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Prognostic factors for adolescent knee pain: an individual participant data meta-analysis of 1281 patients

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ABSTRACT

Adolescent knee pain has a propensity for chronicity, impacting physical activity and health into adulthood. The aim of this study is to investigate prognostic factors in adolescents with knee pain using Individual Participant Data (IPD) meta-analysis. Studies were identified through a systematic search and a collaborative group. We included IPD from prospective studies of adolescents (age 10 - 19 years) with non-traumatic knee pain (13 studies and 1516 adolescents with 1281 unique participants). Primary outcomes were pain intensity and function (Knee Injury and Osteoarthritis Outcome Score "Sport/Rec" subscale). Primary endpoint was 12-months. Risk of bias was appraised with Quality in Prognosis Studies tool. Harmonised IPD was analysed by multi-level modelling. Fifty-one percent reported knee pain after 12-months. Lower baseline pain frequency was associated with lower pain intensity at 12-months (‘less-than weekly’; 12 (95%CI 7 to 17) and ‘monthly’; 15 (95%CI 9 to 22)

points lower on a 100-point pain scale, compared to ‘almost daily pain’). Other factors most strongly associated with one-year pain prognosis were lower quality of life (30, 95%CI 19 to 42 points per unit change in EQ5D index score), female sex (8 points, 95%CI 4 to 12 higher compared to males), and bilateral pain (7, 95%CI 1 to 13 points higher pain). Similar factors were associated with function. Body mass index, pain sensitivity and knee strength were not associated with prognosis of pain or function. Adolescent knee pain is associated with clinically relevant long-term pain and functional deficits. Self-reported characteristics may help identify those at risk of poor prognosis.

Keywords: Pain; Musculoskeletal; outcomes; adolescent

Introduction

Knee and back pain are especially common musculoskeletal disorders among adolescents [8; 12; 15; 16; 27]. Chronic musculoskeletal pain during this critical developmental period can have lifelong individual and societal impacts[33]. Non-traumatic knee pain accounts for the majority of adolescent knee pain[27], and is associated with decreased physical activity and quality of life. The most common knee conditions in adolescents are non-traumatic, such as patellofemoral pain and Osgood-Schlatter Disease (i.e. anterior knee pain)[6; 22]. Adolescent anterior knee pain has a high propensity for chronicity, long term impact and potential susceptibility to future pain. It appears that nearly 50% of adolescents with knee pain may continue to experience knee pain into early adulthood[21]. Determining the longer-term outcomes and factors associated with worse outcomes may support clinicians in targeting appropriate treatments and resources.

Prognostic research requires large numbers of patients needed which are currently lacking in single cohorts of anterior knee pain among adolescents. Systematic reviews have tried to synthesize the literature in this population [13]. However, meta-analyses were precluded for many prognostic factors. Meta-analysis of prognostic factors is notoriously difficult, due to heterogeneity in primary study reports, such as measurement of variables and analysis strategies [1]. Additionally, despite many prospective studies on adolescent knee pain, few evaluate prognostic factors for non-traumatic knee pain[14]. Individual Participant Data (IPD) meta-analysis overcomes these issues as we can select and harmonise prognostic factors and outcomes across studies at the individual participant level to evaluate prognostic factors in all prospective studies on the topic. This provides opportunity to answer questions on expected prognosis and prognostic factors which would be impossible with standard meta-analysis.

The aim of this study is to identify prognostic factors in prospective studies of adolescents with non-traumatic knee pain that are associated with pain and physical function in the short (3-months) and long term (12-months).

Methods

Study Design

This study is designed as an IPD meta-analysis. A protocol was registered on the international prospective register of systematic reviews: PROSPERO (www.crd.york.ac.uk/prospero/), number CRD42019116861 where a full protocol with tracked and dated revisions is available for download. Reporting follows the PRISMA-IPD guidelines[36].

Deviations from protocol

The original protocol was uploaded to PROSPERO prior to beginning this study. Prior to data analysis, we decided to pool studies for a specific prognostic factor outcome relation only if data were available from a minimum of three studies. This was done to minimise the number of analyses with small study numbers and because random effects models are more reliable with a larger number of clusters. This deviation was documented in the update of PROSPERO (which changes dated and marked in the re-uploaded protocol).

Patient and Public Involvement

Patients were involved in the aims, design and conduct of this research. Priority of the research question is informed by our patient advisory group (comprised of youth who have lived with adolescent knee pain) who have provided input into the program of research on adolescent knee pain. Through this engagement, it was highlighted that the lack of clear information on prognosis is frustrating due to the conflicting information they receive when seeking help. One of the important questions to them is if and when they could expect to recover from their knee pain. During the design of the study, a series of interviews were undertaken with school children with knee pain (N =5), parents (N=1) and school teachers (N=3), physiotherapist (N=1) and general practitioner (N=1). These engagements were intended to qualify the research question being asked and to inform us of which prognostic factors they believed could be important. The interviews all consisted of semi-structured single-person interviews. The key points from these interviews were that stakeholders considered too much physical activity/exercises (in the presence of pain), physical inactivity, lack of social support from parents, high body mass index (BMI), and psychological health important for long-term prognosis. These were included in prognostic factors of interest, and

incorporated into the data requested from original trial authors in order to test their associations with outcomes where possible. In particular, we selected item five from the health-related quality of life scale used in many studies to examine psychological health as an prognostic factor (outlined below). Patients will also be involved in developing the dissemination strategy of this study.

