Towards a meaningful self-management intervention to improve long-term prognosis for adolescents with Patellofemoral Pain

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Towards a meaningful self-management intervention to improve long-term prognosis for adolescents with Patellofemoral Pain

Doctoral Thesis (dr.med)

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Pre-face

The work forming this doctoral thesis was done during a period of over 10 years while employed at Aarhus University, Aalborg University, Aalborg University Hospital and the Center for General Practice at Aalborg University. The work is funded by Independent Research Foundation Denmark, Aarhus University, TRYG Foundation, Danish Physio Association, the Danish Rheumatism Association and the Foundation for General Practice.

This work is the culmination of many discussions and thoughts surrounding adolescent pain. When I was first introduced to the idea of investigating the field of adolescent musculoskeletal pain (especially knee pain) by my friend and colleague, Ole Simonsen, I never anticipated to fall into such a time consuming and exciting field with so many unanswered questions. Thank you Ole, for being an incredible mentor and always putting others in front of you. You have inspired me, and much of the development in the Northern Region of Denmark is built on the steppingstones you have given to the people around you.

Thank you to all my co-authors. I am proud to have worked with every one of you. The inter-disciplinary approach and being challenged by people outside my core-domain has been very welcome. We all need to be challenged in adequate doses to make us grow from our experiences.

Lastly, I want to thank my family for all their support. This thesis is dedicated to Carla and Dicte. Hopefully one day you will understand that I rarely use the swing or playground when I am work.

Reading guide

This thesis is comprised of four chapters, followed by a conclusion. The first introduces the topic, and gives a historical overview of the evolution of our understanding and associated terminology of patellofemoral pain (or at least what we today define as patellofemoral pain). This sets the scene for the thesis and identifies the knowledge gaps that this work seeks to fill, ending with the overall aim of the thesis. The next three chapters present the work done during the last 10 years. The second chapter describes the adolescents with PFP, and what characterizes them compared to their pain free peers. Chapter three describes the treatment of adolescent PFP, and is followed by a chapter on prognosis and prognostic factors of adolescent PFP. This is followed by a discussion of future perspectives within the field of adolescent patellofemoral pain is given, together with an overview of the limitations in the current body of work.

The thesis is based on the following publications but include (where relevant) additional work we have conducted within this area:

1: Rathleff, M. S., Vicenzino, B., Middelkoop, M., Graven-Nielsen, T., van Linschoten, R., Hölmich, P., & Thorborg, K. (2015). Patellofemoral Pain in Adolescence and Adulthood: Same Same, but Different? Sports Medicine, 45(11), 1489–1495.

2: Rathleff MS, Winiarski L, Krommes K, Graven-Nielsen T, Hölmich P, Olesen JL, Holden S, Thorborg K. Pain, Sports Participation, and Physical Function in Adolescents With Patellofemoral Pain and Osgood-Schlatter Disease: A Matched Cross-sectional Study. Volume 50 Issue 3 Pages 149-157

3: Rathleff, M. S., Roos, E. M., Olesen, J. L., Rasmussen, S., & Arendt-Nielsen, L. (2013). Lower mechanical pressure pain thresholds in female adolescents with patellofemoral pain syndrome. The Journal of Orthopaedic and Sports Physical Therapy, 43(6), 414–421.

4: Rathleff, M. S., Rathleff, C. R., Crossley, K. M., & Barton, C. J. (2014). Is hip strength a risk factor for patellofemoral pain? A systematic review and meta-analysis. British Journal of Sports Medicine, 48(14), 1088.

5: Rathleff, M. S., Rathleff, C. R., Holden, S., Thorborg, K., & Olesen, J. L. (2018). Exercise therapy, patient education, and patellar taping in the treatment of adolescents with patellofemoral pain: a prospective pilot study with 6 months follow-up. Pilot and Feasibility Studies, 4(1), 73.

6: Rathleff MS, Graven-Nielsen T, Hölmich P, Winiarski L, Krommes K, Holden S, Thorborg K.

Education on activity modification and load management in adolescents with patellofemoral pain – a prospective intervention study including 151 adolescents. Am J Sports Med. 2019 Jun;47(7):1629-1637

7: Rathleff, M. S., Rathleff, C. R., Olesen, J. L., Rasmussen, S., & Roos, E. M. (2016). Is Knee Pain During Adolescence a Self-limiting Condition? Prognosis of Patellofemoral Pain and Other Types of Knee Pain. *The American Journal of Sports Medicine*, *44*(5), 1165–1171.

8: Rathleff MS, Holden S, Straszek C, Olesen JL, Jensen MB, Roos EM. Five-year prognosis and impact of adolescent knee pain: a prospective population-based cohort study of 504 adolescents in Denmark. BMJ Open. 2019 May 28;9(5):e024113

9: Holden S, Kasza J, Winters M, Middelkoop van M, Adolescent Knee Health Group, Rathleff MS. Prognostic factors for adolescent knee pain: an individual participant data meta-analysis of 1281 patients. Pain. June 2021 - Volume 162 - Issue 6 - p 1597-1607

Danish resume

Denne doktordisputats består af 9 artikler, som er baseret på data indsamlet i løbet af en 10 års periode i mine ansættelser på Aarhus Universitet, Aalborg Universitetshospital, Aalborg Universitet samt Center for Almen Medicin ved Aalborg Universitet. Baggrunden for igangsætning af studierne var en generel mangel på viden om børn og unge med knæsmerter, og hvordan vi bedst hjælper børn og unge med knæsmerter. Formålet med disputatsen var at beskrive gruppen af unge med patellofemorale smerter gennem et bio-psyko-socialt perspektiv, beskrive, udvikle og teste alders-specifik behandling og beskrive prognosen for patellofemorale smerter hos unge.

Selve disputatsen består af et narrativt review, et systematic review, en individual participants meta-analyse samt 6 originalstudier. Unge med patellofemorale smerter blev både rekrutteret fra skoler, læge og fysioterapipraksis samt sociale medier. Vi anvendte en række forskellige selv-rapporterede og mere objektive mål for at beskrive deres smerter, funktion, sportsdeltagelse og livskvalitet, og for at beskrive de domæner, som de unge finder relevante.

Samlet set flytter disse 9 studier vores forståelse af patellofemorale smerter hos børn og unge ved at dokumentere følgende:

1: Patellofemorale smerter hos børn og unge er ikke blot en isoleret smerte i knæet. Det har vidtrækkende konsekvenser for deres evne til at deltage i sport og sociale aktiviteter med deres venner, lav livskvalitet og øget smerteføls omhed. Disse studier understreger den negative konsekvens, der kan være af længerevarende patellofemorale smerter hos børn og unge, og viser, at vi bør betragte denne type knæsmerter i et bio-psyko-socialt perspektiv og ikke blot som en lokal biomekanisk problemstilling.

2: Behandling, som har en positiv effekt hos voksne, ser ikke ud til at have den samme effekt hos børn og unge. Der er behov for alders-specifikke strategier, som tager de unges behov i betragtning og hjælper dem med at dosere træning, sport og tilbagevenden til sport og sociale aktiviteter. Vores nye intervention, som består af undervisning i at justere træningsmængde og progression, betød, at 86% af unge havde et tilfredsstillende resultat efter 12 uger og et lignende højt antal efter 6 måneder (77%) samt 12 måneder (81%). Dette var associeret med høj grad af tilbagevenden til sport. Sammenlignet med vores 2 tidligere kliniske studier om behandling af unge med patellofemorale smerter, var disse resultater markant bedre (25-29% versus 86% tilfredsstillende resultat efter 3 måneder).

3: Vores prospektive studie med 5 års opfølgning modbeviser tidligere antagelser om, at patellofemorale smerter, og knæsmerter generelt, er noget som forsvinder, når de unge stopper med at vokse, og ikke har nogen langtidskonsekvens. De kombinerede resultater fra 2 og 5 års

opfølgningen viser, at omkring 4 ud af 10 unge i alderen 15-19 år vil fortsætte med at opleve smerter, selv efter 5 år. Baseret på de selvrapporterede data, er knæsmerterne af en sådan grad, at det påvirker livskvalitet, sportsdeltagelse og i nogle tilfælde valg af job og karriere.

4: Resultaterne fra vores omfattende individual participants meta-analyse med næsten 1300 børn og unge indikerer, at >50% fortsætter med at have knæsmerter selv efter 12 måneder. Gruppen med høj smerteintensitet, bilaterale smerter, høj frekvens af smerte, lang varighed af smerter, lav livskvalitet og specielt de unge piger var i højest risiko for en dårlig prognose med smerter og nedsat funktion efter 12 måneder.

Forskningsfeltet omkring muskel- og ledsmerter hos unge er i udvikling. Denne udvikling er i høj grad baseret på de seneste års forskning, som viser, at de smerter og problemer, som unge oplever, i mange tilfælde fortsætter ind i voksenlivet og kan have betydning for både fysisk aktivitet, livskvalitet og job. Mere og mere tyder på, at langvarige smerter hos voksne er svært at behandle, og resultaterne er ikke altid opløftende. Det er derfor essentielt, at vi fokuserer på udvikling af alders-specifikke interventioner til unge, da dette kan være en af mulighederne for at reducere den store samfundsbyrde, som smerter hos voksne er. Denne afhandling giver ikke svaret på alle spørgsmål, men understreger nødvendigheden i fortsat fokus på denne gruppe, i udviklingen af alders-specifikke behandlinger for at hjælpe børn og unge med længerevarende smerter.

English resume

This doctoral thesis consists of 9 papers that were conducted during a period 10 years during my employments at Aarhus University, Aalborg University, Aalborg University Hospital, and the Center for General Practice at Aalborg University. The background of the series of studies was a general lack of knowledge surrounding adolescent Patellofemoral Pain, which hampered evidence-based treatment of this common condition that affects approximately 6-7% of the school-attending adolescents. The aim of this thesis was to provide an overview of adolescent Patellofemoral using a bio-psycho-social perspective, identifying specific management needs for this age group and the prognosis of adolescent PFP.

This doctoral thesis includes one narrative review, one systematic review, one individual participant meta-analysis and six original studies in adolescents with Patellofemoral Pain. The adolescents in these studies were recruited from both school-based populations, physiotherapy clinics and open populations. We used self-reported measures of pain, symptoms, function, and physical activity levels, as well as objective measures of hip and knee function. We also combined this with psychophysical pain assessments.

Overall, this work improves our understanding of adolescent PFP by from a biopsychosocial perspective as follows:

1) Adolescent PFP is not a simple pain complaint isolated at the knee. The consequences of adolescent PFP are widespread, and affect sporting ability, quality of life, and pain sensitivity. This creates a paradigm shift from previous thinking of adolescent PFP as a local biomechanical problem (requiring simple hip exercises), to a complex condition requiring a bio-psycho-social perspective for assessment, treatment and rehabilitation.

2) Effective treatments for adults with PFP are unlikely to have the same effects in adolescents. There is a need for age-specific interventions that considering adolescent's context and needs. Our intervention aimed at teaching adolescents to manage sports, with a graded return to sport and exposure to knee joint loads. This was associated with high success rates. After 12 weeks, 86% of the adolescents had a successful outcome, with similarly high rates of successful outcome after 6 (77%) and 12 months (81%). There were high rates of return to sport at all time points, which is particularly important as this is an endpoint that is meaningful for this population as it creates identify, social connection and ability to thrive. The rates of successful outcome after 12 weeks were higher than our previous exercise focused studies (29% in a cluster randomized trial among the 15–19-year-olds, and 25% in a pilot study among 12–16-year-olds).

3) Our prospective cohort study with 5-year follow-up underlines the complex nature of PFP in

this population and contradicts the assumption that adolescent PFP is innocuous without long-term consequences. Results reveal that as many as four in ten will continue to experience pain, even after 5 years. The impact of knee pain negatively affects quality of life, sports participation, and in some cases choice of job/career.

4) Our individual participant meta-analysis investigated which baseline characteristics were associated with long-term prognosis of adolescent anterior knee pain, in >1200 adolescents. We found that >50% of adolescents continue to have pain at 12-months. Pain characteristics (pain intensity, frequency, duration and bilaterality), lower health related quality of life and female sex were associated with increased pain and lower sports-related function at 12-months. Moderate anxiety/depression was associated with lower sports-related function.

The field of paediatric musculoskeletal pain is a growing research area. Patellofemoral Pain is one of the most common pain complaints in this population. This series of studies highlights the need for interventions developed based on the context and needs of the adolescent population. Interventions with proven efficacy in adults should be tested before implementing to the adolescent population. Health care practitioners should be cognizant not to assume adolescent PFP is self-limiting. As many as four out of every 10 will continue to experience knee pain even 5 years after the initial diagnosis. This series of studies opens a new area where the is a clear need for additional research to improve care for the many adolescents suffering from Patellofemoral Pain.

1: Introduction and background

1.1: The historical background of Patellofemoral Pain

In 1928 Aleman introduced the term "Chondromalacia Patellae" [1]. This term was framed after clinical observations of pain/symptoms and cartilage changes among patients who were treated surgically for knee complaints. His suspicion was that changes to patellar due to traumatic lesions were the cause of his patient's pain and symptoms. This term was subsequently widely used as a diagnosis, often in the absence of arthroscopy, imaging, or evidence of such cartilage changes. The clinical presentation for this diagnosis was anterior knee pain during activities that load the knee such as running or stair climbing. Several orthopaedic surgeons published case-series reporting on outcomes after surgical treatment of chondromalacia patellae. Outcomes varied from poor to excellent when using clinician-reported ratings [2] [3, 4] [5, 6].

In the seventies, research found no association between cartilage changes and the symptoms reported by patients questioning the previous assumed aetiology [7] [8] [9]. Arthroscopic investigation demonstrated no visible changes to the articular cartilage, despite patients reporting anterior knee pain[7] [8] [9]. Thus began a paradigm shift in understanding anterior knee pain. The suspected mechanism/aetiology included patellar maltracking, irritation of the lateral retinaculum, and increased innervation around the patellofemoral joint or the synovial plicae [5, 6, 9, 10] [11]. It was thought that maltracking of the patella irritated tissues around the knee joint and this was the cause of pain [5, 6, 9, 10] [11] [12].

In the late 90ies, four orthopaedic surgeons published a landmark study on the natural history of anterior knee pain (formerly called chondromalacia patellae). In this study, they followed patients for up to 20 years following initial presentation to the orthopaedic department [13]. Only 22% were pain free after 16-20 years. They concluded that surgical treatment of idiopathic anterior knee pain was not justified, until a procedure provided better outcomes compared to non-surgical treatment.

