Prognostic Factors and Treatment Effect Modifiers for Children and Adolescents with Musculoskeletal Pain: a Protocol for a Systematic Literature Review

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Amendments
The protocol does not represent as an amendment of a previously published protocol. The protocol will be registered in the International Prospective Register of Systematic Reviews (PROSPERO). We have no intention of undertaking protocol amendments after registration.

Introduction
Musculoskeletal (MSK) pain is common among children and adolescents across different populations and nationalities and increases exponentially around the age of 10–14. A recent systematic review reported that two out of every three adolescents report pain with MSK pain as the most common1. Similar findings have been reported in a Danish context where Rathleff et al. reported that two out of every three adolescents reported pain5. The most common pain sites were the knee, back and shoulder, with 33% of all adolescents reporting knee pain6. A two-year prospective cohort study among 1300 Danish adolescents from 11 to 13 years of age showed that 79% of the female participants reported neck pain and 61% reported mid back pain during this period7. MSK pain can have a major impact on the adolescents’ lives and cause them to withdraw from school, social and athletic activities8. The quality of life in adolescents with MSK pain is hence lower than of adolescents without MSK pain9.

Musculoskeletal pain, including knee pain, has previously been described as a self-limiting condition10, but several studies indicate otherwise. In a one-year cohort study of 564 11 year olds with MSK pain, half of the participants still reported pain at follow-up11. Prospective cohort studies from general practice show that between 16–32% of patients with knee pain still report knee pain one year later10,12. In accordance with this, a new study on the clinical course of knee pain showed that 29% of participants aged 10-15 years still reported knee pain after six months13. Kastelein et al. furthermore showed that 21% of patients aged 12-35 years had persistent knee pain six years after they initially contacted their GP10. Collectively, these studies highlight that a significant proportion of adolescents will continue to report pain even years later. The question is who are the adolescents with a particular high risk of long-lasting MSK pain?

There is a paucity of systematic reviews on prognostic factors for MSK pain in children and adolescents. A systematic review on adults in primary care with MSK pain found that higher pain severity at baseline, longer pain duration, multiple-site pain, anxiety and/or depression, higher somatic perceptions and/or distress, low social support, higher baseline disability, and greater movement restriction were all associated with an unfavorable outcome14. Systematic reviews on adults with knee pain suggest that low/middle education level, non-skeletal comorbidity, duration of knee symptoms of >3 months, bilateral knee symptoms, self-reported warm knee, history of non-traumatic knee symptoms and valgus alignment are associated with an unfavorable outcome15. For persistence of low back pain among adults, high
Evidence was found that fear-avoidance beliefs and meagre social support at work were associated with an unfavorable outcome. It is unlikely that all these prognostic factors for MSK pain among adults are also valid among children and adolescents.

Given the consequences and issues related to children and adolescents with MSK pain it is important that researchers illuminate prognostic factors for an unfavorable outcome. The aim of this study is to conduct a systematic review on children and adolescents with MSK pain with a view to determine which baseline patient characteristics are: (i) associated with a poor outcome on follow up regardless of which treatment was provided (prognosis); or (ii) associated with a successful outcome to a specific treatment (treatment effect modifiers).

**Methods**
The review protocol follows the PRISMA-P 2015 statement while the study will be reported using the PRISMA guidelines.

**Eligibility criteria**

**Participants**
Prospective cohort studies (including randomized trials) with a population of children and adolescents aged 10-19 years will be included in this systematic review if they report prognostic factors or treatment effect modifiers (e.g. baseline variables that are associated with outcome). The participants must all have some form of self-reported MSK pain at recruitment. MSK pain is defined according to the International Association for the Study of Pain, IASP as: “pain arisen from muscle, tendon, bone and joint. Excluded from the definition is pain due to serious local causes, such as tumors, fractures, or infections, and systemic and neurological causes”. Types of pain are named according to the region affected, e.g. back pain, neck pain, shoulder pain, elbow pain, buttock pain, hip pain, knee pain, and ankle pain.