Identification of studies

To determine the possibility of undertaking an IPD, we first contacted established research groups focusing on adolescent knee pain and experts in the fields in order to identify data availability, setup a collaborative group of researchers who were willing to share IPD and collectively identify additional cohorts or treatment studies in the field.

Systematic search

To ensure all relevant studies were identified through our collaborative network, we conducted a systematic search for systematic reviews on adolescent knee pain. The following bibliographic databases were searched: Medline via PubMed, EMBASE and Cinahl via EBSCOhost from 1998- November 2019. The full search strategy is available in Appendix 1 (available at http://links.lww.com/PAIN/B256).

Hand-searching

Reference lists of relevant reports were hand searched, and forward citation tracking for potentially relevant studies that were not identified by our search.

Selection of studies

Potentially eligible articles were independently screened by title and abstract by two authors (SH and MSR). Articles selected for full-text screening or identified through network & hand searching were assessed by both authors. Consensus was reached through documentation of reasons and discussion. A third reviewer (MW) was available in case of disagreements.

Inclusion criteria for studies

Type of studies

Prospective studies (including both controlled trials and prospective cohort studies) were considered eligible for inclusion. A minimum follow-up of 6-weeks was required. We included studies with any type of treatment (or no treatment, i.e. wait-and-see). Studies with a minimum of 20 adolescents with non-traumatic knee pain were eligible in order to reduce the risk of small-study bias. The selection of this minimum number of participants was arbitrary. Both published and unpublished studies were eligible, provided a full text report or protocol was available. In order to optimize likelihood for contacting authors and IPD availability, we limited studies to those which have been *completed* since 1998 (i.e. in the past 20 years, with studies prior to this excluded). We included reports or publications in English, German, Dutch, Scandinavian languages, French, Spanish or Italian.

Type of Population

We included adolescents (aged 10 - 19 years) of both/either sex with non-traumatic knee pain. All types of studies examining non-traumatic knee pain were eligible regardless of geographical location. All types of non-traumatic knee pain were eligible to be included (such as patellofemoral pain, patellar tendinopathy, Osgood Schlatter disease) and unspecified knee pain with non-traumatic onset. Studies examining knee conditions with a specific traumatic onset (e.g. anterior cruciate ligament injury, meniscus lesions) were excluded. Non-musculoskeletal conditions (e.g. systemic conditions, cancer, and autoimmune such as juvenile arthritis) were also excluded.

Inclusion criteria was applied within selected cohorts i.e. studies including a wider population of adolescents and adults were considered eligible for inclusion.

Type of prognostic factor

To be included, studies were required at a minimum to include prognostic factors relating to demographic information (sex and age). Other prognostic factors of interest included sociodemographic variables, pain characteristics, psychological characteristics, and health behaviours (detailed below under 'Obtaining the IPD data').

Outcomes and endpoints

Prognosis refers broadly to the course of condition (i.e. expectations on improvements/worsening/stability of symptoms and/or functional limitations). For this study, prognosis was based on 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 considered poorer prognosis.

Therefore, the main outcome measures selected to quantify this were pain intensity (assessed using visual analogue scales (VAS); numeric pain rating scales (NPRS)), and presence of pain at follow-up (yes/no); we pre-specified the final selection for the primary analysis was to be made based on the outcome included in most studies to optimise data availability. Secondary outcome of interest was self-reported physical function evaluated by the Knee Osteoarthritis Outcome Score (KOOS) Sport/Rec sub-scale. The main endpoint of interest was long-term (closest to 12 months). Short term (closest to 3 months) was an additional endpoint of interest.

Obtaining the IPD data

Approaching trial authors and invitation to join collaborative group

Personal emails were sent to authors of eligible studies between June 2018 and June 2019. Corresponding authors were asked to share their data, and to participate in the 'Adolescent knee health group', on behalf of whom the IPD would be published. If the corresponding author could not be reached, other authors were contacted. We sent email reminders (3 attempts) with a 2-week interval in case authors could not be reached. If authors agreed to participate in the 'Adolescent knee health group', a data processing agreement was signed by the investigators of the IPD (SH/ MSR) and the original trial investigators.

Data requested:

The data requested was based on our previously outlined approach for identifying relevant prognostic factors and included (when available):

Baseline measures (prognostic factors):

Prognostic factors of primary interest were:

1. Sociodemographic variables including age, sex, height, weight or BMI, body composition, pubertal status, baseline physical activity and/or sports participation, socioeconomic status (parental education and household income), health related quality of life, and parental pain complaints.
2. Pain characteristics including diagnosis (if specified), pain intensity, pain duration, pain sensitivity, physical function (self-reported and objective measures) pain impact, and pain locations (including bilateral pain and multi-site pain).
3. Psychological factors (e.g. anxiety, depression, somatic symptoms and externalizing behaviours)
4. Adverse health behaviours such as smoking, alcohol, and sleep.

Outcome measures:

1. All available data on self-report pain (presence and intensity), and physical function data at time-points nearest to 3 months and 12 months.

Data transfer and storage

Data was requested and shared in an anonymised format through an encrypted service and stored on a secure encrypted server at Aalborg University, Aalborg, Denmark to which only the first and last author had access to. Data was accepted in all formats (including Microsoft Excel, SPSS, Stata, SAS and other statistical software) providing the data were clearly labelled and in wide-format. Any data labels not in English or Danish were transferred to a blank excel sheet and translated by an individual fluent in the native language and checked for correct interpretation with original trial author. Any further queries regarding the data were handled by the first author (SH) directly with the original trial author.