Following this, three orthopaedic surgeons published the results of conservative management 100 patients with chondromalacia patellae seen at their sports medicine clinic [14]. The management was based on gradual loading through exercises and predefined rules for return to sport. They observed that 82% had a successful return to athletic activities. They surmised that "Chondromalacia Patellae" is not a meaningful clinical diagnosis as the patient population is most likely heterogenous, consisting of different aetiologies.

In 1986 Australian physiotherapist Jenny McConnell published the now most highly cited paper on the management of this condition. The title was "The Management of Chondromalacia Patellae: A Long-Term Solution" [15]. It described a management approach that focused on optimizing biomechanics to improve patellar alignment. This was due to the prevailing belief that poor biomechanics was the cause of PFP. This is often described as the first paper on conservative treatment for PFP, despite Dehaven et al was published 7 years earlier [14]. The multimodal biomechanical approach sparked an entire line of research that lasted for many years. Only recently, has it been acknowledged that biomechanics are not fully able to explain the development of PFP, or the associated pain experiences [16] [17]. As a result, the research community started to explore alternative methods to understand PFP.

1.2: From chondromalacia patellae to defining Patellofemoral Pain by exclusion

The terminology has now changed from chondromalacia patella to Patellofemoral Pain [18]. Patellofemoral Pain is not easy to define, as patients experience a variety of different symptoms and physical impairments, many of which vary considerable from patient to patient [19] [20] [21]. Despite many years of research, the terminology used to describe pain in the anterior part of the knee is still debated and despite international consensus from the research community of PFP [18], many different terms are used. Anterior knee pain, chondromalacia patella, patellofemoral arthralgia, patellar pain, patellar pain syndrome and patellofemoral pain are often used synonymously [22] [23] [18]. The term "anterior knee pain" (AKP) is suggested to encompass all pain-related problems of the anterior part of the knee. By excluding anterior knee pain due to intra-articular pathology, tendinopathies around the knee, bursitis, plica syndrome, Sinding-Larsen-Johansen disease, Osgood Schlatters disease, neuromas and other rarely occurring pathologies, those who present with anterior knee pain can be diagnosed with what is now called PFP [18]. The term patellofemoral pain seems appropriate, as no distinction can be made as to which specific structure of the patella, or the femur are affected, and pain is the indicating symptom that patients experience.

1.3 The unknown pathophysiology

Patellofemoral pain is a heterogenous pain complaint with many features, not dissimilar to unspecific low back pain [22]. Several anatomical structures may be involved in the pathophysiology, including subchondral bone, the synovium, the retinaculum, and the infrapatellar fat pad [11] [24]. All of these have been suggested as playing a role [11]. Recently, van Heijden and colleagues published two separate papers on 64 young patients with PFP which were compared to 70 controls without knee pain [25] [26]. Using high resolution 3-T MRI imaging and delayed gadolinium-enhanced MRI of

cartilage, they showed no difference in structural changes or in the cartilage composition between those with PFP and the healthy control group without knee pain, suggesting these characteristics may not be implicated in PFP [25] [26]. These findings were later extended into the perfusion of the patellar bone (another suspected part of the pathophysiology of PFP)[27]. Dynamic contrast-enhanced (DCE)-MRI perfusion was used to compare patients with PFP and controls without knee pain. The results showed no difference between groups, indicating that altered perfusion is unlikely to be involved in the pathophysiology of PFP [27]. Similar methods have also been used to explore the involvement of Hoffa's fat pad. Similarly, novel MRI methods failed to identify higher amounts of T2FS-hyperintense lesions (typically classified as Hoffa synovitis) [28]. Cumulatively, this indicates no clearly identified pathology. It remains unclear which anatomical structures could be involved in the pain associated with PFP, and if this differs between adolescents and adults. Currently, evidence is inconclusive and point towards no specific pathology - similar to other chronic musculoskeletal pain complaints such as non-specific low back pain. As pain is defined by the International Association of the Study of Pain (IASP) as "*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*" [29], it is clear that tissue damage is not a perquisite for pain. Pain can. Therefore it is likely PFP is a pain condition incited by factors (such as mechanical loading), which can over time lead to pain due to the potential threat of tissue damage. Importantly, it is an emotional experience, indicating that regardless of whether pain is caused by actual or potential tissue damage, there is a psychological component. Focus primarily on the implicated structures and biomechanics neglects this critical aspect of the pain experience [29].

1.4: The assumed aetiology

Aetiology is the study of causation, or reason for a condition. From the beginning, PFP was suspected to be caused by tissue injury and later biomechanical factors such as patellar alignment. The biomechanical focus has been evaluated in prospective cohort studies recently synthesized in a systematic review [30]. This review included a total of 18 prospective cohort studies testing 116 variables where the majority being biomechanical (i.e., hip or knee strength) and anthropometrical variables (age, weight, height, BMI). There was a lack of psychosocial factors included, due to few original studies. The conclusion was that lower strength of the knee extensors were associated with an increased risk of PFP (moderate evidence) but that this was not a strong risk factor. The standardized mean difference between those developing PFP and those that stayed pain free was 0.32 (95%CI: 0.22-0.42) [30].

Powers et al [16] recently constructed a theoretical framework to show how biomechanics was explain

the cause and development of PFP. This was based mostly on small cross-sectional studies. This framework may help to systematize a complex range of range of physical features and provide a rationale for biomechanically oriented treatments. However, when viewed in isolation, this framework implies that patellofemoral pain is due to peripherally based nociception caused by altered loading of the patellofemoral joint. This poorly explains some of the classic features of patellofemoral pain, including pain spanning decades, the limited impact of biomechanically focussed treatment on prognosis, and that patient's symptoms may improve substantially despite no changes in their biomechanics [17]. Further, it is in contrast to the IASP definition of pain, and neglects the subjective, emotional and psychological experiences of patients.

An alternative (or complimentary) framework on the aetiology of PFP is the tissue homeostasis model [11]. This model focuses on the biological processes that may underpin PFP. In his landmark paper, Scott Dye argues that a range of possible pathophysiologic processes often caused by overload may explain the development of PFP for most patients. Many different tissues around the knee, inflamed synovial lining, fat pad tissues, retinacular neuromas, increased intraosseous pressure, and increased osseous metabolic activity of the patella have all been suspected as contributing to the subjective perception of anterior knee pain [11]. These different tissue processes can be characterized as loss of tissue homeostasis. This can be initiated by high loading conditions of the patellofemoral joint. Once initiated, the loss of homeostasis may persist indefinitely. In this framework, differences in structure may matter little in the pain free condition as long as tissue homeostasis is maintained.

No concluding evidence show us which of these models are most accurate and reflect the development of PFP. However, emerging evidence suggests that patellofemoral pain should be considered in a framework that encompasses the biological, psychological and social aspects which can influence the perception and maintenance of pain. Neither of these two models adequately consider this [21 31 32]. It is time to consider PFP in the same light as other persistent musculoskeletal pain complaints.

1.5: A common knee complaint in both adolescents and adults

We conducted a systematic review to describe the incidence and prevalence among adolescents and adults [33]. Twenty-three studies were included with the majority being adults (>18 years of age). The results showed that the incidence varied substantially between studies. The incidence rates in military based cohorts were between 9.7 and up to 571.4 per 1000 person-years. Some of the

highest estimates came from studies where military recruits were exposed to a very vigorous exercise and loading. In amateur runners it was 1081/1000 person years and in adolescent amateur athletes 5-15% developed PFP over one season. The pooled prevalence estimates in adolescents were 7.2%, with estimates of 22.7 in female adolescent athletes. This highlights the higher prevalence among the sports active people, especially younger females. Highly repetitive and/or excessive loading could be involved in the development of PFP. This would support the tissue homeostasis model [11].

In Danish primary care, there is an eightfold increase in the number of contacts to general practice due to knee symptoms between 5–9 and 10–19 years of age [34]. In UK general practice knee problems are the fourth most common reason for a patient to consult, and involve the second highest number of consultations, accounting for approximately 10% of the childhood musculoskeletal caseload for GPs [35]. The number of consultations for adolescent knee pain is between 119-200 adolescents per 10.000 registered patients in a typical practice. This highlights that many of these patients suffering from knee complaints (including PFP) seek medical care for their symptoms [35] [36]. Despite the high prevalence of PFP among adolescents, limited knowledge existed on its impact, or how to support young individuals suffering from PFP.

1.6 Objective of the thesis

The aim of this thesis is to 1) use a bio-psycho-social approach to describe Patellofemoral Pain in adolescents, 2) present and discuss an age-specific management strategy and 3) describe the prognosis of adolescent Patellofemoral Pain.

2 Who are the adolescents with Patellofemoral Pain?

2.1: Adolescents with Patellofemoral Pain

To characterise adolescents with PFP, we compared them to pain-free controls, and adolescents suffering from Osgood Schlatter (a common anterior knee pain condition in adolescents) [20]. We recruited 151 adolescents with PFP, 51 adolescents with OSD and 50 pain-free controls. Comparisons to adolescents with OSD allowed us to identify potential characteristics distinct to PFP. PFP was diagnosed according to established recommended criteria[18] and common inclusion criteria were used:

1. Insidious onset of anterior or retro-patellar knee pain and provoked by at least two of the following positions or functions: prolonged sitting or kneeling, squatting, running, hopping or stair walking
2. Tenderness on palpation of the patella, or pain with stepping down or double leg squatting
3. Worst pain during the previous week of at least 30 mm on a 100-mm visual analogue scale.

OSD was diagnosed as localised pain at the tibial tuberosity that increased with palpation and resisted isometric knee extension. This is in line with current literature [37]. Exclusion criteria for both groups with knee pain included: patella instability, Sinding-Larsen-Johansson disease, concomitant injury or pain from the hip, lumbar spine, or other structures of the knee; i.e. tendinopathy; previous knee surgery; patellofemoral instability; knee joint effusion. If more than one knee condition was present, the most severe condition as reported by the adolescent determined inclusion or exclusion for that group. The inclusion criteria for the pain-free adolescents were: no current musculoskeletal pain, no prior surgery in the lower extremity, no self-reported neurological or medical conditions, and no contraindications to MRI scan.

Self-report questionnaires characterised pain, sports participation, knee function, quality of life and use of pain medication in each group. We used isometric handheld dynamometry to measure isometric hip and knee strength. Objective physical activity was captured using wearable 3-axis accelerometers (ActiGraph GT3X). To assess pain and symptoms, we used the two subscales from the self-reported Knee Injury and Osteoarthritis Outcome Score (KOOS) [38], and asked participants to rate their worst pain for the past week (0-10 scale, with 0 being no pain). Pain duration was quantified as response to the question “for how long have you experienced knee pain”. In addition to the KOOS pain and symptoms subscales listed above, Activity in Daily Living (ADL), Function in Sport and Recreation (Sport/Rec), knee-related quality of life (QoL) subscales were used. This has previously been used in adolescents with knee pain. Health related quality of life was measured

by the youth version of the European Quality of Life 5 dimensions (EQ-5D Y) [39].

Pain, knee function and sport

Adolescents with PFP reported their knee pain began at a median age of 11 years (Interquartile range, IQR: 10-12) (Figure 1). Both adolescents with PFP and OSD reported an average symptom duration of 21 months. Mean worst pain intensity in the past week was 6.5 (SD 2.0) for adolescents with PFP. KOOS pain was 66 points (IQR 63-70) for adolescents with PFP, compared to 100 (IQR 100-100) among pain free controls (Figure 2). Over 50% with PFP reported that they had reduced their sports participation. The most common cause was "pain", followed by fear of damaging their knee. Despite reported reductions in sports, adolescents with PFP accumulated more than 240 minutes (4 hours) of moderate to vigorous physical activity per each day as quantified by ActiGraphs. This included school yard play, transportation, physical education classes and their sports activities. All adolescents with PFP had a desire to return to full sports participation. Self-report sports function was impaired in adolescents with PFP with a median of 54 points (IQR 50-58) on the KOOS sport-rec compared to 100 (IQR 100-100) among the pain free controls. There was no evidence of knee extension strength deficits in those with PFP. This confirms a previous smaller study among adolescents aged 12-16 [40], but contrasts with what has been observed in older adolescents aged 15 and 19 years[41]. The younger populations with a shorter pain duration may not have yet developed deficits caused by PFP due to reduced activity. Growth and maturation is associated with positive muscular adaptations[42], which may be blunted in adolescents who do not engage in adequate activity and muscular overload during this key period. As a result, deficits in strength adaptations due to pain and reduced activity in those with PFP may only become evident post puberty.

On the other hand, adolescents with PFP had slightly lower hip extension and hip abduction strength (effect size 0.21-0.36). Hip extension strength and pain intensity were associated with KOOS Sport/Rec, with higher hip extension strength and lower pain were associated with better sporting function [20]. This indicates the need to consider hip strengthening in those with PFP.

Figure 1: Duration of knee pain of males and females across the three cross-sectional studies and the time of self-reported onset of knee pain. Data presented as a combined box and whiskers plot and individual participant data.