Inclusion criteria:
- 10 to 19 years of age
- Self-reported musculoskeletal pain

Exclusion criterion:
- Younger than 10 or older than 19 years of age

**Interventions**
All interventions used to treat MSK pain in children and adolescents will be included. Conservative as well as non-conservative interventions. Conservative intervention is defined as utilization of non-surgical treatment options, such as but not limited to the following: physiotherapy, immobilization, bandaging, drug therapy, wait and see and injections with NSAID, glucocorticoid/steroid - intraarticular, intramuscular and intratendinous. We will also include studies that do not contain interventions.

**Comparators**
We expect that most studies have not used a comparator as they are prospective cohort studies. If the study design is a randomized trial, we will include all types of comparators.

**Outcome**
We will search for all baseline patient characteristics that are: (i) associated with a poor outcome on follow up regardless of which treatment was provided (prognosis); or ii) associated with a successful outcome to a specific treatment (treatment effect modifiers). These may include intrinsic variables (such as age, height, weight, pain intensity, pain duration and similar) or extrinsic variables (such as social status, parental education, sports participation and similar). As a secondary outcome we will include the proportion that report themselves free of MSK pain at follow-up in the included studies.
Timing
We will include patient characteristics that are associated with both short and long term outcomes. These will be divided in three endpoints i.e. short term (3 months) medium term (3-12 months) and long term (more than 12 months).

Setting
There will be no restrictions in type of setting.

Language
Articles reported in English, German, Danish, Norwegian, Swedish, French, Spanish, Japanese, Chinese, Thai, Arabic, Persian, Turkish and Hindi will be included.

Information sources
This systematic review search will be conducted in the following electronic databases; Medline, Embase, Cinahl, Web of Science, Cochrane and SportDiscus without limitation on dates.

Search strategy
The search strategy is divided into 7 parts. 1. Pain, 2. Musculoskeletal defined in components, 3. Anatomic regions, 4. Musculoskeletal conditions in general and those common among children and adolescents, 5. Children and adolescents and synonyms, 6. Predictive factors and synonyms and 7. Final search string to be applied in above mentioned electronic databases and also tested in Medline with 5336 hits.

Medline Search (pilot search performed on the 30th of May 2016 to test the search strategy)
1. Pain/ 646496
2. Musculoskeletal OR Joint OR Tendonitis/ 477245
3. Neck OR Cervical OR Jaw OR Limb OR Shoulder OR Arm OR Elbow OR Wrist OR Carpal OR Hand OR Finger OR Collar OR Vertebral OR Lumbar OR Back OR Hip OR Knee OR Patell* OR Retropatellar OR Leg OR Ankle OR Foot OR Heel/ 2025078
4. Arthritis OR Arthralgia OR Fibromyalgia OR Osteochondritis OR Osgood OR Growing Pain OR Scheuermann/ 308148
5. Juvenile OR Adolescen* OR Preadolescence OR Preschool OR Child* OR Prepubertal OR Kids OR Pediatric OR Paediatric OR Youth/ 3380052
6. Predict* OR Long-term OR Cohort OR Prognosis OR Prognostic OR Effect/ 5393422
7. #1 AND #2 AND (#3 OR #4) AND #5 AND #6/ 5336

Study records
Data management
To reveal overlaps and extract duplicated references from the rest, EndNote will be used as a tool toward organization of collected references and abstract and full text screening. Author names will be juxtaposed. A PRISMA flow diagram will be created.

Selection process
The process of study selection will be conducted by two reviewers (NP and AR). They will independently identify studies from the electronic database search and screen title and/or abstract with relevance to the question: what are the prognostic factors for children and adolescents with MSK pain? Studies kept after the primary inclusion will be screened by full text and then selected for a final inclusion. Any excluded studies will be recorded, including a reason for the exclusion. There will be no blinding of the review authors to the journal titles, authors or institutions. Reference lists of all included studies will be screened for eligible publications that may have been missed during the initial search.
Any disagreements inside the reviewer group will lead to involvement of a third reviewer (MSR).