Data harmonisation and checking

After acquisition of data, data from individual data sets were relabelled and recoded to ensure consistency between data formats to enable pooling. For example, physical activity was measured in different ways, and being sports active was defined as participating in sport at least once per week, or responding 'yes' to whether they played sport. Data integrity of the individual patient data was checked by undertaking completeness and consistency checks on individual participant data to identify missing or invalid (e.g. out of range) items. Missing information or inconsistencies were checked and rectified as necessary. For the analysis, pain intensity measured on NRS (0-10) and VAS (0-100) were converted to 100-point scales to enable pooling and comparison with KOOS.

Data extraction at the study level

Data was independently extracted at the study level by one reviewer and cross-checked by a second using an a-priori standardised extraction form, following applicable items of the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS)[19]. The data that were extracted included publication details, eligibility criteria, population, outcomes, potential prognostic variables, interventions (if applicable), sample size, response rates and missing data.

Risk of bias assessment in individual studies

Risk of bias was appraised with a modified version of the Quality In Prognosis Studies (QUIPS) tool[11]. We did not assess the last two domains of the QUIPS, as these are related to the statistical analysis conducted in the original study as by using IPD we overcome the limitations in original studies analyses. Additionally, many studies did not examine the relation between prognostic factors and outcome. Two researchers independently appraised

each original study following the QUIPS. We focused on the major domains of bias that are related to data collection/measurement (i.e. selection bias (participant selection), attrition bias (study attrition), misclassification bias (prognostic variable measurement), and detection bias (outcome measurement) only. The rating was done on both study-level and on the individual prognostic factor and outcome association. If agreement was not reached, a third author was available to make the final decision.

Statistical analysis

Changes in pain and function over follow-up

Growth curve models were used to investigate whether there were nonlinear changes in pain and over time. Both linear and quadratic components for time were included in the model. The linear slope was allowed to vary between studies, but the quadratic was not (due to the limited number of parameters that could be estimated with three time-points).

Prognostic factors

Data were analysed using the one-step approach for IPD[4; 7] . For each prognostic factor of interest, we fit linear mixed effects models with fixed effects for the prognostic factor, random intercepts for each study (to account for within study clustering), and a random slope allowing coefficients for the prognostic factor to vary between studies. For the covariance structure, separate variances were assumed for the random intercept and random slope, and that these were independent due the limited number of studies per analysis. In cases of non-convergence of the model, we excluded the random slope from the model.

Separate regression models were fit for each pair of prognostic factor and outcome due to the anticipation of heterogeneity of data availability from original studies, with different numbers of studies available for each of the prognostic factor-outcome pairs. Separate models were used for the outcomes and endpoints of interest i.e. pain (short and long – term), and function

(short and long – term). Data were pooled, and models fitted if data were available from a minimum of three studies. This was pre-specified in the protocol before any data processing, harmonisation or analyses occurred. All analyses were undertaken in IBM SPSS Statistics version 25 (Chicago, IL, USA). Syntax are available in Supplementary material (Appendix 2, available at http://links.lww.com/PAIN/B256).

Additional analyses

Pain intensity was selected for the primary analysis according to our pre-defined hierarchy and with most studies including this variable.

Separate generalised linear mixed models with a binary distribution and logit function were run for the primary endpoint (12months) for pain as a binary outcome, to determine the robustness of findings across outcomes. Studies that did not include pain presence as a binary outcome were dichotomised with <2 'little/no pain' and ≥ 2 considered as having pain. This was selected based on optimising sensitivity and specificity based on studies with both NRS and binary outcomes (data not shown).

Results

Study selection and IPD obtained

In total, 13 studies were included from the network and systematic search (Figure 1 PRISMA IPD Flow-chart). Characteristics of the original study characteristics from which the individual participant data originate are displayed in Supplementary Appendix 3 (available at http://links.lww.com/PAIN/B256). The number of participants included from original studies ranged from 20 to 504, with a total of 1516 participants included in the original studies (1281 unique participants). Baseline characteristics per study are outlined in Table 1, and an overview of participant descriptives of the entire cohort are displayed in Figure 2. The mean

age of participants in each cohort ranged from 12 to 17 years, with between 40% and 100% of participants in the cohorts being female.

Changes in pain and function over time

At baseline, the mean pain was 57mm on a 0-100 VAS scale (95% CI 49 to 64). There was a clinically relevant linear decrease in pain over time (-31mm, 95% CI -38 to -23; P<0.0001). The quadratic function exhibited a non-linear component (9 95% CI 0.7 to 1.2 Figure 3 suggests an accelerated decrease in the first three months.

At baseline, the mean sports-related function was 53 (95% CI 51 to 55). There was a linear increase in function over time (22 95% CI 16 to 28). The quadratic function indicated a non-linear component (-7 95% CI -10 to -5) (Figure 3). Figure 3 suggests an accelerated decrease in the first three months.

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Risk of bias

The risk of bias ratings using the QUIPS tool are shown in Supplementary material (Appendix 4, available at http://links.lww.com/PAIN/B256).

Prognostic factor outcome relationships across studies were at low to moderate risk of bias for study participation (selection bias) and outcome measurement (detection bias). Study attrition was judged as at moderate to high risk of bias across studies.

Overall, individual prognostic factor outcome relationships were judged as moderate risk of bias for the majority of associations. However, the risk of bias was high for those associations that involved prognostic factors self-reported pain duration and self-reported BMI.