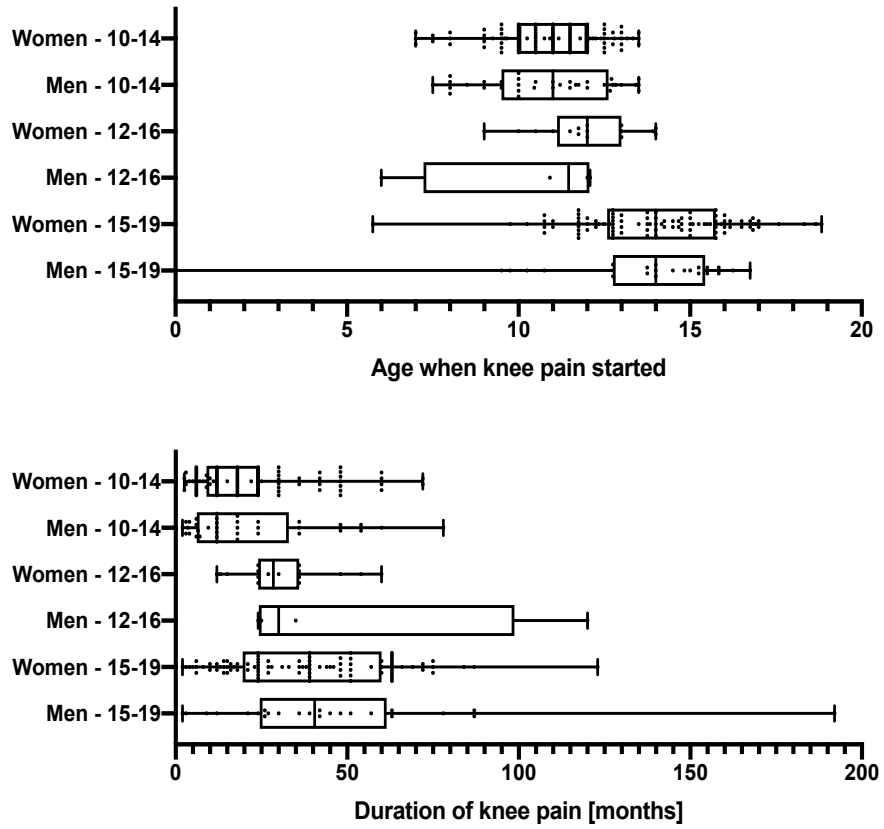
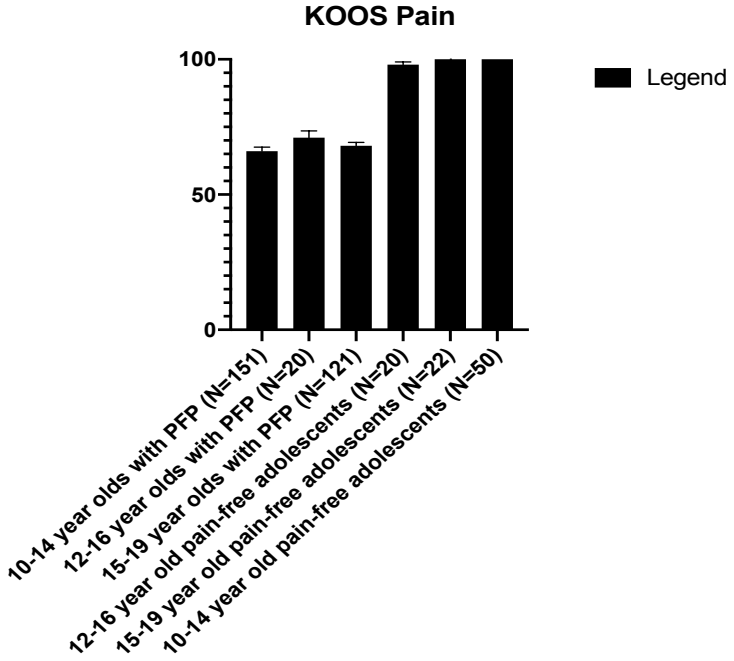


Figure 2: Mean Knee Injury and Osteoarthritis Outcome Scale (KOOS) pain scores in adolescents with Patellofemoral Pain aged 10-14, 12-16 and 15-19 years compared with age matched controls.



2.2: Not a localised knee problem

Quality of life is a multi-dimensional concept capturing how individuals' well-being is affected by a condition [43]. Until recently, this was largely unexplored in adolescents with PFP. Using cross-sectional data from three groups aged 10-14, 12-16 and 15-19 years of age, my research highlights the impact of PFP on QoL [20 40 41]. Health related quality of life was measured by "European Quality of Life 5 dimensions" (EQ-5D), either normal or youth version pending the age-group [39]. Knee-specific quality of life was captured with the KOOS Quality-of-Life subscale [38]. Two samples [40 41] were recruited from school-based populations, while another group with PFP aged 10-14 years were recruited from the community using both social media and local schools [20]. Identical inclusion and exclusion criteria were used as previously described. In all three studies, we recruited pain-free controls. From these three studies [20 40 41] we saw large differences between pain-free controls who scored around 100 on KOOS QoL compared to between 43 and 50 points in adolescents with PFP from the three cross-sectional studies. This indicates substantially impaired knee specific as measured by the KOOS QoL. There were limited differences between the younger and older adolescent cohorts. EQ5D index scores were between 0.72 and 0.78, which is substantially lower than pain free controls who score 1.0 (Figure 4). Lower quality of life scores were primarily due to problems with mobility, usual activities and pain/discomfort. Across the three different populations of adolescents with PFP, around 10% report either moderate or severe anxiety/depression. This is higher than controls between 10 and 14 years of age (0% reporting moderate or severe problems), but similar to older pain-free adolescents (11% reporting moderate or severe problems in the category of anxiety/depression).

Figure 3: Mean score of the Knee Injury and Osteoarthritis Outcome scale (KOOS) subscale Quality of Life among adolescents with Patellofemoral Pain between the age of 10-14, 12-16 and 15-19 and compared with pain-free age matched controls.

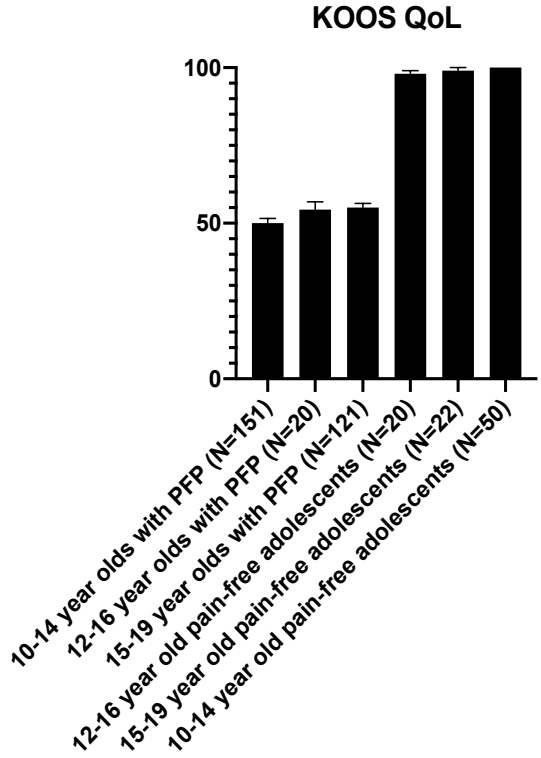
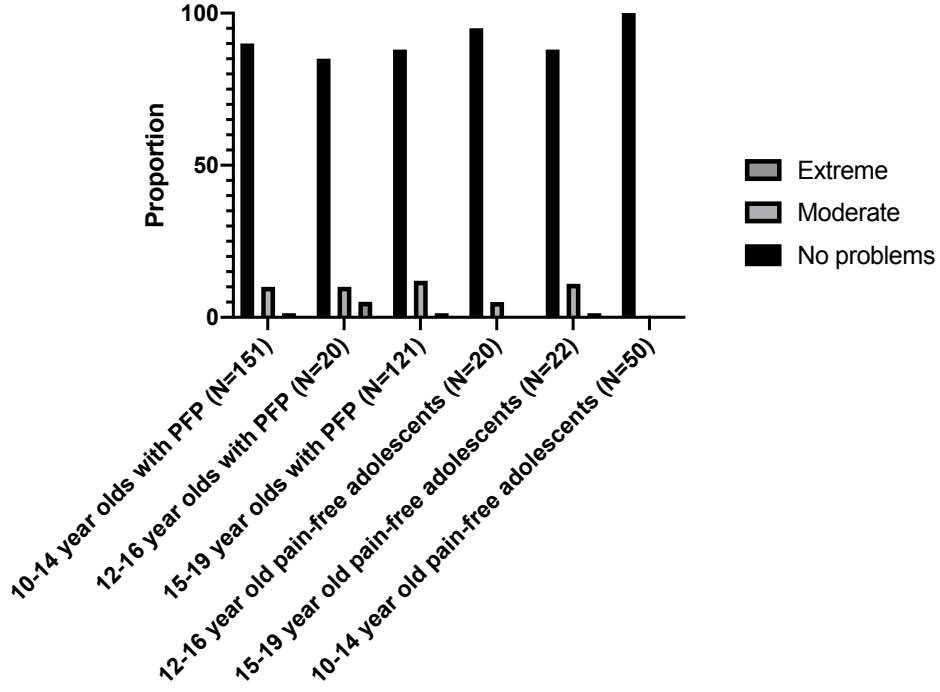


Figure 4: proportion of adolescents from each study reporting problems in the category of anxiety/depression



Similar to other long-standing pain complaints

This suggests that PFP has far wider reaching impact than previously suspected. These findings resemble younger individuals suffering from chronic pain, juvenile arthritis, and other long-standing and chronic conditions that affect many domains of these young lives [44 45]. Additionally, PFP is associated with a reduction in sports participation, and in the longer term, a complete stop of sport for some [46]. As sport during adolescence is not only about physical activity, but also social relationships this can have large impact as they are withdrawn from their social circle [47].

Why do PFP have such an impact on some?

Recent qualitative research explores how PFP impacts individuals. These studies build on the cross-sectional research to describe in more detail how PFP impacts on people's lives using the patients' narrative. These studies have been performed in youth who have been suffering from PFP since adolescence [48], as well as in older adults with PFP [21]. Collectively, these studies show that patients with PFP often feel a loss of identity and having to redefine themselves as they are not always capable to perform the same activities as previous. These findings underscore that PFP is not only a peripheral pain condition isolated to the knee but should be considered from a biopsychosocial perspective. There is a need to understand the interconnection between biology, psychology and social/environmental factors to understand PFP, and shape how treatment can address these components [32].

Pain sensitivity

PFP among adolescents is not always characterized by a good prognosis, with many suffering for a long duration with significant impairments in sport and knee function, as outlined previously [46]. PFP tends to become chronic [49], and shares many common attributes in terms of impact, as many other chronic pain conditions [44 50, 51], despite being considered by many to be innocuous. One observation in pain science, is that exposure to longstanding pain in older adults with chronic conditions such as osteoarthritis, appears to be associated with altered pain processing [52] indicating increase pain sensitivity in the nervous system. Specific manifestations include hyperalgesia- a relative increase in pain (output) to stimuli that evoke pain (such as pressure, heat) both locally and remotely, as well as altered pain modulation evaluated by experimental paradigms [52 53].

It was previously unknown if such characteristics manifest in young adolescents with pain. To evaluate this, we measured Pressure Pain Thresholds (PPTs) at four sites around the patellar (as a measure of local hyperalgesia – an increased pain response to painful stimuli) and on the tibialis anterior (to examine spreading hyperalgesia) [54]. We tested 22 pain free controls and 57 female

adolescents with PFP. All were recruited from the same background population. Aolescents with PFP had lower PPTs at the patella and the tibialis anterior. This suggested local hyperalgesia and spreading hyperalgesia.

These findings [54] demonstrate that adolescents with PFP display a similar magnitude of local hyperalgesia as patients with knee osteoarthritis [53]. Decreased PPTs at non-painful sites in patients with PFP indicate that central pain mechanisms might be altered as well. Hyperalgesia at the tibialis anterior muscle could reflect segmental spreading of hyperalgesia [55 56]. Temporal summation is another surrogate of central pain mechanisms. It is indicated by an increase in pain to repetitive noxious stimuli of the same intensity[57]. This phenomenon is facilitated in patients with chronic pain relative to controls [53]. The increase in perceived pain indicates a net gain from the combined effects of excitatory and inhibitory signals[57]. To evaluate whether this may be present in adolescents with PFP, we recruited young adults with PFP since adolescence from the APA2011 cohort. We included 20 young females with long-standing PFP, and 20 healthy pain-free matched controls from the cohort. The aim [55] was to assess 1) temporal summation of cuff-induced pressure pain, 2) conditioned pain modulation (CPM) assessed by cuff algometry, and 3) widespread mechanical hyperalgesia in young female adults with PFP compared with age-matched healthy pain-free controls. We used identical in and exclusion criteria as mentioned previously. All measurements were performed with the assessor blinded to patient status (PFP or control), which was not done in the first study.

We used an automated system that uses cuff pressure to provide the painful stimulus. The system was operator independent, computer-controlled cuff pressure algometer (NociTech, Aalborg, Denmark) with an air-filled tourniquet cuff (VBM, Sulz, Germany). First, the cuff slowed inflated (1kPa/sec) to assess the pain detection threshold (the pressure at first onset of pain) and pain tolerance (the max pressure that could be tolerated) thresholds. Subjects did this using an electronic 10- cm visual analogue scale (VAS; “0 cm” representing “no pain” and “10 cm” representing “maximal pain”) with which they first moved the slider when they experience pain and continued to rate the pain intensity until they could no longer tolerate it. At this point they pushed a handheld switch which released the pressure. To measure temporal summation of pain we provided 10 short-lasting stimuli (1 second each) at the level of the pain tolerance threshold with a 1-second break in between stimuli. Conditioning pain modulation was assessed by re-evaluating the pain threshold during the presence of a painful conditioning stimulus to the contralateral leg. The conditioning stimulus was induced by inflation of a tourniquet around the contralateral lower leg (at an intensity

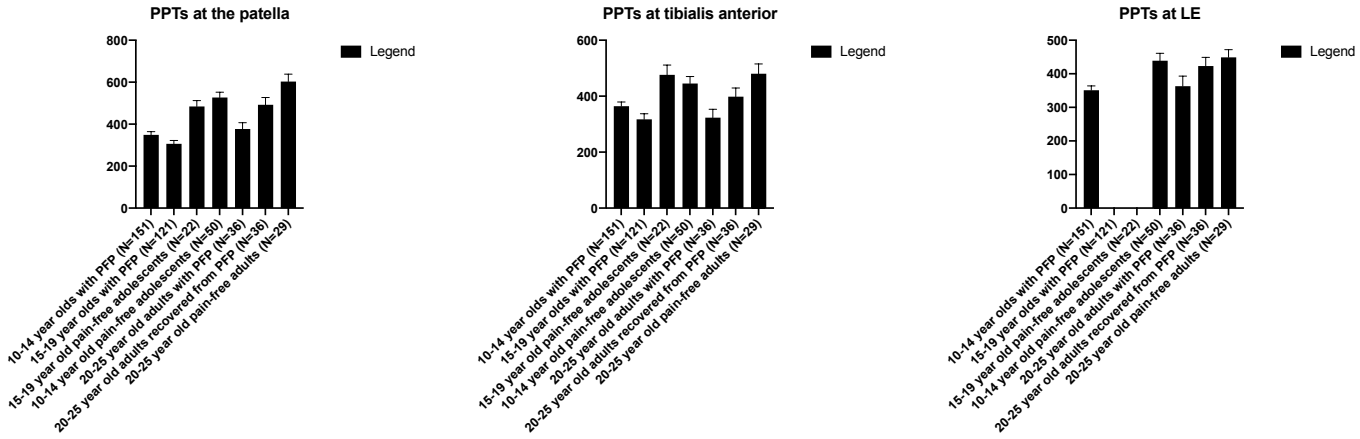
of 60 kPa).The percentage change in pain thresholds at baseline to during conditioning was quantified as the conditioning pain modulation effect. CPM is thought to be the psychophysical paradigm used in humans to evaluate diffuse noxious inhibitory control and thus reflective of the endogenous descending pain modulation [58].