Data collection process
NP will extract data using a pre-defined data extraction form (Appendix 1), inspired by The Cochrane Collaboration, Data collection form for intervention reviews: RCTs and non-RCTs. All the extracted data will afterwards be validated by a second person (MSR). The collected data will include a description of the participants, setting (e.g. general practice or population-based cohort) and results (including all patient characteristics tested for association with outcome).

We will contact the corresponding author with a request of information, if any concerning ex. intervention or outcome is missing from an included study. The intention is to increase thoroughness of description of intervention and outcome in this study.

Data items
Inclusion of studies examining children and adolescents with MSK pain aged 10 to 19 years. If a study reports on an age range that extends this, we will contact the corresponding author and ask for data on the 10-19 year olds. The requested data will be included if it can be retrieved within one month from inquiry.

Outcomes and prioritization
There will be no prioritization of outcomes.

Risk of bias in individual studies
The QUIPS risk of bias tool for prognostic studies will be used to assess the quality of each paper. This tool contains items and considerations for six bias domains i.e. study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting (Appendix 2). Each of the six potential bias domains will be rated by NP as high, moderate, or low risk of bias. When assessing the overall risk of bias in each study, a study will be described with a low risk of bias when either a) most of or b) the most important (determined a priori) or c) all of the six bias domains are rated with a low risk of bias. The same applies to moderate and high risk of bias.

Data synthesis
A narrative synthesis is planned, for the reason of expected substantial heterogeneity in our results. If the prognostic factors or treatment effect modifiers are adequately homogenous, we will conduct a meta-analysis and pool the individual variables. Data will be divided into two main separate groups: prognostic factors and treatment effect modifiers and then sub-grouped into regions of MSK pain, gender and age.

Dissemination of results
The manuscript will be submitted for publication in an appropriate peer-reviewed journal. In addition to this we will produce material to be distributed to general practitioners and other health care providers, who manage children and adolescents with MSK pain. This will be done in the form of a short animation video, visualizing the main study results from the systematic review. The animation will be distributed through social media, websites and patient associations. This will ensure dissemination of our results to our target audience.
Appendix 1
Data Extraction Form

Review title:
Study ID (surname of first author and year):
Reviewer and form completion date:

General Information
- Author contract details
- Publication type + study funding source

Eligibility
- Inclusion criteria
- Exclusion criteria
- Type of study
- Participants
- Intervention
- Outcome

Population and Setting
- Total no. of participants at start of study
- Population description (from which study are participants drawn from)
- Method of recruitment
- Setting (location and social context)
- Inclusion criteria
- Exclusion criteria

Description of participants
- Age + gender
- Race + ethnicity, including country of origin
- Number of years living in Denmark IF parents non Danes
- Weight + height + BMI
- Severity of MSK pain (intensity, frequency and other ways descriptive of pain severity)
- Institution (elementary school, high school, university, other educational institution)
- Parental education and profession
- Trauma or surgery to musculoskeletal region
- Neurologic illness + rheumatologic illness
- Other concurrent illness/comorbidity
- Congenital hip dislocation
- Smoking + alcohol + substance abuse
- Hypomobility or hypermobility (criteria of either modified version of Carter and Wilkinson or Beighton Scale)
- Puberty status, Tanner stages
- Medicine, vitamin supplements
- Sports/practice vigorous exercise

Psychosomatic symptoms
- Headache + abdominal pain
- Depressive feelings (Children’s Depression Inventory (CDI)25)
- Difficulties in falling asleep +/- waking up during the night +/- day tiredness
- Reported school absence

**Intervention**
- Description
- Location and duration
- Frequency and duration of each episode
- Provider (profession, training, ethnicity, race)

**Outcome**
- Persistent MSK pain (Y/N)
- Time point measured
- Unit of measurement (VAS or other)

**Methods**
- Study aim
- Study design
- Start date + end date
- Duration of participation
  - Up to 3 months follow up
  - 3-12 months follow up
  - more than 12 months follow up