Prognostic factors and association with pain and function

Supplementary Appendix 5 outlines the specific studies with data available in each prognostic factor & outcome relation, and studies and numbers of participants with follow-up data included in each analysis (available at http://links.lww.com/PAIN/B256). The time-points selected for each study 'closest to three months' (short term) and 'closest to twelve months' (long-term) are outlined in Table 1. The number of studies per model and model fit (indicated by Schwarz's Bayesian Criterion; BIC) are included in Supplementary Appendix 6 (available at http://links.lww.com/PAIN/B256).

Primary analysis (pain and function in the longer term)

Sociodemographic characteristics

Pain intensity at long-term follow-up was 8 points (95% CI 4 to 12) higher (on a 100-point scale) for female's relative to males. One increase in HRQoL index score on the EQ5D was associated with a 30 (95% CI 19 to 42) point lower pain intensity at long-term follow-up. Age, and BMI did not appear associated with pain intensity at long-term follow-up (Figure 4).

For function (KOOS Sport/Rec subscale), females had 8 points (95% CI 4 to 13) lower function at long-term follow-up. Per year increase in age, there was a 2 point (95% CI 1 to 4) decrease in function at long-term follow-up. One index score better HRQoL on the EQ5D was associated with 42 point (95% CI 20 to 64) better function. BMI was not associated with worse function (Figure 4).

Pain characteristics

Having bilateral pain was associated with a 7 point (95% CI 1 to 13) higher pain intensity at long term follow-up. Those with weekly and monthly pain had a 12 (95% CI 7 to 17) and 15 (95% CI 9 to 22) points respectively decreased pain intensity at follow-up, relative to those who had almost daily at baseline. For each additional 10-point increase in baseline pain intensity there was a 2 point (95% CI 1 to 3) higher pain intensity at follow-up. There was a 2 point (95% CI 1 to 3) increase in pain intensity at long-term follow-up per additional year of symptoms at baseline. Pressure pain sensitivity did not have strong associations with pain intensity at long-term follow-up (Figure 4).

Participants with bilateral pain at baseline, had a 6 (95% CI 0 to 12) point lower function at long-term follow-up. Per 10-point increase in baseline pain intensity there was a 2 (95% CI 1 to 3) point decrease in function at follow-up. There was also a 2 point (95% CI 1 to 3) decrease in function at long term follow-up, per additional year of symptoms reported at baseline. Patients with weekly or monthly pain at baseline, had 14 (95% CI 9 to 18) and 20 (95% CI 14 to 25) points respectively higher function at long-term follow-up compared to those with almost daily pain at baseline. Pressure pain sensitivity did not have a strong association with function at long-term follow-up (Figure 4).

Sports activity and objective function

There was no evidence that being sports active and objective knee strength was associated with pain intensity at long-term follow-up (Figure 3). Being sports active was associated with a 5 (95% CI 0 to 9) point higher function at long-term follow-up.

Psychological characteristics

Participants reporting moderate anxiety/depression (relative to none) at baseline had a 5 (95% CI -1 to 11) point decrease in pain at follow-up. Participants reporting moderate anxiety/depression (relative to none) at baseline had an 8 (95% CI 3 to 12) point decrease in function at long-term follow-up (Figure 4).

Secondary analysis (pain and function in the short term)

Sociodemographic characteristics

Pain intensity at short-term follow-up was 5 (95% CI -1 to 12) points higher for female's relative to males. One increase in HRQoL index score on the EQ5D was associated with a 16 (95% CI 1 to 31) point lower pain intensity at short-term follow-up. There was a 1.5 (95% CI 0 to 3) year increase in pain intensity at short term follow-up per year older age. BMI was not associated with pain intensity at long-term follow-up (Figure 5).

For function (KOOS Sport/Rec subscale), females had 5 points (95% CI -1 to 10) lower function at short-term follow-up. Per year increase in age, there was a 2 point (95% CI 1 to 4) decrease in function at short term follow-up. One index score better HRQoL on the EQ5D was associated with 36 point (95% CI 25 to 47) better function at short-term follow-up. BMI was not strongly associated with worse functional outcomes in the short term (1, 95% 0 to 2-point increase in pain per point increase in BMI; Figure 5).

Pain characteristics

Having bilateral pain was associated with a 6 point (95% CI 0 to 11) higher pain intensity at short term follow-up. For each additional 10-point increase in baseline pain intensity there was a 2 point (95% CI 0 to 4) higher pain intensity at follow-up. Compare to those who had almost daily pain at baseline, those with monthly baseline pain had an 11 (95% CI -8 to 29) point decreased pain intensity at follow-up. There did not appear to be an association between pain duration at baseline and pain intensity at short-term follow-up (Figure 4). Pressure pain sensitivity (at both local and remote locations) was not associated with pain intensity (Figure 5).

Participants with bilateral pain at baseline, had a 7 (95% CI 2 to 12) point lower function at short-term follow-up. Per 10-point increase in baseline pain intensity there was a 2 (95% CI 0 to 3) point decrease in function at short-term follow-up. There was a 1 point (95% CI 0 to 3) decrease in function at long term follow-up, per additional year of symptoms reported at baseline. Patients with weekly or monthly pain at baseline, had 7 (95% CI 2 to 13) and 1 (95% CI -4 to 24) points respectively higher function at long-term follow-up compared to those with almost daily pain at baseline.

There was no evidence that pressure pain sensitivity was associated with function in short term (Figure 5).

Sports activity and objective function

Being sports active, (compared to not) was associated with a 5 point (95% CI -3 to 12) lower pain intensity at short-term follow-up. There was no evidence that objective knee strength was associated with pain intensity at short term follow-up (Figure 5).