Young female adults with long-standing PFP were characterized by impaired CPM and widespread hyperalgesia. In support of our hypothesis, females with PFP had facilitated temporal pain summation. This was the first study to provide evidence of altered pain processing among young female adults suffering from long-standing PFP. It raises questions surrounding how early such manifestations may arise and if they have implications for later in life. These findings led us to suspect that PFP might have an important pain-processing component which might be relevant for understanding prognosis and have implications for management [55]. To further explore this phenomena, we performed a subsequent study during the 5-year follow-up of the APA2011 cohort [59]. The aim of this study was to investigate the anti-nociceptive and pro-nociceptive profiles in young females with long-standing (above 5 years of symptoms) PFP (current-PFP), those who recovered from adolescent PFP (recovered-PFP), and pain-free controls. We included 36 who were diagnosed with PFP as adolescents and currently still suffered from PFP, 22 who were recovered from PFP during adolescence, and 29 pain-free controls. The primary outcome was CPM while secondary outcomes included pressure pain thresholds at the knee, shin, and forearm, and temporal summation of pain. Compared with the recovered-PFP, the current-PFP had impaired CPM (mean difference: 11.6%; $P<0.004$) and reduced pressure pain thresholds at the knee, shin, and forearm which were also reduced compared to current-PFP (mean difference: 85-225 kPa; $P<0.05$). Both those with current PFP and those recovered from PFP demonstrated facilitated temporal summation of pain, compared to controls (mean difference: 0.7-0.8 visual analogue scale change; $P<0.05$). Compared with controls, the recovered-PFP also had reduced pressure pain thresholds at the knee, which were significantly higher than the current-PFP (mean difference: 110-225 kPa; $P<0.05$). This study[59] builds on the previous two studies [55] [54] and demonstrates that in addition to those who still suffered from PFP since adolescence, those who had recovered also displayed altered pain mechanisms compared to controls with no history of knee pain. This was despite resolution of symptoms in the recovered-PFP group. Such maintained pain sensitivity and facilitated pro-nociceptive mechanisms in the recovered-PFP group may shed light onto the recurrent nature of PFP. These individuals may be predisposed to experience a new episode of pain, when exposed to a lowed intensity stimulus than would normally be required to illicit a pain response. This could partly explain both the poor prognosis and recurrent nature of PFP.

Pain sensitivity: same features in adolescents and adults

The research on the contribution of peripheral and central pain mechanisms is still early, and more work is needed. However, these findings show that adolescents and adults are characterized by the same manifestations of peripheral and central sensitization [53]. The similarities underline the need to consider the wide-ranging impact PFP have and may be needed to be considered when designing interventions to improve the long-term prognosis.

Figure 5: Pressure Pain Thresholds (PPTs) at the Patella, Tibialia Anterior and Lateral Elbow (LE) among adolescents with PFP and age matched controls, 15-19 year olds with patellofemoral pain and matched controls and among 20-25 year olds (from the same cohort) who currently have PFP, are recovered from PFP or have never experienced PFP.



The importance of muscle strength during adolescence and adulthood

Continuing to examine the characteristics of PFP brings us to the much-studied area of muscular strength. Many papers describe deficits in hip strength in patients with PFP (as it is reduced [60]), with many speculating that low hip strength is a risk factor for developing PFP [60]. It was thought that relatively higher hip strength (a) improves biomechanics thought to predispose PFP (outlined above in Chapter 1) and (b) decreases the load on the knee joint through greater force absorption during tasks such as running or jumping [16]. However, there was a lack of empirical evidence supporting these hypotheses. To investigate this, we performed a systematic review [60]. The aim was to synthesize the literature to differentiate between whether hip strength was a risk factor or a consequence, and explore this across different age ranges (from adolescence to adulthood). We performed a comprehensive systematic review, searching MEDLINE, EMBASE, CINAHL, Web of Science, Google Scholar, SportDiscus. Databases were searched from inception until November 2013. The search leveraged the search terms used for PFP in a Cochrane review on diagnosis and

combined these with terms for hip strength. We used the Epidemiological Appraisal Instrument (EAI) [61] to appraise study quality. We included 24 independent studies, with three prospective and the rest cross-sectional. There were notable differences between cross-sectional and prospective studies. Across all studies of adults, the meta-analysis indicated that individuals with PFP have weaker hip musculature compared to pain-free individuals. Contrary to this, our meta-analysis of a small number of prospective studies found no association between isometric hip strength and risk of developing PFP. These findings indicate that reduced isometric hip strength may be the result, rather than one of the causes of PFP. There was limited evidence showing that adolescents may not have the same hip strength deficits as adults with PFP. Most studies investigated adults (ie, >18 years old), with only two studies, one prospective and one cross-sectional, investigating hip strength among adolescents. Overall, these studies did not support the presence of hip strength deficits as a risk factor for or as a feature of PFP among adolescents, which may suggest that PFP have a different aetiology in adolescents than adults. Additionally, this suggests that the impairments in hip strength seen in adults may result from long-standing pain associated with PFP which may lead to reduced physical activity or muscle inhibition [60 40 62].

The review included two previous studies done within the APA2011 cohort [40, 41]. We found reductions in knee extension strength among adolescents aged 15–19 years but not in a younger cohort of adolescents aged 12–16, despite we used the same methodology and both groups were recruited from the same closed population. Our newer larger study (presented earlier) including 151 adolescents with PFP between the age of 10 and 14 support these findings with a lack of large differences in hip and knee strength between PFP and pain free controls [20]. Following this systematic review, a new prospective study investigated if hip strength was associated with the development of PFP during adolescence [63]. They found that *higher* strength rather than lower was associated with an increased risk of developing PFP. They theorized that the cause of this finding was that greater hip abduction strength may be due to increased eccentric loading of the hip abductors associated with increased dynamic valgus biomechanics, demonstrated to underlie increased PFP incidence. An alternative explanation could be that the association between increased hip strength and PFP is confounded by physical activity levels. Adolescents with the highest amount of physical activity and sports participation per week may be at risk of developing PFP. Due to the demands of their sport, they would also be the ones with highest hip strength. However, as physical activity levels were not reported or adjusted for in the analysis this remains a speculation.

The desire to return to sport and type of population

The recruited patient population may be important in terms of which deficits they experience as well as the underlying cause. The majority (92%) of included studies did not explain where patients were recruited from (e.g., general practice, physiotherapy clinics or open populations of non-care seeking individuals) [60]. This makes meaningful comparisons difficult. In the studies included in this thesis on adolescents aged 10-14 years, almost all were involved in sports [64]. Among the 15- to 19-year-olds, 1/3 were not involved in sport [65]. The longitudinal data from the APA2011 cohort suggest that 40% will reduce or stop participating in sports because of knee pain [46]. This may explain differences between the younger and older adolescents with PFP. This may have implications for intervening early to influence the decisions that adolescents with PFP make regarding physical activity and sport, after long-standing symptoms.

Data driven change in the perception of PFP

Patellofemoral pain has been viewed as a self-limiting condition with little impact, especially during adolescence. The series of studies done within this thesis, and on the APA2011 cohort combine self-report measurements, objective physical activity, muscle strength and quantitative sensory testing to reveal that adolescent PFP is not isolated to the knee with low impact. PFP affects these young individuals in a number of important domains, and hampers their ability to engage in valued activities. Our studies using psychophysical pain measures revealed that like other chronic pain conditions, there may be central pain mechanisms implicated. This needs to be acknowledged and investigated in longitudinal study designs to understand if it associated with prognosis, or can influence responsiveness to treatment.

3 Treatment of adolescent Patellofemoral Pain

3.1 The rationale for exercise therapy

Systematic reviews and consensus reports recommend exercise therapy (usually in the form of resistance exercise) as the cornerstone of treatment for PFP in adults [66]. Prescribing exercises to improve hip and knee strength to address the observed strength deficits, improve loading capacity and biomechanics. The efficacy and effectiveness of exercise therapy has been established in adults with PFP is superior to placebo [67]. The first cluster randomized trial among adolescents with PFP was conducted during my PhD and compared the added effect of exercise therapy to patient education [65]. Exercise therapy and patient education combined was superior to patient education only. The number needed to treat for the primary endpoint after 12 months was 11. Differences between a minimal intervention (30 minutes of patient education) and supervised exercise therapy for 12 weeks were smaller than anticipated. Many of the secondary outcomes (quality of life, function, and pain intensity) did not reach a level of clinical significance (e.g., <10 points difference in KOOS subscale Scores, <20mm difference in pain on a 100mm VAS), and others (QoL) demonstrated neither statistically nor clinically relevant differences between groups at 12 months [65]. The potential reasons for this underwhelming effect were speculated on in our narrative review "Same same but different" [24]. I hypothesized that the following could explain the poorer effect of exercise therapy among adolescents:

1: Smaller strength deficits among adolescents, which is a key target for exercises

2: The long duration of symptoms among the adolescents enrolled in the trials

3: Low adherence to exercise therapy

To determine if trajectory could be changed by intervening earlier in younger adolescents, I conducted a smaller pilot study to test the same intervention, in a younger age group (12-16 years of age) who I anticipated would have shorter duration of pain [68].

3.2 Exercise therapy in the 12- to 16-year-olds

The aim of this pilot study was to investigate the adherence to the intervention. A secondary aim was to explore the magnitude of potential effect of an exercise therapy intervention, on self-reported Global Rating of Change (GROC), knee function (KOOS) and muscle strength in young adolescents with PFP. The study was a prospective trial of 20 adolescents with PFP [68]. Participants were recruited from the APA2011-cohort. The same in and exclusion criteria were used as previously outlined. One physiotherapist involved in administering the intervention to older adolescents (15–19 years of age) delivered the intervention to all participants. The content of the

intervention was the same as the cluster RCT [65].

Intervention and outcomes

The patient education was a single session lasting approximately 30 minutes (depending the amount of questions from adolescent and their parents). Content included: (1) why does it hurt, (2) pain management, (3) how to modify physical activity, (4) how to return slowly to sports, (5) how to cope with knee pain, (6) information on knee alignment during sit-to-stand, standing, walking, stair walking and bicycling, and, (7) questions from the adolescent or the parents. The information was also summarised and delivered in an 8-page leaflet.

Group-based exercise therapy was offered three times per week for 12 weeks. All exercises were available in three to four different levels to allow for tailoring to each adolescent's performance and to enable progression in load and difficulty of the exercises, pending pain [69]. Additionally, they were instructed to perform home exercises four times per week and if they missed the group exercises. Home-based exercises mimicked the group exercises and included quadriceps and hip muscle resistance exercises and stretching. We used both patient-reported outcomes and isometric strength and collected data on adherence to both supervised and home-based exercises. Adolescents filled in self-report questionnaires at baseline, 3, and 6 months and isometric strength measures were collected at baseline and 3-month follow-up (immediately after the intervention).

Poor compliance and limited clinical effects

Adolescents participated in a median of 16 (IQR 5.5–25) supervised group sessions during the 12 weeks. None participated in over 80% of the 39 training sessions, with 40% participating in < 40%. Participants performed a median of 2 (IQR 2–3) home training sessions per week and a median of 26 home-based training sessions during the 12 weeks (approx. 50% of the prescribed home exercise dosage). Only five adolescents had a successful outcome (either 'much better' or 'completely recovered') after 3 months, with the same number at 6-months. Three of these had a successful outcome at both time-points, highlighting the recurrent nature of PFP. Eleven participants were highly satisfied or very satisfied with the results of the treatment after 3 months, and nine after 6 months. Improvements in self-report outcomes were small and not clinically relevant, with no substantial changes in hip or knee strength. We expected this young adolescent population would be better responders due to their relatively shorter symptom duration and thus severity/chronicity relative to older adolescents. The intervention demonstrated no clear effect, with low adherence to

the intervention, and little involvement from parents [68]. Poor adherence to the intervention was documented in another study monitoring adherence objectively using a valid and reliable elastic-band sensor to monitor how much the adolescents performed the exercises [70, 71]. Based on the low adherence and lack of improvement, it was not feasible to undertake a large scale RCT in this population. We realised that it was critical to create a specific and meaningful intervention for adolescents with PFP, that addressed their specific context.

The "rethink" and missing element

Exercise focused trials in both adolescents and adults with PFP have neglected activity modification and load management [24]. We included some advice on how to reduce sports participants and then slowly increase the training load as symptoms improved, this was brief and few adolescents adhered to the recommendation, possibly due to the focus on exercises [65]. In both younger and older adolescents, we observed no modifications in sports participation. If we hypothesize that "too much, too soon" without adequate recovery, can be a 'perceived threat' leading to pain in sports active adolescents, then this may explain the limited effect of exercise therapy as it does not address one of the fundamental the underlying causes of PFP [24]. It was clear that a new intervention shouldn't be focused solely on exercises, but rather should encompass other aspects of the biopsychosocial model and the other domains in which adolescents are impacted (sports participation, quality of life and coping with pain). As the targeted behaviours (on sports participation and slow progression back into sports) did not work as intended it was clear that this information need be targeted to the needs and context of adolescents to ensure adolescents had the capability (skills and knowledge, providing support tools), motivation (enablement, and understanding how this can benefit them in the long run) and opportunity (fitting it into their environment and daily lives).

2.3 Specific tools to fit their needs

Based on the findings and observations in the series of papers (both cross-sectional studies, intervention studies and our two reviews) and input from adolescents and parents, we developed a management strategy specifically for adolescents needs, that fit their desires of return to sport and giving them the knowledge and skills to self-manage [72]. It was important to create simple tools to help adolescents implement them in their context. To do this, we saw a need to help them use their pain as a guide to learn when to push forward and when to hold back. We based this on the Thomee

pain monitoring model [73]. This was originally introduced in his seminal paper on a treatment model for young adult females with PFP. The model presents a visual representation of pain (on a scale from 0-10), and indicates what level of pain should be tolerated. The original model presents pain between 0 and 2 as safe, 2-5 as acceptable and above 5 as high risk [73]. To simplify and avoid difficult or scary language, we simplified this to an "OK zone" and a "Not OK zone". This was to help adolescents decide what level of pain during activities and sports were ok, and when they should not continue/ press forward with. This provided them a tool they could use at home and in their life, and outside of structured consultations. Qualitative research supports this as a critical challenge for adolescents with knee pain, and this was essential to support them [48].

