïsoleerde PFOA, COA of geen tekenen van artrose op de röntgenfoto's. Multivariate logistische regressie werd gebruikt om patiënt karakteristieken geassocieerd met de specifieke groep met artrose (OA) te identificeren. Het cohort bestond uit 845 patiënten (gemiddelde leeftijd 55.9 jaar). Op baseline hadden 116 patiënten PFOA en geen enkele patiënt had TFOA of COA. Van deze 116 patiënten, ontwikkelde 66.3% COA na 5 jaar follow-up. Na 2 jaar follow-up, hadden 77 patiënten PFOA (10.9%), 39 patiënten TFOA (5.5%) en 83 patiënten COA (11.8%). Multivariate regressie analyse toonde dat patiënten met röntgenologisch PFOA of TFOA niet significant verschilden in klachten en symptomen van hun knie. De resultaten van deze studie laten zien dat OA vaak begint in het PF gewricht en daarna uitbreidt naar COA. Verschillen in klachten en symptomen tussen de TFOA en PFOA groepen werden niet aangetoond.

Sinds 2006 is het in Nederland niet meer noodzakelijk om een verwijzing van de huisarts te hebben om een fysiotherapeutische behandeling te ondergaan. Het is reeds bekend dat er een verschil is tussen patiënten met lage rugklachten die door de huisarts verwezen zijn naar een fysiotherapeut en patiënten die niet verwezen zijn (zelfverwijzers). Of dit verschil ook aanwezig is bij patiënten met knie of enkel klachten is niet bekend. In **Hoofdstuk VIII** werd daarom onderzocht of er verschillen zijn in patiënt karakteristieken, hoeveelheid behandelingen, type symptomen en uitkomst van de behandeling tussen patiënten met knie- en enkelklachten die verwezen werden door de huisarts en zelfverwijzers. De data werd verzameld vanuit de NIVEL Primary Care Database. De data bestond uit longitudinale data vanuit fysiotherapeut praktijken in de eerste lijn. Er werd bij alle patiënten vastgesteld of ze verwezen waren door de huisarts, of dat ze zelfverwijzer waren. Voor de analyse werden beschrijvende statistiek, niet gepaarde t-test, chi-square test en logistische regressie analyse toegepast. De studie omvatte 6794 patiënten met knie of enkel klachten. De hoeveelheid zelfverwijzers steeg van 26% in 2006 naar 57% in 2012 en stabiliseerde tussen 2010 en 2012. Zelfverwijzers waren jonger, waren hoger opgeleid en hadden een kortere duur van de klachten in vergelijking met patiënten die door de huisarts werden verwezen. Helaas konden we de duur van de behandelingen en het type behandelingen niet onderzoeken, omdat hiervan teveel gegevens ontbraken. Concluderend zijn zelfverwijzers met knie en enkel klachten jonger, hoger opgeleid, hebben ze vaker recidiverende klachten en minder lang klachten dan patiënten met

een verwijzing van een huisarts. Na 2009 stabiliseerden de hoeveelheid zelfverwijzers voor een fysiotherapie behandeling.

Hoofdstuk IX is de algemene discussie en geeft een beschouwing op bovenstaande studies en hoofdstukken.

Dankwoord

Het is bijna af... nog 1 laatste hobbeltje, het dankwoord.

Uiteraard heb ik het schrijven van dit hoofdstuk uitgesteld tot het allerlaatst; het is het hoofdstuk van mijn proefschrift dat waarschijnlijk het meest gelezen gaat worden en bovendien ben ik bang ben dat ik mensen ga vergeten! Maar ik ga een poging wagen:

Allereerst wil ik alle patiënten die hebben deelgenomen aan de verschillende onderzoeken in mijn proefschrift bedanken.

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Beste co-auteurs: Di-Janne Barten, Jurgen Damen, Rianne van der Heijden, Margreet Kloppenburg, Bart Koes, Robbart van Linschoten, Roxanne Meerhof, Edwin Oei, Yvonne van Trier en Prof.dr. Verhaar; hartelijk bedankt voor jullie opmerkingen en toevoegingen aan mijn artikelen.

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Curriculum vitae

Nienke Elisabeth Lankhorst is op 3 april 1987 geboren in Rotterdam. Na het behalen van haar VWO diploma aan de Christelijke Scholengemeenschap Walcheren te Middelburg in 2005 is zij begonnen met de studie geneeskunde aan de Erasmus Universiteit in Rotterdam. In 2009/2010 deed zij bij de afdeling huisartsgeneeskunde 21 weken onderzoek naar factoren geassocieerd met het Patellofemorale pijn syndroom. Dit resulteerde in 2 internationale publicaties, en 2 poster presentaties op een internationaal congres. Na het behalen van het artsenexamen in 2011 werd zij in oktober 2011 aangenomen als AIOTHO (arts in opleiding tot huisarts en onderzoeker) aan de Erasmus Universiteit te Rotterdam. Tussen oktober 2011 en maart 2012 heeft zij gewerkt bij Reade te Amsterdam. In maart 2012 is zij begonnen aan haar AIOTHO-traject. Zij werkte 2 jaar (2012/2013, 2014/2015) aan haar promotietraject. In augustus 2014 behaalde zij haar Master of Science in de klinische epidemiologie aan het Netherlands Institute for Health Sciences (NIHES). Het eerste jaar van de huisartsopleiding volgde zij in het Medisch Centrum Reeuwijk (2013/2014). Vanaf maart 2015 is zij gestart met het tweede jaar van haar huisartsopleiding. Nienke is getrouwd met Bas Aerts.

PhD Portfolio

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: Nienke. Aerts-Lankhorst	PhD period: 2012 - 2015
Erasmus MC Department: General Practice	Supervisor: S.M.A. Bierma-Zeinstra
Research School: NIHES	Co-supervisor: M. van Middelkoop
1. Vocational Training	Year
GP training	2012-present
Department of General practice, Erasmus MC, Rotterdam	
2. PhD Training	
	Year
	Workload (Hours/ECTS)
General courses	
- MSc in Clinical Epidemiology, NIHES, Rotterdam	2012-2014 70 ECTS
Seminars and workshops	2014 30 hours
- Good clinical practice	
Presentations	
Oral:	
- Osteoarthritis Research Society International, Seattle, USA (Young Investigator Award)	2015 20 hours
- Sports Medicine Congress, Copenhagen, Denmark (2x)	2015 40 hours
- North American Primary Care Research Group, New York, USA	2014 20 hours
- International Patellofemoral Research Retreat, Vancouver Canada	2013 20 hours
- Vereniging voor Sportsgeneeskunde, Ermelo, The Netherlands	2012 20 hours
Poster:	
- Nederlands Huisartsengenootschap Scientific meeting, Leiden, The Netherlands	2013 16 hours
- International Patellofemoral Research Retreat, Vancouver, Canada	2013 16 hours
- International Patellofemoral Research Retreat, Gent, Belgium (2x)	2011 16 hours
(Inter)national conferences	
- NHG scientific meeting, Maastricht, The Netherlands	2012 8 hours
3. Teaching	
	Year
	Workload (Hours/ECTS)
Lecturing	
- Scientific meeting VSG, Bilthoven, The Netherlands	2015 4 hours
- GP trainees scientific meeting, Rotterdam, The Netherlands	2014 4 hours
Supervising Master's theses	
- Roxanne Meerhof	2014 20 hours
- Thessa Vollebregt	2012 10 hours
Other	
- Supervising critical reading course (2x)	2014 2 hours
	2012 2 hours
- Supervision of medical research assistant	2013 40 hours

List of publications

This Thesis:

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