Being sports active was associated with a 5 (95% CI -2 to 11) point higher function at short-term follow-up, while evidence that knee strength was associated with short-term function was lacking (Figure 5).

Psychological characteristics

Participants reporting moderate anxiety/depression (relative to none) at baseline had a 6 (95% CI -3 to 14) point decrease in pain at short term follow-up (figure 5).

Participants reporting moderate anxiety/depression (relative to none) at baseline had an 9 (95% CI 2 to 15) point decrease in function at short-term follow-up (Figure 5).

Sensitivity analyses

Pain (dichotomised)

Three of the thirteen studies included IPD on pain presence as a binary variable. Two studies included in the IPD only had outcome data available at primary endpoint (12months) as a dichotomous variable i.e. pain presence (yes/no)[15]. These studies did not provide IPD for pain intensity or KOOS Sport /Rec as outcomes and were not included in any other analyses. Dichotomisation in the other studies was based on transformation of pain NRS/VAS into a dichotomous variable.

Based on this, 51% of patients were categorised as continuing to have pain at long term follow up. The sensitivity analysis revealed that HRQoL, pain duration, remained similarly associated with 12 months pain prognosis (Supplementary Appendix 7, available at http://links.lww.com/PAIN/B256; Table 1). In contrast, sex was not associated with pain

presence (full details Supplementary Appendix 7, available at http://links.lww.com/PAIN/B256). There was no evidence of an association between of sports participation or socioeconomic status (SES) on pain presence at 12 months follow-up.

Other analyses

Results for the sensitivity models excluding small studies (N<20) are available in Supplementary material (Appendix 7, available at http://links.lww.com/PAIN/B256). Due to the small number of studies available after exclusion of small studies, some of the sensitivity analyses did not converge. The models that successfully converged confirmed no major deviations from the findings in the primary analysis. Similarly, sensitivity analyses excluding cases of traumatic knee pain (from one study which included a mixed population) revealed no major discrepancies (Appendix 7, available at http://links.lww.com/PAIN/B256).

Discussion

Principal findings

This IPD meta-analysis obtained individual participant data from 13 individual studies, including data from 1281 unique adolescents suffering from knee pain. The pattern of the observed improvements in pain and function occurred primarily in the short-term, with limited to no improvements from short to longer term (closest to 12 months). Pain characteristics (pain frequency, bilateral pain and pain duration), lower health related quality of life and female sex were associated with a worse prognosis and were consistent across both pain and functional outcomes. Contrary to expectations from stakeholders, high BMI was not associated with poorer prognosis.

Explanation of findings

The largest improvement in pain occurred during the three-month follow-up, with limited improvement between 3 and 12 months. The changes in pain in the initial phase may indicate regression to the mean and are consistent with reports of adult populations with chronic musculoskeletal pain conditions[2; 10]. The use of KOOS sport/rec demonstrated that this young population continued to experience difficulties with sports and recreational activities to a relatively high degree in the long term. Credible information on the prognosis is one of the important answers adolescents and their parents want.

Our findings underline that adolescent knee pain may need ongoing management and not be considered a short-lived self-limiting condition, so clinicians should be wary of giving over-optimistic expectations early. We included a wide range of pain durations ranging from three weeks up to most of their lives included in this IPD meta-analysis. Pain duration (years) was associated with an increase in pain and decreased function of two points per additional year of symptoms. This may be clinically relevant for an adolescent presenting with 4-5 years of pain, compared to those with a recent onset (weeks/months). Of the pain characteristics (frequency, bilateral pain and pain intensity), pain frequency appeared to have the strongest and most clinically relevant association with both pain and function in the longer term across outcomes. Some of the prognostic factors were not statistically significant (i.e. the confidence interval included null), but more importantly the magnitude of effects were not large enough to be considered clinically relevant for some factors which did appear statistically significant. Overall, pain frequency and HRQoL were the factors most strongly associated with outcomes after 12 months, and can easily captured during history taking in a consultation. Sex and older age are two factors which had very weak associations with outcomes.

It is unclear if the association between age and poorer prognosis is caused by older adolescents having a longer baseline duration of pain, or other neurobiological, psychological or contextual factors that develop/change during adolescence. Regarding sex, a previous systematic review found inconsistent findings from five single studies in a range of musculoskeletal conditions[14]. We were able to pool individual participant data from seven studies and found approximately 10 points worse pain and function at follow-up for females. Non-specific anterior knee pain (patellofemoral pain) is more common among females[31] and has a high propensity for chronicity[26], and the majority of participants included in the current investigation as a result were female.

Psychological characteristics were identified as potentially important candidate prognostic variable from our stakeholder involvement. Moderate symptoms (relative to none) appeared associated with physical function. This may be due to the link between anxiety/depression and physical inactivity[5]. Being sports active at baseline did tend to be associated with better function in the long-term Interestingly, a similar association with psychological characteristics was not found for the outcome of pain, despite beliefs that chronic pain and psychological conditions/mood disorders may share common neurobiology[3; 18; 35] This area warrants future investigation, given the association between chronic pain and psychological disorders such as anxiety and depression. For other chronic pain conditions, reviews indicate that psychological therapies appear effective only immediately post treatment, and not at follow-up[9].