As adolescents with long-standing knee pain find it difficult to manage their sports participation, we wanted to give them a pathway forward for returning back to full sport participation, which is the goal for many [20]. We created the activity ladder to supplement the pain monitoring tool to guide progression. This was based on feedback from previous adolescents and parents, research, and clinical expertise. The combination of the pain monitoring tool and the activity ladder provided them with a path forward, that consisted of a series of steps and a feedback mechanism to know when they should press forward on the ladder and when to hold back. The idea was that this would prevent the "boom and bust" cycle that we witnessed in previous studies, with individuals trying too much and experiencing a worsening in symptoms [24].

Once the education and intervention materials were developed, we designed a multicentre prospective study of adolescents with PFP (with 1 centre in Aalborg, Denmark, and 1 in Copenhagen, Denmark) to test the new intervention [72]. Adolescents with knee pain were recruited from local schools, social media, and general practice and subsequently assessed for PFP. We used identical eligibility criteria as previously. The aim was to test this treatment strategy that was specific to adolescents with PFP. The intervention focused on educating them on activity modification and load management. Outcomes included self-reported global rating of change, knee-specific function, KOOS, hip and knee strength, and use of painkillers.

The intervention

Overall, the intervention aimed to change behaviours thought to contribute to PFP; high knee joint loading through high volume of sport/ physical activity. Objective measures of physical activity (wrist ActiGraphs) were used to quantify the target behaviour, together with self-report

questionnaires. Physiotherapists delivered the intervention to all participants, irrespective of current sport participation. After eligibility and consent, adolescents and parents attended four visits with the physiotherapist over a 12-week period. Parents were required to take part in all visits. This was supplemented with a patient leaflet they could keep, which included details on the intervention.

The intervention comprised of three blocks (each 4 weeks), with specific tools. After an initial reduction in sports participation (to reduce knee joint loads), participants were gradually introduced and exposed to increasing knee joint loads. This graded exposure is used in chronic conditions when sensitisation is present and helps address the psychological component, build confidence and address fears of aggravating pain [74-76]. The initial activity and load modification in block 1 included a temporary removal from sports participation and avoidance of activities that aggravated knee pain (using the pain-monitoring model).

During block 2, participants conducted progressive home-based hip and knee exercises and progressing their sport participation using the activity ladder. The aim was to gradually expose adolescents to activities with higher knee joint loads, based on symptoms (using the pain monitoring model). When participants could perform an activity within the OK zone, without a pain flare-up, they were instructed to progress to the next level.

In block 3, participants performed home-based weightbearing hip and knee exercises and gradually returned to sport through a pre-planned model. This helped participants start to engage with sports specific exposures but first participating in warm-up and then adding 15 minutes per week. The pain-monitoring model helped guide the progression. Return to play was initiated only if they had reached level 6 on the activity ladder.

Outcomes

Self-reported data were collected with paper questionnaires. We used a 7-point global rating of change (GROC) scale (ranging from ‘‘much improved’’ to ‘‘much worse’’) at 12-week follow-up as the primary endpoint. This outcome was used in previous trials of adults and in studies of adolescents with PFP [65, 68]. Adolescents were categorized as having a successful outcome if they rated their knee pain as ‘‘much improved’’ or ‘‘improved.’’ Secondary outcomes included the patient-reported KOOS [38], and health-related quality of life measured by the youth version of the European Quality of Life 5 Dimensions–Youth (EQ-5D-Y) [39]. Adolescents were asked about worst knee pain during the past week with a numeric rating scale, and if they considered themselves to be

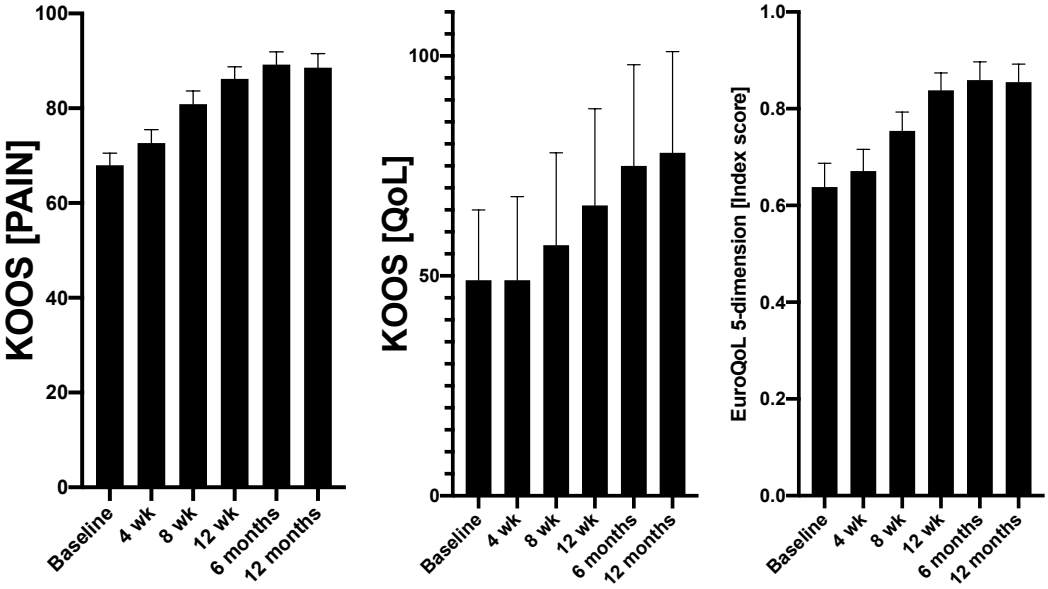
completely free of knee pain at each follow-up. Additional follow-ups were done at 4 weeks, 8 weeks, 6 months, and 12 months.

Sports participation was collected with questions about sports participation per week (training and competition), and type of sport. Wrist ActiGraphs (ActiGraph) collected objective levels of physical activity. We also assessed isometric knee extension torque, hip abduction, and hip extension torque using similar methods as previous studies [40].

High rates of successful outcome

We recruited 151 adolescents with PFP between 10 and 14 years of age. Participants had a median age of 13 years (IQR, 12-14 years), and a median symptom duration of 18 months (IQR, 9-24 months). One in four used pain killers. During the intervention there was an average decrease of 20 min per day (95% CI, 12-28 min/d) in moderate to vigorous physical activity (MVPA) after instruction in the activity modification. In total, 87 of the 136 adolescents reduced MVPA, with 35 of the 136 reducing their MVPA by more than 45 min/d. After 12 weeks 86% had a successful outcome, with similar rates at 6 months (77%) and 12 months (81%). There were high rates of return to sport (68% at 12 weeks, 79% at 6 months and 81% at 12 months). There were large and clinically relevant within-group improvements in the KOOS pain, sport/recreation and QoL (21-28 points) and pain intensity (4.3 points), large improvements in hip and knee strength (20-33%) with only 7% using pain killers after 3 months.

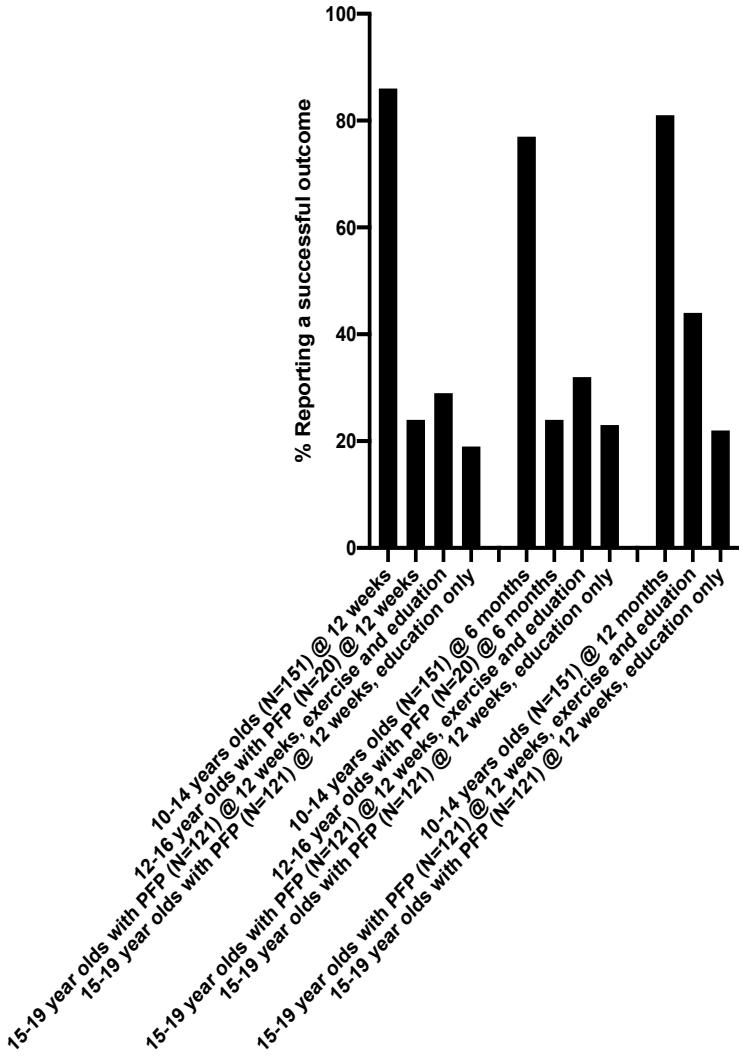
Figure 6: Mean KOOS Pain and QoL score from baseline to 12 months follow-up and EQ-5D index score.



In context of previous studies

This treatment strategy was associated with higher rates of successful outcome after 12 weeks compared to the previous studies (29% in our cluster randomized trial in 15–19-year-olds, and 25% in the pilot study of 12-16 year olds).

Figure 7: Proportion reporting a successful outcome after 3, 6 and 12 months across the three studies including adolescent aged 10-14, 12-16 and 15-19 years of age.



There are several explanations for the higher effect seen in this intervention. Firstly, participants reduced sports and activities that may be associated with knee pain. Furthermore, the intervention provided a structured approach to expose adolescents to build up their tolerance of aggravating activities, guiding them back to sports in a graded manner. This could avoid the ‘‘all or nothing’’ approach that some patients take if not guided on how to balance this. This is the balance that seem particularly difficult for adolescents. The graded exposure would also target some of the

psychological and pain sensitisation manifestations associated with long-standing pain [74-76].

Despite the positive results, improvements stagnated after 12 weeks, and mean KOOS–Sport/Recreation remained at 83 points at 12 months, which is lower than controls. The sustained impairments in sports function and participation indicate this is a long-term condition that needs ongoing management. As a high proportion of adolescents will stop playing sports because of knee pain, effective treatments need to factor in how to target return to sport, as this is an important aspect of their life. Two-thirds successfully returned to sport at 3 months, one-third did not. At 12 months, 1 in 5 were still not back playing sport. The majority reported a desire to return, but 4 adolescents had given up because of knee pain. Despite the limitations in the study design, this provides indications that this strategy may be more effective than previous studies. Despite good short-term results, many of these individuals continue to be bothered by knee pain after a year.

3.4 A small amount of heterogenous studies

In addition to these interventional studies, there have been few other clinical studies looking at interventions in this population (Table 1). Eng et al. [77] showed that the addition of soft orthotics was more effective than exercise on their own. This study only included females a pronated foot posture and had a short follow-up of 8 weeks. Selhorst et al [78] randomized adolescents (12 and 19 years of age) to either a sequential treatment algorithm considering psychosocial and physical impairments, or to a conventional rehabilitation considering only physical impairments. The sequential treatment algorithm was associated with larger improvements in their primary outcome. They followed up this study with a novel trial [79] where adolescents were randomly assigned to view a brief psychologically informed video to target pain-related fear and pain catastrophizing, or control video related basic anatomy and factors involved in PFP. They observed a larger short-term improvement in pain-related fear among those receiving the video compared with the control group, but there was no difference between groups in pain or function at 3 months follow-up.

Considering that one in 14 adolescents are affected by PFP, and as many as one in two of these continue to experience knee pain after 5 years [49], the evidence-base for managing PFP is poor. This highlights the need to further strategic efforts in this area. Based this, the question becomes: who are the adolescents with a particular poor prognosis, and can we identify where we might need to increase support and attention?

Table 1: Overview of trials on adolescents Patellofemoral Pain.

Study	Study design	Sampling frame	Intervention	Diagnosis	Age	Height (cm)	Weight (kg)	BMI	Sex, % females	Symptom duration at inclusion(months)
Eng et al 1993	Randomised trial	Not mentioned	Exercise versus exercise and orthotics	Adolescents with PFP	14.8 (1.2)	160.0 (7.2)	51.7 (8.9)	N/A	100%	10 (10)
Rathleff et al. 2015	Cluster randomized trial	Recruitment from a school-based population	Patient education or patient education combined with supervised exercise therapy	Adolescents with PFP	17.2 (1.0)	172.0 ± 8.7	64.7 ± 12.1	21.7 ± 2.9	80	39 (21-60) **
Rathleff et al. 2019	Prospective cohort study	Adolescents with knee pain were recruited from local schools, social media, and general practice	The 12-week intervention included 4 supervised sessions with a physical therapist.	Adolescents with PFP	12. 6 (1.2)	162.0 (9.6)	50.4 (9.4)	19.0 (17.2-20.8)	76%	18 (IQR: 9-24)
Rathleff et al. 2016.	Obser-vational feasibility study	Recruitment from a school-based population	6 weeks exercise intervention that covered three weekly exercise sessions (one group-group based session and two unsupervised session at home)	Adolescents with PFP	17 (15-19) **	167 ± 6	60 ± 8	n/a	90%	3.5 ± 1.4
Rathleff et al. 2018	Pilot study	Recruitment from a school-based population	Multimodal intervention (patient education, exercise therapy and patella taping).	Adolescents with PFP	14.6 ± 1.1	167.0 ± 10.0	55.2 ± 9.0	19.5 (18.2-20-7) **	80%	28.5 (24-36) **
Selhorst et al. 2018	Randomised trial	Four outpatient	The sequential cognitive and physical	Adolescents with PFP	14.3 ±	N/A	N/A	23.8 ± 6.0	66%	16 weeks (IQR 6;38)

		physical therapy clinics of a pediatric hospital	approach (SCOPA) group (n=28) was treated based on sequential testing and treatment of activity-related fear, flexibility, kinematics, and strength. The comparator group (n = 27) was treated with a non-sequential physical impairment–based approach. Both groups received treatment two times a week for up to six weeks.		1.8					
Selhorst et al. 2021	Double-blind randomized controlled trial.	Outpatient physical therapy clinics of a single pediatric hospital.	Adolescents were randomly assigned to view a brief psychologically informed video (n=34) or control video (n=32). The psychologically informed video targeted pain-related fear and and the control video related basic anatomy and factors involved in PFP.	Adolescents with PFP	14.8 ± 1.7			23.1 ± 5.4	65%	18 weeks (IQR 7-53)

Data/Values are presented as mean ± SD or count unless otherwise indicated.