**Risk of bias assessment, to be judged as low, unclear or high**
- Selection bias
- Performance bias
- Detection bias
- Incomplete outcome data (attrition bias)
- Selective outcome reporting (reporting bias)
  - Interviewer bias

**Other information**
- Key conclusions of study author
- References to other relevant studies
### Appendix 2  
**QUIPS**

#### Domains:

<table>
<thead>
<tr>
<th>Items for Consideration:</th>
<th>Ratings:</th>
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<tbody>
<tr>
<td><strong>Study Participation</strong></td>
<td></td>
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<tr>
<td>a. Adequate participation in the study by eligible persons</td>
<td>High bias:</td>
</tr>
<tr>
<td>b. Description of the source population/population of interest</td>
<td>Moderate bias:</td>
</tr>
<tr>
<td>c. Description of the baseline study sample and recruitment</td>
<td>Low bias:</td>
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<tr>
<td>d. Adequate description of the sampling frame and recruitment</td>
<td></td>
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<tr>
<td>e. Adequate description of the period and place of recruitment</td>
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<tr>
<td>f. Adequate description of inclusion and exclusion criteria</td>
<td></td>
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<tr>
<td><strong>Study Attrition</strong></td>
<td></td>
</tr>
<tr>
<td>a. Adequate response rate for study participants</td>
<td>High bias:</td>
</tr>
<tr>
<td>b. Description of attempts to collect information on participants who dropped out</td>
<td>Moderate bias:</td>
</tr>
<tr>
<td>c. Reasons for loss to follow-up are provided</td>
<td>Low bias:</td>
</tr>
<tr>
<td>d. Adequate description of participants lost to follow-up</td>
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<tr>
<td>e. There are no important differences between participants who completed the study and those who did not</td>
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<tr>
<td><strong>Prognostic Factor Measurement</strong></td>
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<tr>
<td>a. A clear definition of the PF is provided</td>
<td>High bias:</td>
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<tr>
<td>b. Method of PF measurement is adequately valid and reliable</td>
<td>Moderate bias:</td>
</tr>
<tr>
<td>c. Continuous variables are reported or appropriate cut points are used</td>
<td></td>
</tr>
<tr>
<td>d. The method and setting of measurement of PF is the same for all study participants</td>
<td></td>
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<tr>
<td>e. Adequate proportion of the study sample has complete data for the PF</td>
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<tr>
<td>f. Appropriate methods of imputation are used for missing PF data</td>
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<tr>
<td>Outcome Measurement</td>
<td>High bias:</td>
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<tr>
<td>a. A clear definition of the outcome is provided</td>
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<tr>
<td>b. Method of outcome measurement used is adequately valid and reliable</td>
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<tr>
<td>c. The method and setting of outcome measurement is the same for all study participants</td>
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</table>

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<tr>
<th>Study Confounding</th>
<th>High bias:</th>
<th>Moderate bias:</th>
<th>Low bias:</th>
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<tbody>
<tr>
<td>a. All important confounders are measured</td>
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<tr>
<td>b. Clear definitions of the important confounders measured are provided</td>
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<tr>
<td>c. Measurement of all important confounders is adequately valid and reliable</td>
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<tr>
<td>d. The method and setting of confounding measurement are the same for all study</td>
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<tr>
<td>e. Appropriate methods are used if imputation is used for missing confounder data</td>
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<tr>
<td>f. Important potential confounders are accounted for in the study design</td>
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<tr>
<td>g. Important potential confounders are accounted for in the analysis</td>
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<tr>
<th>Statistical Analysis and Reporting</th>
<th>High bias:</th>
<th>Moderate bias:</th>
<th>Low bias:</th>
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<tr>
<td>a. Sufficient presentation of data to assess the adequacy of the analytic strategy</td>
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<td>b. Strategy for model building is appropriate and is based on a conceptual framework/model</td>
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<tr>
<td>c. The selected statistical model is adequate for the design of the study</td>
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<tr>
<td>d. There is no selective reporting of results</td>
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