Comparison to previous studies

This study is the most comprehensive analysis of prognostic factors in the field of adolescent musculoskeletal pain condition to date. A previous systematic review on prognosis in general adolescent musculoskeletal pain[14], was unable to pool data leaving a lot of descriptive

reports and inconsistent findings due to including study-level data that used different reporting of results. Our IPD approach enabled us to circumvent these limitations and test 14 different prognostic factors for outcomes of both pain and physical function in a larger number of cohorts. Despite some problems with risk of bias in the study attrition domain, our results confirm single studies that identified pain severity, and HRQoL as prognostic factors[26]. Our analysis provided evidence of robustness of potential prognostic factors across both pain and physical function. This is important as the previous review on prognosis across MSK conditions identified no study which examined prognostic factors for disability. Interestingly, assumptions include BMI, knee strength and pain sensitivity as prognostic factors, but our IPD contradicts this. Factors such as BMI, knee strength and pain sensitivity did not have any significant or clinically relevant association with outcomes. The lack of association with BMI is similar to what has been found in other MSK conditions in youth[14]. We confirmed the previously reported lack of association between pain sensitivity and outcomes [13] with data from four independent cohorts. However, this single cohort [13] found temporal summation of pain was associated with outcomes following treatment. However, this was not evaluated in this IPD as there were no other studies to pool the data with.

Strengths and Limitations

For most prognostic factor and outcome association, the overall RoB was “moderate” except for associations that involved self-report BMI and pain duration where it was “high”. On a study level the highest risk of bias was generally in the domain "study attrition" where most had a moderate or high risk of bias. We did not include treatment received in original studies in the models, as prognostic factors were measured at baseline prior to any treatments so treatment is not expected to affect the prognostic factor of interest. We used pain intensity

and function as outcomes of interest. However, it must be noted that patients rate the experience of pain differently depending on for example prior pain experiences and psychological factors. This could not be taken into account in our analyses.

The heterogeneity in the available data made it impossible to test the independent effects of the prognostic factors in a multivariable analysis. Future validation studies are needed. Regarding the generalisability of our data, we received all data requested. Anterior knee pain, the most common type of pain in this population comprised of the majority of data. Conditions such as Sindig Larsen johansen or patellar tendinopathy constituted a minority of cases in the individual participant data which may limit generalisability to these conditions. Furthermore, a number of the cohorts originated in Denmark which may make the current results less generalizable to other countries.

Conclusion and implications

Despite the high prevalence of adolescent knee pain, limited research exists on this young population and their prognosis. This IPD found that >50% of adolescents with knee pain also 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 function at 12-months. This is important, because if factors associated with chronic pain are known, clinicians can intervene early to reduce the likelihood of future morbidity and mortality. Studies are urgently needed to improve care for these adolescents, such as how to design and deliver personalised interventions and facilitate the clinical decision-making process. This comprehensive IPD provides a step change, and can facilitate discussions on realistic expectations about the prognosis and improvements over the short and longer term.

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References

[1] Abo-Zaid G, Sauerbrei W, Riley RD. Individual participant data meta-analysis of prognostic factor studies: state of the art? BMC Med Res Methodol 2012;12:56.

[2] Artus M, Campbell P, Mallen CD, Dunn KM, van der Windt DAW. Generic prognostic factors for musculoskeletal pain in primary care: a systematic review. BMJ Open 2017;7(1):e012901.

[3] Boakye PA, Olechowski C, Rashiq S, Verrier MJ, Kerr B, Witmans M, Baker G, Joyce A, Dick BD. A Critical Review of Neurobiological Factors Involved in the Interactions Between Chronic Pain, Depression, and Sleep Disruption. Clin J Pain 2016;32(4):327-336.

[4] Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. Stat Med 2017;36(5):855-875.

[5] Choi KW, Chen CY, Stein MB, Klimentidis YC, Wang MJ, Koenen KC, Smoller JW. Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study. JAMA Psychiatry 2019;76(4):399-408.

[6] de Lucena GL, dos Santos Gomes C, Guerra RO. Prevalence and associated factors of Osgood-Schlatter syndrome in a population-based sample of Brazilian adolescents. Am J Sports Med 2011;39(2):415-420.

[7] Debray TP, Moons KG, Abo-Zaid GM, Koffijberg H, Riley RD. Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? PLoS One 2013;8(4):e60650.

[8] Dissing KB, Hestbaek L, Hartvigsen J, Williams C, Kamper S, Boyle E, Wedderkopp N. Spinal pain in Danish school children - how often and how long? The CHAMPS Study-DK. BMC Musculoskelet Disord 2017;18(1):67.

[9] Fisher E, Law E, Dudeney J, Palermo TM, Stewart G, Eccleston C. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev 2018;9(9):Cd003968.

[10] Green DJ, Lewis M, Mansell G, Artus M, Dziedzic KS, Hay EM, Foster NE, van der Windt DA. Clinical course and prognostic factors across different musculoskeletal pain sites: A secondary analysis of individual patient data from randomised clinical trials. Eur J Pain 2018;22(6):1057-1070.

[11] Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158(4):280-286.

[12] Hebert JJ, Møller NC, Andersen LB, Wedderkopp N. Organized Sport Participation Is Associated with Higher Levels of Overall Health-Related Physical Activity in Children (CHAMPS Study-DK). PLoS One 2015;10(8):e0134621.

[13] Holden S, Rathleff M, Thorborg K, Holmich P, Graven-Nielsen T. Mechanistic pain profiling in young adolescents with patellofemoral pain before and following treatment: a prospective cohort study. Pain 2020.

[14] Huguet A, Tougas ME, Hayden J, McGrath PJ, Stinson JN, Chambers CT. Systematic review with meta-analysis of childhood and adolescent risk and prognostic factors for musculoskeletal pain. Pain 2016;157(12):2640-2656.