**Presented as median and interquartile range

4. Prognosis of Patellofemoral Pain

Prognosis is the likely course of a medical condition, or the chances of getting better, or recurrence. Previously, it was assumed that PFP was innocuous with good prognosis, despite studies already questioned this in the 1990ies [80]. Patellofemoral pain was described as "self-limiting", particularly among adolescents. In 2012 a systematic review on the long-term prognosis was published [81]. It included all retrospective and cohort studies with a follow-up of at least 12 months. In total, 16 studies were included, published over a time span of 70 years (from 1940 to 2004). In patients with PFP, only one in three was pain free after 12 months, and one in four would stop sports after being diagnosed. The systematic review demonstrated a lack of high quality studies investigating prognosis [81] as the majority included were retrospective studies, and/or in select populations such as the military.

No studies prospectively investigated the prognosis of adolescent PFP. This was an important research gap needed impeding clinical practice with no evidence base for responding to adolescents' and their parent's questions "will it go away in time"? and "What will the impact be on my ability to play sport or work?" [81]. The APA2011-cohort enabled us to investigate this in a population-based sample of adolescents with PFP. We included all adolescents, both those with traumatic and non-traumatic knee pain, into a cohort that we planned to follow over time [36]. The strength of this approach was the high generalizability of the cohort, as it was recruited from a population-based sample of school attending adolescents. This allowed us to answer the following questions:

1: What is the prognosis of adolescent PFP?

2: Is the prognosis of adolescent PFP different than other types of knee pain in adolescents?

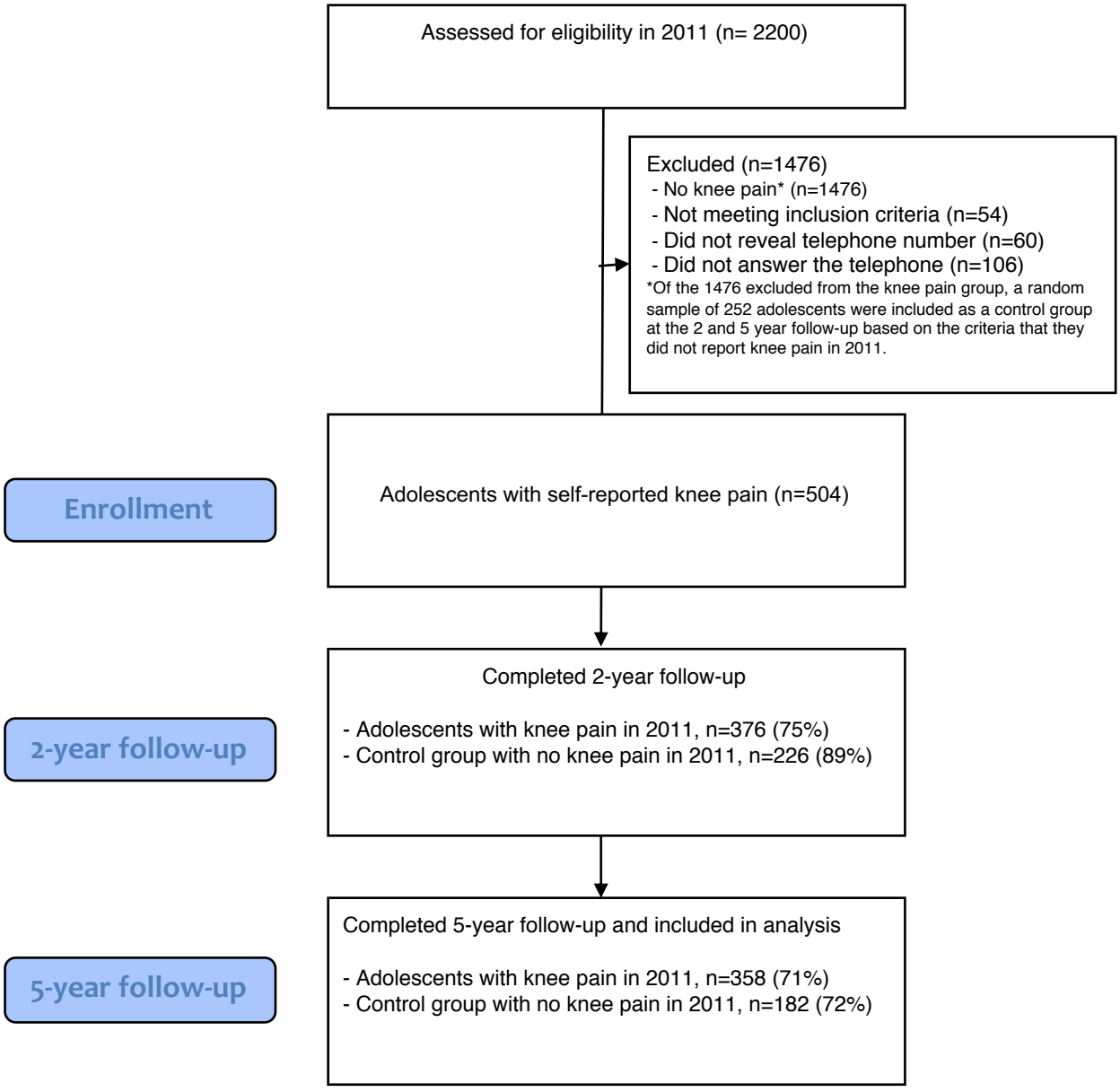
2: What is the long-term impact of adolescent PFP?

Recruitment of the APA2011 cohort

In 2011, we approached the four upper secondary schools in the municipality of Aalborg and asked them to be part of a study aimed to investigate the prevalence and treatment of adolescent knee pain [69]. In September 2011, all students at 4 upper secondary schools in the municipality of Aalborg were invited to answer an online questionnaire and to be part of the APA2011 cohort (Figure 8). From 2846 potential responders in the four upper secondary schools, 2200 adolescents (77%) responded to the questionnaire. A total of 670 adolescents reported they experienced knee pain monthly or more frequently. We reached 504 adolescents (83% of those who reported their telephone numbers). Those with anterior knee pain of non-traumatic onset (204 participants) were invited to a clinical examination, and 180 accepted. From these, 153 were diagnosed with PFP. We

used criteria similar to current consensus on diagnosis of PFP, outlined in previous chapters. At the 2-year follow-up in September 2013 and the 5-year follow-up in 2016, all 504 adolescents were contacted (by telephone) and requested to answer an online questionnaire. If they agreed to participate, an e-mail with a link to the questionnaire was sent to them.

Figure 8: Flowchart of the recruitment of the APA2011 cohort.



Self-report outcomes after two- and five-years' follow-up

In both 2013 (2-year follow-up [46]) and in 2016 (5-year follow-up [49]), the primary outcome was presence of knee pain "during the past week". The (KOOS), pain intensity (Numeric Rating Scale 0-10), pain frequency, health-related quality of life measured with the EQ5D 3L, sports

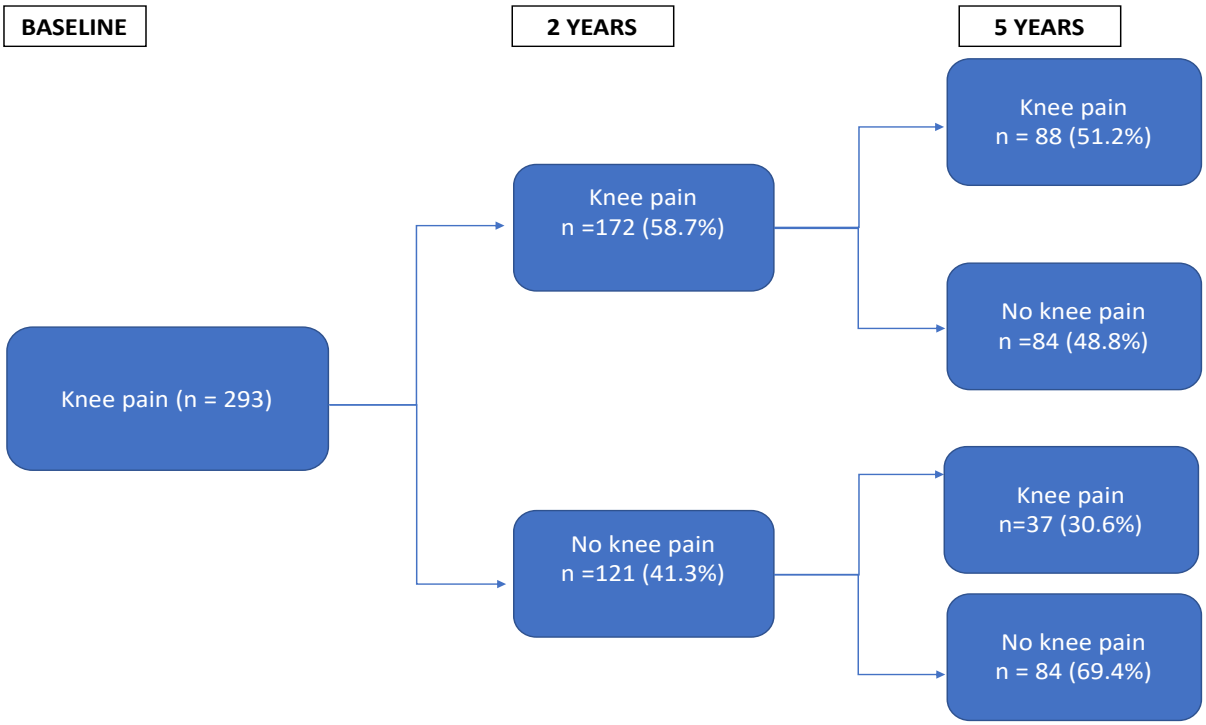
participation and physical activity level were also collected.

At the five-year follow-up we evaluated sleep (quality and efficiency), healthcare consultations & treatment for knee pain, use of painkillers, impact on choice of job or career, effect of knee pain on mood, if/when knee pain resolved, and pain in other body regions. In both the 2- and 5-year follow-up electronic questionnaire captured responses from participants.

Response and prognosis of pain

At the 2-years, 75% of participants completed the questionnaire, with 71% completed the primary outcome at the 5-year follow-up. At 2-years, 55.9% (95% CI, 50.8%-60.9%) still reported knee pain (defined as pain during the past week). Those diagnosed with PFP at baseline had a 1.26 [95% CI, 1.05-1.50] higher risk of knee pain at the 2-year follow-up. At the 5-year follow-up, 40.5% (95% CI: 35.4% to 45.6%) of participants reported knee pain at the 5-year follow-up (figure 9) demonstrates the trajectories of participants with knee pain at 2 and 5 years.

Figure 9: The trajectory of knee pain across 5 years including those which responded at both baseline, 2 and 5 year follow-up.



4.1 Impact of adolescent knee pain after 5-years

Almost one in two continued to experience pain after 5 years. In the 2-year follow-up we divided the adolescents with knee pain up into two groups: those with PFP at baseline and those with other types of knee complaints. In the 5-year follow-up, these groups were combined as the specific knee diagnosis at baseline would not be as relevant after 5-years. An explorative analysis (unpublished data) confirms this.

Pain

Thirty percent of those who continued to experience pain had daily knee pain. The worst pain in the previous week (measured on an NRS) was 4.7. Almost 80% reported pain in other body sites. The KOOS pain was 74 (95%CI: 72-76).

Physical activity levels and sport after 5 years.

Despite 60% reported reducing sports participation due to knee pain at the 5-year follow-up, 78% still participated in sport a median of 2 times per week. Worryingly, 87% reported having moderate-severe problems running (KOOS sport/recreation item 2), and only 30% had no problems with walking downstairs. Based on the IPAQ, 90% met The WHO minimum requirements for physical activity.

Quality of life, mood, and impact on career

At the 2-year follow up, we observed no differences between adolescents diagnosed with PFP and those with other types of knee pain at baseline [46]. All with persistent pain demonstrated low health related quality of life as measured with the EQ5D (index score of 0.82). This was also evident in the knee specific QoL (KOOS-QoL) where the PFP group scored 66 (95%CI 62-69) and the group with other types of knee pain scored 69 (95%CI 67-72). At 5-years follow-up the Eq5D score was 0.79 among those who still reported knee pain and the KOOS-QOL was 58 (95%CI 55-61) which was lower than the KOOS-QoL at the 2-year follow-up. This indicates a deterioration from the 2 to 5-year follow-up. At the 5-year follow-up, those that no longer reported knee pain had higher EQ5D index scores (0.94 (95%CI: 0.93-0.96)) and higher KOOS-QoL of 83 (81-85) compared to those who continued to experience knee pain. Those who continued to experience knee pain, had QoL similar to their baseline scores, indicating almost no improvement over time. Those that no longer suffered from knee pain had significantly higher QoL scores. Thirty three percent of those with knee pain at follow-up reported that their knee pain affected their mood and 26% (95% CI 19-34%) reported that their knee pain influenced their choice of job and/or career.

Use of health care resources and treatments

In the 12 months preceding the 5-year follow-up, 34% of those still reporting knee pain had consulted a healthcare professional (HCP), with physiotherapist (21% of all) and general practitioner (11% of all) being the most common HCPs. The most common actions were no treatment initiated by the HCP (41%) (probably due to the perception that it would be self-limiting), 40% was prescribed exercises and 21% were prescribed pain killers. At the 5-year follow-up, 31% reported using painkillers for their knee pain.

Prognosis and impact of Patellofemoral pain versus other long-standing pain complaints

The combined results from the 2 and 5-year follow-up highlight the commonality of persistent pain, even after 5 years. The impact of their knee pain negatively affects quality of life, sports participation, sleep, mood and choice of job or career. Since our systematic review in 2012 on the prognosis of PFP [81], we published the 2- and 5-year follow-up [46, 49]. In addition to our cohort study, an Australian and Dutch study pooled data from two randomized trials on adults and assessed the 12 months and 5–8-year outcomes [82 83]. After 12 months, 40% had an unfavourable outcome, which was almost the same at 5-8-year follow-up (43%). At the 5–8-year follow-up, KOOS pain was 81 and KOOS QoL was 59 highlighting long-term impairments. These scores were not divided into "favourable and non-favourable outcomes" hampering a comparison with our 5-year follow up.