[15] Junge T, Runge L, Juul-Kristensen B, Wedderkopp N. Risk Factors for Knee Injuries in Children 8-15 Years: The CHAMPS-Study DK. Med Sci Sports Exerc 2015;48(4):655-662.

[16] Kamada M, Abe T, Kitayuguchi J, Imamura F, Lee IM, Kadowaki M, Sawada SS, Miyachi M, Matsui Y, Uchio Y. Dose-response relationship between sports activity and musculoskeletal pain in adolescents. Pain 2016;157(6):1339-1345.

[17] Kastelein M, Luijsterburg PA, Heintjes EM, van Middelkoop M, Verhaar JA, Koes BW, Bierma-Zeinstra SM. The 6-year trajectory of non-traumatic knee symptoms (including patellofemoral pain) in adolescents and young adults in general practice: a study of clinical predictors. Br J Sports Med 2015;49(6):400-405.

[18] Lumley MA, Cohen JL, Borszcz GS, Cano A, Radcliffe AM, Porter LS, Schubiner H, Keefe FJ. Pain and emotion: a biopsychosocial review of recent research. J Clin Psychol 2011;67(9):942-968.

[19] Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, Reitsma JB, Collins GS. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med 2014;11(10):e1001744.

[20] Rathleff CR, Olesen JL, Roos EM, Rasmussen S, Rathleff MS. Half of 12-15-year-olds with knee pain still have pain after one year. Dan Med J 2013;60(11):A4725.

[21] Rathleff M, Holden S, CL. S, Olesen J, Jensen M, Roos E. Five-year prognosis and impact of adolescent knee pain: a prospective population-based cohort study of 504 adolescents in Denmark. BMJ Open 2019.

[22] Rathleff M, Winiarski L, Krommes K, Graven-Nielsen T, Hölmich P, Olesen J, Holden S, Thorborg K. Pain, sports participation, and physical function in 10-14 years olds with Patellofemoral Pain and Osgood Schlatter: A matched cross-sectional study of 252 adolescents. J Orthop Sports Phys Ther 2020 50(3):149-157.

[23] Rathleff MS, Bandholm T, McGirr KA, Harring SI, Sorensen AS, Thorborg K. New exercise-integrated technology can monitor the dosage and quality of exercise performed against an elastic resistance band by adolescents with patellofemoral pain: an observational study. J Physiother 2016;62(3):159-163.

[24] Rathleff MS, Graven-Nielsen T, Holmich P, Winiarski L, Krommes K, Holden S, Thorborg K. Activity Modification and Load Management of Adolescents With Patellofemoral Pain: A Prospective Intervention Study Including 151 Adolescents. Am J Sports Med 2019;47(7):1629-1637.

[25] Rathleff MS, Rathleff CR, Holden S, Thorborg K, Olesen JL. 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 Feasibility Stud 2018;4:73.

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

[27] Rathleff MS, Roos EM, Olesen JL, Rasmussen S. High prevalence of daily and multi-site pain--a cross-sectional population-based study among 3000 Danish adolescents. BMC Pediatr 2013;13:191.

[28] Rathleff MS, Roos EM, Olesen JL, Rasmussen S. Exercise during school hours when added to patient education improves outcome for 2 years in adolescent patellofemoral pain: a cluster randomised trial. Br J Sports Med 2015;49(6):406-412.

[29] Rathleff MS, Roos EM, Olesen JL, Rasmussen S, Arendt-Nielsen L. Self-reported Recovery is Associated With Improvement in Localized Hyperalgesia Among Adolescent Females With Patellofemoral Pain: Results From a Cluster Randomized Trial. Clin J Pain 2016;32(5):428-434.

[30] Rathleff MS, Samani A, Olesen JL, Roos EM, Rasmussen S, Madeleine P. Effect of exercise therapy on neuromuscular activity and knee strength in female adolescents with patellofemoral pain-An ancillary analysis of a cluster randomized trial. Clin Biomech (Bristol, Avon) 2016;34:22-29.

[31] Rathleff MS, Vicenzino B, Middelkoop M, Graven-Nielsen T, van Linschoten R, Holmich P, Thorborg K. Patellofemoral Pain in Adolescence and Adulthood: Same Same, but Different? Sports Med 2015;45(11):1489-1495.

[32] Rathleff MS, Winiarski L, Krommes K, Graven-Nielsen T, Holmich P, Olesen JL, Holden S, Thorborg K. Activity Modification and Knee Strengthening for Osgood-Schlatter Disease: A Prospective Cohort Study. Orthop J Sports Med 2020;8(4):2325967120911106.

[33] Rosenbloom BN, Rabbitts JA, Palermo TM. A developmental perspective on the impact of chronic pain in late adolescence and early adulthood: implications for assessment and intervention. Pain 2017;158(9):1629-1632.

[34] Selhorst M, Rice W, Jackowski M, Degenhart T, Coffman S. A sequential cognitive and physical approach (SCOPA) for patellofemoral pain: a randomized controlled trial in adolescent patients. Clin Rehabil 2018;32(12):1624-1635.

[35] Soltani S, Kopala-Sibley DC, Noel M. The Co-occurrence of Pediatric Chronic Pain and Depression: A Narrative Review and Conceptualization of Mutual Maintenance. Clin J Pain 2019;35(7):633-643.

[36] Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. Jama 2015;313(16):1657-1665.