This may be similar to other pain complaints during adolescence. The most recent systematic review of prognosis of adolescent musculoskeletal pain reveals that among the 25 studies included (>18,000 participants up to the age of 19), 54% with general musculoskeletal pain will report pain after 1 year, and more than 50% even after 4-9 years. However, most of these studies followed adolescents for no more than 3 years. None investigates the 5-year prognosis of knee pain or the associated impact on other domains (e.g. function, and QoL). The best available evidence on the impact may be from the Global Burden of Disease studies [84]. Globally, musculoskeletal pain complaints and the back pain is the third most common cause of years lived with disability among adolescents, only surpassed by depression and headaches. This shows the global impact of adolescent pain and musculoskeletal pain.

Prognosis in context of treatment

There are indications that prognosis may be changed by different management strategies. Comparing the outcomes between our cluster RCT [65 72] and our cohort study using patient education and activity modification, it appears that the provision of a standard 30 min education session is the least effective for adolescents with PFP. Patient education and 12 weeks of supervised

exercise therapy slightly improves the outcomes compared to patient education alone, but four sessions of education on activity modification and load management appears to be associated with the highest rates of successful outcomes after both 12 weeks and 12 months [72]. The prognosis presented in the 5-year cohort study may be improved with more effective treatment. But, we should be careful not to state that adolescent PFP is a self-limiting condition with no long-term outcome as the only prospective data we have refutes this notion.

4.2 A focus on those with a poor prognosis

From the prospective cohort studies and cluster randomized trial we learnt that not all adolescents with PFP have a favourable prognosis. The discovery of a heterogenous response to treatment and different prognostic trajectories is well known within musculoskeletal pain research. The previous body of literature have tried to understand the different trajectories for common musculoskeletal pain complaints including low back pain, shoulder pain, PFP in adults, and general musculoskeletal pain [85] [86]. Based on the heterogenous response in treatment, we also sought out to identify prognostic factors in the data we collected on adolescents with PFP. Such information can support clinicians when patients ask, "what is my likely prognosis; how will it impact me; when will it go away or when can I expect to play sport without suffering from pain".

Prognostic factors for 2 and 5-year outcome in the APA2011-cohort

We used the data from the APA2011 baseline questionnaire data and diagnosis (PFP versus other types of knee pain) to explore factors associated with pain at two years [46] and subsequently five years. The two-year analysis included 376 adolescents between 15 and 19 years of age when they were enrolled. We identified baseline exposures that were associated with the outcome. In this analysis we found that diagnosis, sex, sports participation, health-related QoL (HRQoL), pain frequency and pain duration were associated with risk of having knee pain after 2 years. In the multivariable analysis evaluated the independent effects of these exposures. A higher pain frequency was the only factor that remained significantly associated with prognosis of pain. Poorer HRQoL, a diagnosis of PFP, and female sex also seemed to be associated with a poorer prognosis but the estimates were imprecise with wide 95%CI. We conducted a similar analysis using the 5-year follow-up [87]. We found that female sex, low HRQoL, daily pain, and multi-site pain were associated with an increased odds of knee pain after 5 years (odds ratio: 1.41–3.37). We included a functional outcome, as the previous review found this lacking in all studies on prognostic factors for any musculoskeletal pain. Higher baseline sports participation was associated with less problems running at follow-up (odd ratio 0.49). Interestingly the number of pain sites increased from a median of 2 (IQR 1–3) to 4 (IQR 2–6) at the 5-year follow-up ($P<0.05$). Those with multi-site pain

at follow-up after 5 years had significantly worse self-reported knee function, compared to those who only reported one pain site.

Twelve weeks outcome in 10–14-year-olds with PFP

We performed a similar analysis in the dataset of 151 adolescents between 10 and 14 years of age [72] undergoing activity modification. Interestingly, none of the baseline measures were associated with 12 weeks outcomes. Important differences in this dataset compared with the APA2011-cohort is that: 1) it only contained 151 adolescents at baseline, 2) the rate of successful outcomes were much higher with only 14% with a poor outcome (defined as a non-successful outcome based on the GROC) compared to 56% of 504 among in the APA2011-cohort, and 3) the younger age group. Despite being underpowered, none of the baseline measures appear to be substantially different between group. This was surprising as we could not replicate the findings from the most recent review investigating prognostic factors for PFP [88]. In this review the most consistent prognostic factors were duration of symptoms (3 studies) severity of symptoms (greater usual pain severity and lower baseline anterior knee pain score) and older age. It may be that prognostic factors in this age group may differ from adults with PFP. Again, this highlights the need to explore prognostic factors in adolescents populations.

Individual participant data meta-analysis

One of the issues with the studies on prognostic factors is the lack of research designed specifically to identify prognostic factors, and the small sample sizes of individual studies. Studies are restricted to the exposures that were collected at baseline for that specific study. For many studies this translates into exposures being restricted to measures of severity of the conditions (using many ways to characterize it) and demographics (e.g., age and sex and BMI) [89]. Available baseline exposures are limited, the sample-sizes are often too small for testing exposure-outcome relationships, and findings are rarely replicated in independent cohorts to validate their prognostic value [90]. Pooling study level data is difficult as studies in this population have rarely evaluated prognostic factors. To counteract this, we performed an individual participants meta-analysis to obtain individual participant data from all available cohorts [91]. This would allow us to answer the question: which prognostic factors (exposures) are associated with pain and function (outcome measured through the KOOS sport/rec) after 3 and 12 months (endpoints) in adolescents with non-traumatic anterior knee pain (patients) receiving any type of treatment or receiving no treatment. We used a systematic approach to identify eligible studies through a systematic review and a

forming a collaborative group (the adolescent knee health group) with authors in the field. We included prospective studies with a minimum follow-up of 6-weeks. We did not include any restrictions on the type of treatment being received in the studies and included prospective studies without treatment. To avoid the problems of small study bias we set a minimum threshold of 20 adolescents with non-traumatic anterior knee pain. We included both published and unpublished studies as long as we could obtain a full text or protocol. We included studies conducted within the last 20 years and included reports or publications in English, German, Dutch, Scandinavian languages, French, Spanish or Italian.

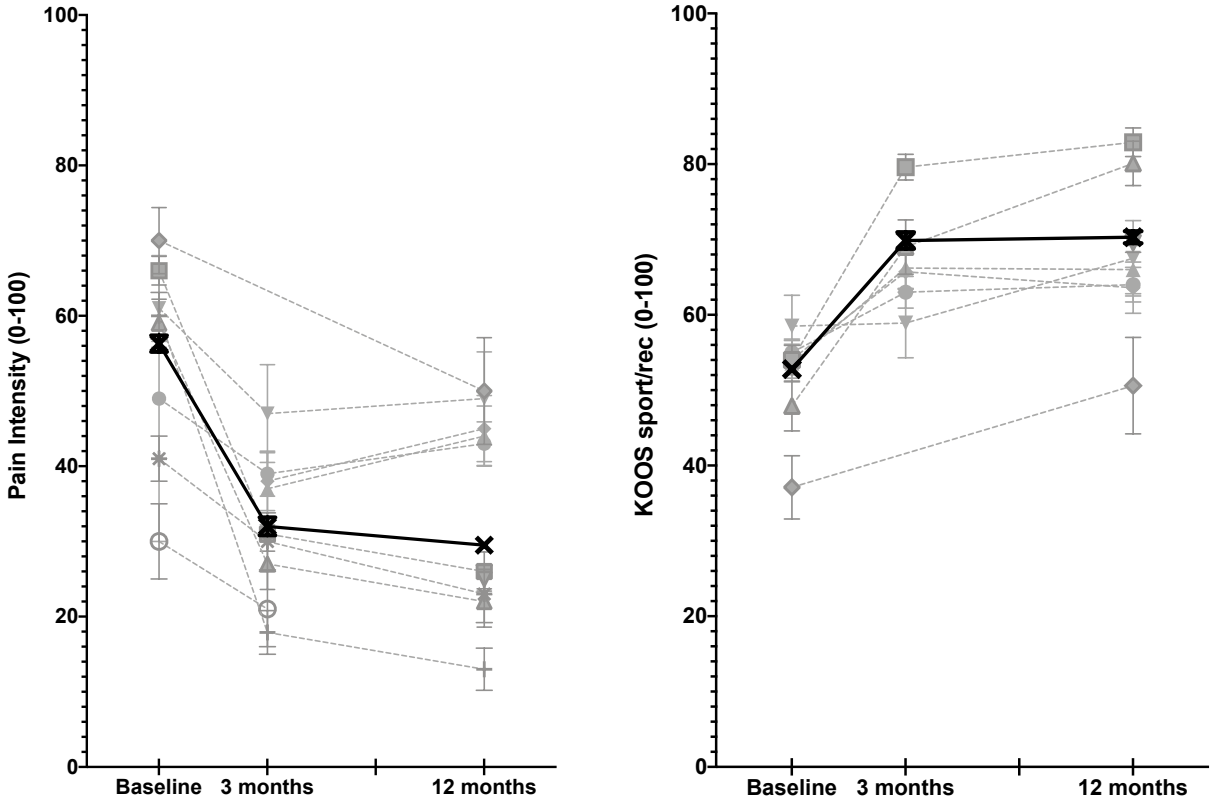
We included adolescents between 10 and 19 years of age (both sexes) with non-traumatic knee pain. Non-musculoskeletal conditions (e.g., systemic conditions, cancer, and autoimmune such as juvenile arthritis) were excluded. Inclusion criteria were applied at the individual participant level rather than study level. This meant that the study (and its data) could still be included pending they could supply individual data for the 10–19-year-olds who fit the inclusion criteria, even if the study also included adults. To be included in the analysis studies were required to at a minimum include data on at least one outcome (pain or function), and demographic information (sex and age) which could be used to evaluate exposure – outcome relations. Other exposures of interest included sociodemographic variables, pain characteristics, psychological characteristics, and health behaviours.

The main outcomes of interest were pain (the primary complaint for this population) and sports-related function. The presence of pain, higher pain intensities and lower function/larger impairments in sports related function were all considered part of poorer prognosis. The main outcome measures selected to quantify this were pain intensity. This could be measured as either a visual analogue scales (VAS); numeric pain rating scales (NPRS)), or presence of pain at follow-up (yes/no). The main endpoint of interest was at the timepoint closest to 12 months (which we defined as long term) while closest to 3 months was chosen as an additional endpoint of interest. The full methods of how data was obtained, handled, and harmonized can be found in the publication of these results [91].

We included 13 prospective studies with IPD on 1281 adolescents with anterior knee pain. The number of participants in the original studies ranged from 20 to 504. The median age of participants in studies ranged from 12 to 17 years, with 40-100% of participants female. The numbers available for each analysis ranged from 117 participants for PPTs at remote location, up to 717 for pain duration. Interestingly, the pattern of the observed improvements in pain and function occurred

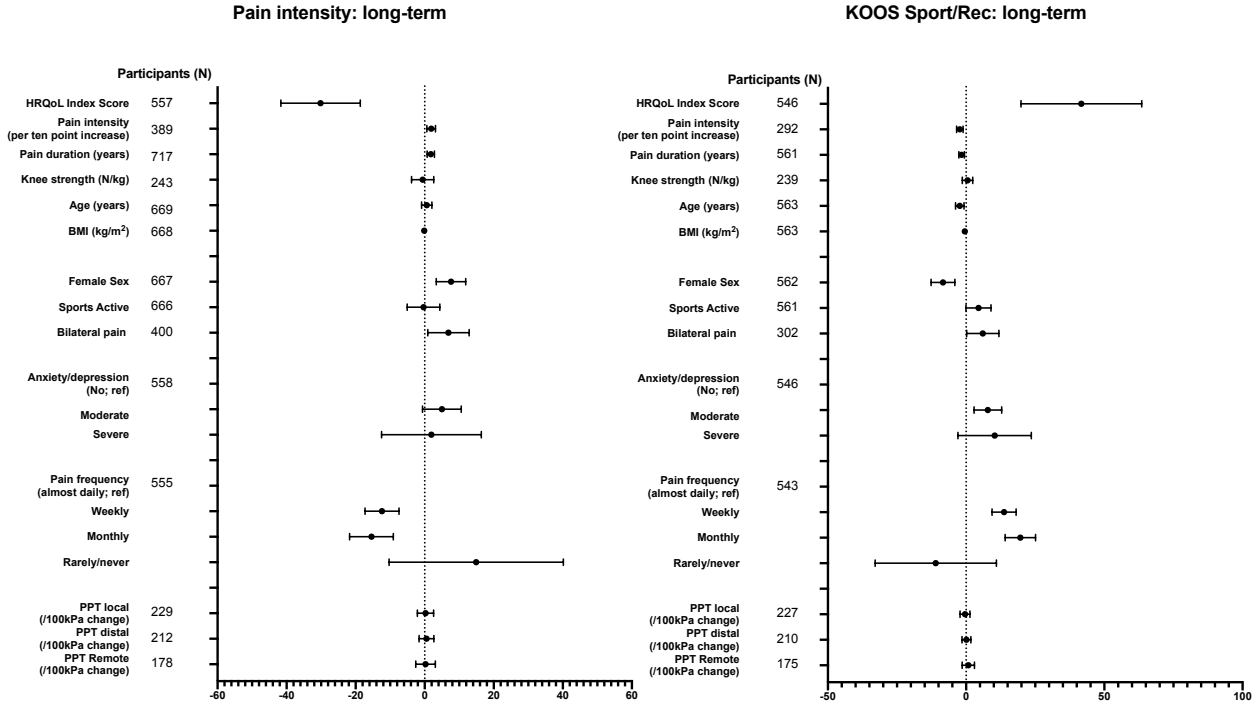
primarily in the short-term (from 0 to 3 months), with limited to no improvements from 3 to 12 months (figure 10).

Figure 10: The trajectory of pain intensity and KOOS sport/rec score from baseline to 12 months follow-up divided into the individual studies including in the individual participant data meta-analysis. Mean (95% CI) observed values for pain intensity (left panel) and function (right panel). The grey dashed lines indicate individual studies while black line (bold with crosses) indicates group average.



Pain characteristics (pain frequency, bilateral pain, and pain duration), lower health related quality of life and female sex were associated with a worse prognosis. This was consistent across both pain and functional outcomes. Sports activity was slightly protective for sports related disability, while moderate anxiety depression increased the risk of higher sports related disability in the longer term. There was also a small association between older age and sports related disability. There was no association between BMI, lower limb muscle strength or pressure pain sensitivity and either outcome. Pain frequency and health related quality of life were the characteristics most strongly associated with outcomes, giving potential questions that can easily be asked in the clinic to give an indication of those who may be at higher risk of poor prognosis [91].

Figure 11: Coefficient and 95% confidence intervals for the association between each prognostic factor and the outcome. Figure on the left shows the associations with pain intensity (0–100-point scale), with values to the left indicating improvements (e.g., decrease in pain) per unit change in prognostic factor. The figure on the right shows knee function measured by the Knee Osteoarthritis Outcome Score (KOOS) Sport/Rec sub-scale (0-100-point scale), with values to the right indicating improvements (e.g., increases in function) per unit change of the prognostic factor.