[37] van Middelkoop M, van der Heijden RA, Bierma-Zeinstra SMA. Characteristics and Outcome of Patellofemoral Pain in Adolescents: Do They Differ From Adults? J Orthop Sports Phys Ther 2017;47(10):801-805.

Figure legends

Figure 1. PRISMA-IPD Flowchart

Figure 2. Distribution of age (bottom left pane), body mass index (top left pane), pain duration (top right pane) and average physical activity* (bottom right pane) derived from the included individual participant data. Solid horizontal lines indicate median value.
*physical activity data is based on self-report data available from N = 351 participants

Figure 3. Mean (95% CI) observed values for pain intensity (left panel) and function (right panel) from baseline to short and long-term follow-up. Grey dashed lines indicate individual studies, black line (bold with crosses) indicates group average.

Figure 4. Coefficient and 95% confidence intervals for each prognostic factor-outcome relation tested in the primary analysis. Left hand panel shows prognostic factor – outcome relations for pain intensity (0-100-point scale), with values to the left indicating improvements (i.e. decrease in pain) per unit change in prognostic factor. The right-hand panel shows function measured by the Knee Osteoarthritis Outcome Score (KOOS)

Sport/Rec sub-scale (0-100-point scale), with values to the right indicating improvements (i.e. increases in function) per unit change of the prognostic factor.

Figure 5. Coefficient and 95% confidence intervals for each prognostic factor-outcome relation tested in the secondary analysis for short term outcomes. Left hand panel shows prognostic factor – outcome relations for pain intensity (0-100-point scale), with values to the left indicating improvements (i.e. decrease in pain) per unit change in prognostic factor. The right-hand panel shows function measured by the Knee Osteoarthritis Outcome Score (KOOS) Sport/Rec sub-scale (0-100-point scale), with values to the right indicating improvements (i.e. increases in function) per unit change of the prognostic factor.

Table 1. Characteristics of included participants and studies. Descriptive data are mean (SD) unless otherwise stated.

Study	**Country**	**Number of adolescent participants with knee pain**	**Age (years)**	**Female** Sex **(%)**	**BMI**	**Short-term time-point (closest to three months)**	**Short-term response rate (N (%))**	**Long-term time-point (closest to 12 months)**	**Long-term response rate (N (%))**
Rathleff et al. 2013 DMJ [20]	Denmark	215	13.7 (0.9)	57%	19.4 (2.8)	NA	NA	12months	164 (76%)
CHAMPS – DK cohort 2015 [15]	Denmark	172	11.7 (1.2)	60%	NA	NA	NA	12 months	208 (100%)
Rathleff et al. 2015 BJSM [28]	Denmark	121	17.2 (1.0)	80%	21.7 (2.9)	3 months	101 (83%)	12 months	110 (91%)
Kastelein 2015 – HONEUR [17]	Netherlands	65	14.9 (2.3)	52%	21.0 (3.29	3 months	41 (63%)	12 months	48 (74%)
Rathleff et al. 2016 CJP [29]	Denmark	57	17.3 (1.1)	100%	20.5 (1.9)	3 months	39 (68%)	12 months	52 (91%)
Rathleff et al. 2016 Clin Biomech [30]	Denmark	57	17.2 (1.1)	100%	20.6 (1.9)	3 months	47 (82%)		
								NA	NA
Rathleff et al. 2016 J Phys [23]	Denmark	20	17.4 (1.0)	100%	21.9 (2.4)	6 weeks	14 (70%)	NA	NA
Rathleff et al. 2016 AJSM [26]	Denmark	504	17.3 (1.0)	72%	22.0 (3.1)	NA	NA	24 months	356 (71%)
Middelkoop et al 2017 – TripleP [37]	Netherlands	28	16.8 (1.8)	52%	20.5 (3.4)	3 months	17 (61%)	12 months	17 (61%)
Rathleff et al. 2018 Pilot and feasibility [25]	Denmark	20	14.6 (1.1)	80%	19.7 (2.1)	3 months	18 (90%)	6 months	18 (90%)
Selhorst et al. 2018 [34]	United States of America	55	14.3 (1.8)	66%	23.9 (5.9)	6 weeks	46 (84%)	6 months	46 (84%)
Rathleff et al 2019 OJSM [32]	Denmark	51	12.7 (1.1)	49%	20.3 (3.2)	3 months	45 (88%)	12 months	42 (82%)
Rathleff et al. 2019 AJSM[24]	Denmark	151	12.6 (1.2)	76%	19.1 (2.7)	3 months	133 (88%)	12 months	120 (79%)

Identifications

Screening and eligibility

Available data

Analysed data

Collaborative group

Studies identified through sources including authors own network & requests sent to researchers

18 potentially eligible studies identified

Systematic search

N=429 identified through database search for reviews on prospective studies of adolescent knee pain

56 full texts reviewed for potentially relevant articles

14 potentially eligible studies identified including forward citation tracking

Hand search & forward citation tracking relevant reviews (N = 6 potentially eligible studies identified)

9 duplicate studies identified through both sources

23 potentially eligible studies after duplicates removed

23 potentially eligible studies screened by full-text

N =10 Studies excluded:
Wrong design (N=4)
Incorrect outcomes (N=2)
Not non-traumatic knee pain (N=4)

Sought IPD data from 13 studies eligible for inclusion

IPD data provided by 13 studies (N = 1516 participants)

All data analysed (N=1516)
Primary endpoint:
N=772 pain intensity;
N = 877 function;
N = 1246 knee pain (dichotomous outcome)