Can we predict the outcome of adolescents with non-traumatic knee pain?

Based on the IPD analysis, including almost 1300 adolescents we conclude a large proportion will continue to experience pain and functional limitations, even after 12 months [91].. The only factors having a marked effect on prognosis was HRQoL, and to a lesser extent pain frequency. The question becomes if HRQoL and pain frequency have an additive effect on prognosis or if they are somehow related. As we were not able to perform a multivariable analysis due to heterogeneity in the studies with available exposure data for the different exposures, it is unclear if the investigated factors represented individual effects or are strongly associated with each other. One might speculate that those with a higher pain frequency experience more functional limitations leading to lower HRQoL [91]. Several of the exposure we found associated with prognosis, may in fact also be associated with each other [87]. Research is needed to validate our identified prognostic factors in multivariable models.

The findings from the IPD align with the broader field of musculoskeletal pain and demonstrate that predicting outcome (based on how a patient presents at the initial consultation) is difficult. To date, there are no tools able to predict prognosis with a high degree of certainty. As there are no tools to predict prognosis, it may be worth exploring individual changes over time and use group-based prognosis to inform adolescents and the parents if they ask about their likely prognosis.

5 Discussion, future perspectives and limitations

The rise of research in the field of adolescent musculoskeletal pain

Musculoskeletal disorders pose a threat to adolescent health, and can have implications into adulthood. Each year, 8% of an adolescent population contacts their general practitioner due to musculoskeletal pain [35]. Musculoskeletal pain is therefore one of the most common health problems in this age group together with mental health issues [84]. Already in early adolescence, back and neck pain alone are the fourth leading cause for years lived with disability globally in 10–14-year-olds, and similarly for the adolescents between the age of 15 and 19 years of age.

One out of two adolescents annually develop a pain complaint that last for 2 weeks [92-94]. One in four will develop pain lasting for more than one month, and 50% will continue to have similar recurrent pain episodes even years later that will last into adulthood[92-94]. These pain complaints affect health-related quality of life, health behaviour such as physical activity, and are associated with anxiety, depression, and sleep problems [44 95 49, 87]. This results in pain having big impact on many domains of their health young lives.

The last years of improved understanding on adolescents' health and its development has formed the basis for recent articles on the need for improved focus on the adolescent period, and also the period where investments in health may give the largest return on investment. Dahl et 2018 wrote in Nature " *The developmental science of adolescence is providing new insights into windows of opportunity during which we can have especially strong positive impacts on trajectories of health, education, social and economic success across the lifespan*". "*Strategic and developmentally informed investments in adolescents could contribute to a positive impact on the adolescents themselves, their future lives as leaders in adult society, and the next generation to whom they will be parents*" [96]. Ten years ago, there were less than 5 original papers on adolescent PFP specifically, and less than 10 papers which included adolescent PFP as part of a larger group of patients. Today, there are more than 30 papers specifically on adolescent PFP indicating a

substantial rise in research focus. There are still only few interventional studies and not any comprehensive high-quality clinical practice guidelines on this topic. This indicates a continued need for research in this area. There are 4 trials registered that includes adolescent PFP (WHO trial registry) which seems low compared to the prevalence and impact of the condition.

Learning from the adult musculoskeletal health field

How do we develop, test, and implement relevant treatments for adolescent patellofemoral pain (and other types of adolescent MSK health problems)? The field of adolescent MSK Health is not as mature compared to research on adults. One of the current focus areas in the general MSK research area is to make sure that treatments and management strategies meet patient-needs and support patients in managing their MSK condition. This requires a larger involvement from patients early on to uncover their needs and preferences. This is an unexplored area in adolescent PFP where limited studies exist on preferences of rehabilitation and management, lack of user-involvement during the designs of studies and interventions, and generally small sample-sizes. To impact the field of adolescent MSK complaints, larger multi-centre studies are needed combined with adequate time and considerations on intervention development and subsequent implementation into clinical practice.

Early management appears effective, a need to develop interventions aimed at those with long-standing knee pain and concurrent pain complaints.

Recently, Lancet published a series on back pain [97]. This series of papers focused on epidemiology, treatment, costs and implementation of research into practice. A striking figure from that series is the direct costs associated with treatment of back pain across the world. Most types of back pain are benign and last less than 4 weeks, and treatments offer only little to moderate additive effect compared to advice to stay active, reassurance and simple education. Part of the message from the Lancet series and other topical reviews in the area is that we must not neglect the self-management approach of pain conditions. Empowering patients to manage their pain in an appropriate way, might be one of the most potent and highly scalable solutions to the increasing burden of musculoskeletal conditions. It is interesting to see the difference in successful outcomes between the intervention tested in the cluster randomized trial with 12 weeks of supervised exercise therapy, versus the self-management approach where the focus was placed on teaching the adolescents and parents to self-manage [65, 72]. One possible explanation for the improved success is that this approach aims at changing behaviours and teach them how to manage their knee pain when it arises. Investigating the long-term implications of a “library of self-management” on health care utilization and coping would be relevant. As many skills and competences are taught and learnt

during adolescence, this might be the optimal place to add that to the standard curriculum of growing up to create a resilient population that understands how to manage their pain [96]. Adolescent PFP have many features in common with other long-standing musculoskeletal health problems, and is not just a biomechanical problem. This re-conceptualization of the common pain complaint, now also need to extend into new rehabilitation strategies that explore how we can support patients to manage their pain and stay active, as is the key message for adult low back pain.

Joint health, overall health and staying active

In our cohort study of 151 adolescents between 10-14 years of age, 81% were back playing sport after 12 months [72]. They participated a median of 4 times per week and only 7% used pain killers after three months (down from 24% at baseline). In the supervised exercise therapy intervention among 15–19-year-old adolescents, 63% were back after 12 months and participated a median of 1.5 times per week. The non-randomized nature of this comparison hampers any strong conclusions, but it does suggest that more adolescents get back to sports after being exposed to the intervention focused on patient education to support self-management. Among the 151 between 10 and 14 years of age we advised them to stop doing sport for a short period of 4 weeks and then provided them with a series of milestones before the return to sport. The reason was that this population often have an "all or nothing" approach and we aimed to take them out of their aggravating activities to allow the pain to settle before exposing them to higher knee joint loads though specific activities and exercise for the knee and hip. It is currently unclear if a period of 4 weeks is needed, also in the context of being away from sport, friends and not being exposed to physical loading which is an important part of adolescence to stimulate healthy bone, muscle and joint development [98, 99]. Similarly, it is unclear what to do with a young adult (such as one from the 5-year follow-up) who has been suffering from knee pain for many years. Should they be advised to continue with his or her sport? Will sport keep aggravating the knee pain, or is the continued loading from sport beneficial despite it causes pain? And what should be the recommendation for those who have stopped all sports completely? We now understand that pain is not always a good indicator for injury status, and that in very long-standing conditions, the pain experienced may be influenced by multiple factors [29]. Future research should explore this to keep these young adults, with long-standing PFP, as active as possible.

Symptoms without an identifiable pathology

Cross-sectional and cohort studies have shown that adverse life events during childhood, psychological distress, and depressive/anxiety disorders are associated with many different medical

symptoms without any clearly identified pathology [100, 101]. In both the primary sector and secondary sector, patients with poorly defined pathological mechanisms (irritable bowel syndrome and fibromyalgia) present with higher rates of anxiety and depressive disorders than do patients with comparable, well-defined medical diseases and similar symptoms [102] [100, 101]. Other studies document that even after adjustment for the severity of the primary medical condition, those with depression or anxiety have more symptoms have more medical symptoms without identified pathology compared to patients with a similar medical disease alone [100]. Patellofemoral Pain can in several ways be compared to other pain syndromes as it does not have a specific tissue pathology and in some cases co-exist with psychological distress, depressive and anxiety disorders. As with other pain syndromes, medical symptoms without identified pathology suggest we need to understand the biopsychosocial cause of these symptoms and this information should inform our management [17] [103]. The field of PFP is changing towards a biopsychosocial model of understanding pain, the next step will be on how these findings can be implemented in next-generation rehabilitation strategies for these patients. The increased focus on these aspects is underlined by our recent 3-stage consensus document where we established the clinical and research priorities on pain features and psychological factors in persons with patellofemoral pain [32]. This included conducting two systematic reviews, an online survey of health care professionals and persons with patellofemoral pain; and (3) a consensus meeting with expert health care professionals. The overall results showed that pain catastrophizing, pain self-efficacy and fear-avoidance beliefs were factors considered important in the planning of treatment, clinical examination, and assessment of prognosis. Quantitative sensory tests for pain (as those used in several of studies included in this thesis) were not regarded clinically important, but were deemed research priorities (to understand prognosis), as were most psychological features. This provides further evidence on the paradigm shift within this research area.

The holy grail - stratified care based on subgroups?

One proposed action of developing new intervention that fits with the patient needs (so-called targeted interventions), is through subgrouping of patients. The concept of subgroups is based on the premise that 1) there are distinct subgroups with PFP that can be identified, 2) that identified subgroup needs a different management plan to maximize benefits of treatment. The preliminary work from Selfe et al, on adults documents that despite best effort to identify three distinct subgroups within adults with PFP, there are a lot of overlap between the groups and so far it is unclear if the three groups they identified need a differential treatment to improve outcomes [104]. One of the features they used to create subgroup was foot posture. Foot posture have been the focus

for a lot of research in PFP as the biomechanics paradigm has suggested that a pronated foot posture (i.e. flattening of the foot arch) will force the lower leg to internally rotate leading to patellar maltracking [16]. This approach has been substantiated by research demonstrating that patients with a more mobile foot (i.e. more foot pronation) are more likely to benefit from foot orthoses (which are intended to help control the foot arch and decrease internal rotation of the lower leg and prevent patellar maltracking). However, methodological considerations in previous literature, such as lack of a comparator treatment and potential overfitting of models for outcomes may have created spurious findings meaning that people to quickly drew conclusions on the increased efficacy of foot orthoses for those with a mobile foot (compared to those who did not have a mobile foot) [88]. A recent high-quality study overcame the previous limitations and tested if the subgroup of patients with a mobile foot were more likely to respond favourably to foot orthoses compared to hip exercises [105]. This large trial involving 218 patients, demonstrated that the subgroup of patients with PFP with a mobile foot were not more likely to respond to foot orthoses. Importantly, the study demonstrated equal benefit of foot orthoses compared to hip exercises suggesting that despite a potential clearly defined subgroup, theoretical and preliminary evidence, the intervention thought to be more effective among a subgroup, was not. This is all research based on adults and it is unclear if there are specific subgroups among adolescents with PFP.

Another method for creating subgroup is based on patient's prognostic profile. Hill et al. tested such an approach in 2011 demonstrating that a stratified care approach, based on patients' risk of a poor prognosis, improved patient outcomes compared to non-stratified care among patients suffering from low back pain [106]. Such an approach has not been tested among patients with PFP (or adolescents with PFP) but the preliminary evidence from the IPD [91] and the two studies we conducted specifically on adolescent PFP [46, 87] questions if such an approach is realistic. Despite identifying some relevant characteristics associated with outcome in our IPD, there were not very strongly associated with outcome after 12 months. This questions if these features can be used to clearly identify specific prognostic subgroups that need specific treatments. The literature suggest that such an approach may help deliver the exact amount and type of treatment for the individual (e.g., the least amount of treatment for those with a good prognostic profile and the highest amount of support and treatment for those with a prognostic profile indicating a poor outcome) [106]. Many research groups are conducting general MSK research within this domain and the future will tell if this is possible or other, simpler approaches are needed.

A simpler, but none the less relevant approach is stepped care [107]. This approach differs from

stratified care by not trying to base early treatment decisions on prognostic profile or patient characteristics. In this approach all patients are offered the same "base" treatment, and then based on the patient's treatment response (i.e. improving or not improving) additional treatment will be added on if the initial treatment does not cause improvement. Such an approach would fit well into e.g., general practice as it would reduce the need for specific questionnaires to uncover their prognostic profile or collect specific information on characteristics to guide the initial treatment. The potential negative consequence from such an approach is that additional care and treatment may be delayed for those with a poor prognostic profile. As symptom duration when treatment is started seems to be associated with outcome, this may worsen outcome for those with the worst prognostic profile [91]. This needs to be considered closely as it may result in both over-treatment and under-treatment depending which approach is taken.

Limitations and needs of a specific adolescent PROM

In the series of studies on adolescent PFP, we used a combination of self-report outcomes assessing pain, function, and quality of life. A limitation is that none of these outcomes have been developed specifically for adolescents with patellofemoral pain. Using patient-reported outcomes that are not designed for a specific population, includes the risk of measuring domains not relevant to the individual, or missing out on things that are important to the individuals. During several occasions of this research, we interviewed adolescents with PFP about the questionnaires we used, and the tools we used to collect data. This was done to ensure that the adolescents found our questions relevant, and they understood what the questions meant. But despite this effort, it is unclear if the outcomes used, missed out on domains important to the adolescents. There is a need for adolescent specific patient reported outcomes, not only for knee pain, but for general pain complaints. As this field is developing quickly it seems relevant to focus on a core outcome set to allow for data pooling and synthesis in the future. This includes development of adolescent-specific PROMs. Developing adolescent specific PROMs and agreeing on a core outcome set may help many of the problems observed in the IPD analysis of prognostic factors.

6 Conclusion

The field of paediatric musculoskeletal pain is an emerging research field. Patellofemoral pain is one of the most common pain complaints in this population. The studies included in this thesis underline the widespread impact on both self-reported measures of pain, function, and quality of life as well as pain sensitization. Health care practitioners should be cognizant not to assume adolescent PFP is self-limiting. The data presented here show that as many as 4 out of every 10 will

continue to experience knee pain even 5 years after the initial diagnosis. From the cross-sectional and cohort studies we now understand the need for interventions developed specifically for adolescents. The interventions developed and tested as part of this thesis provides insights into how we can support adolescents to self-manage. A self-management approach tailored to the adolescent and their context appears to be associated with higher rates of success compared to traditional treatment methods focused on supervised exercise therapy. This highlights the potential for a multidimensional approach embedded within the biopsychosocial model that may be needed. It is unlikely that focusing solely on finding the perfect exercise prescription will address the complex nature of pain and its's impact on all domains. There are still many unanswered questions related to adolescent PFP, and this series of studies opens a new area where the is a clear need for additional research to improve care for the many adolescents suffering from Patellofemoral Pain.

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