The Child and Adolescent Musculoskeletal (ChiBPS) Pain cohort: what are the bio-psycho-social prognostic factors for persistent pain? Protocol for a prospective nationwide cohort study in general practice

Authors
Pourbordbari N[1], Jensen MB[1], Olesen JL[1], Holden S[1], Rathleff MS[1]

Authors and contact information
Corresponding author Negar Pourbordbari MD,
Research Unit for General Practice in Aalborg,
Department of Clinical Medicine,
Aalborg University,
Denmark.

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Introduction

Musculoskeletal (MSK) pain is common among children and adolescents across different populations and nationalities with an exponential increase in incidence around the age of 10(1-4). A systematic review investigating the prevalence of chronic pain in adolescents reported that 40% experienced musculoskeletal pain at some point during the last 6 months(3). Similarly, Rathleff et al. reported high prevalence rates in a Danish context, with two out of every three adolescents reporting to have had MSK pain at any time(5). The most common pain sites were knee, back, and shoulder, with 33% of all adolescents reporting knee pain of whom approximately 2/3 had pain weekly or more often than that(6). A two-year prospective cohort study among 1300 11 to 13-year-old Danish adolescents found that 79% of the female participants had a lifetime prevalence of neck pain and 61% mid back pain and that the pain was likely to progress, to more locations, higher frequency, and higher pain intensity over a two-year period(7). Musculoskeletal pain can have a major impact on the adolescents' lives and cause them to withdraw from school, social and athletic activities(8), (9). The quality of life for adolescents with MSK pain is also lower than of adolescents without MSK pain(4, 10).

Musculoskeletal pain in adolescents is much more persistent than commonly appreciated. It has previously been described as a self-limiting condition(11), but several studies indicate otherwise. In a cohort study of 564 11-year olds with weekly MSK pain, 50% of the participants still reported pain after one year(12). Prospective cohort studies of adults in general practice show that 16-32% of patients with knee pain still have pain after a year(11, 13). In accordance with this, Kastelein et al. found that 21% of 12 to 35-year-old patients had knee pain six years after initial general practitioner (GP) contact(11). Collectively, these studies highlight that a significant proportion of adolescents will continue to report pain even years after the initial onset of pain.

Can we identify the adolescents with a high risk of MSK pain at follow-up? Our recent systematic review on children and adolescents with MSK pain indicates that female sex, depression, anxiety, and parental pain are associated with a higher risk of MSK pain at follow-up(14). However, the validity of these prognostic factors may be questioned as they have been tested in single cohorts and not validated in new external cohorts. Moreover, in accordance with our results, other studies identify emotional problems, psychological symptoms, and frequent exercise associated to a higher risk of MSK pain at follow-up(13, 15, 16). Huguet et al. reports low to very low quality of evidence for the association between female sex, depressive feelings, frequency of pain, participation in sports and type of MSK pain and prognosis(17). Given the paucity of high-quality evidence for prognostic factors in childhood and adolescent MSK pain, robust studies are needed to further explore prognostic factors in this population(17). We want to follow up on this need and conduct a cohort study with a similar aim as in our review; to investigate prognosis in youth MSK pain. In this cohort study, we will limit our participant group to those who are 8-19 years old, because our participants have to be able to provide self-reported data on a questionnaire. We will not include participants aged 0-7 years as they will have difficulties in doing so and because they i) only represent 2% of all patients consulting GPs in Denmark, with a musculoskeletal complaint(18) and ii) were sparsely represented in our systematic review which included a total of 23.933 patients(14).

At present we lack age-specific prognostic factors in adolescents with MSK pain, although multiple prognostic factors have been identified in adult MSK pain. One systematic review found that higher pain severity upon presentation to the GP, 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 a poor prognosis(19). Systematic reviews on adult knee pain suggest an association between 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, valgus alignment and an unfavorable prognosis(20). Similar to findings in patients with adult low back pain, there was high evidence that fear-avoidance beliefs and meagre social support at work were associated with an poor prognosis(21).

According to Smith et al. there is a statistically significant association between parental pain acceptance on child functional disability, which can be mediated by parent protective behavior and child pain acceptance(22). We also know from previous research that parents' emotional, cognitive, and behavioral responses are highly influential upon children's pain and functional outcomes(23-25). What valuable information can we extract from the parents of children and adolescents with MSK pain at follow-up? These statements highlight the importance of inclusion of parent characteristics including parent pain acceptance when investigating prognostic factors.

If future studies are to tailor and target treatment for the adolescents with the highest risk of long-standing MSK pain, there is a need to identify prognostic factors for an unfavorable prognosis. The aim of this prospective cohort study is to identify the most important prognostic factors for adolescents with MSK pain in general practice.

Framing a research question

To help frame our research question, and re-evaluate its strength and feasibility, we used the PEO approach (Population, Exposure, and Outcome) in conjunction with the FINER criteria (Feasible, Interesting, Novel, Ethical, and Relevant) (26, 27).

PEO

P	Population	Children, adolescents, youth, kids, young adults, teenagers
E	Exposure	Prognostic factors, prognosis
O	Outcome of interest	MSK pain at follow-up

This leads to the **objective** of our study:

The objective of this study is to investigate which descriptive patient variables (**exposures**) among 8-19-year-old children and adolescents with self-reported MSK pain (**population**), collected at time of recruitment, are associated to a higher risk of pain (**outcome**) at follow up.

FINER

F	Feasible	-Adequate no. of subjects: 500 -Technical expertise: N/A -Affordable in time and money: Time: short amount of time spent on recruitment per patient and recruitment executed by a GP employee or the GP. Money: a minimum cost per patient, according to rates by The Committee of Multipractice Studies in General Practice. -Manageable in scope: yes
I	Interesting	-Yes, high persistence of youth MSK pain and parental child pain acceptance
N	Novel	-Yes, lack of knowledge of prognostic factors in youth MSK pain and in the setting of general practice
E	Ethical	-Yes, approved by the National Ethics Committee (NVK)(28), without cause for further application.
R	Relevant	-To scientific knowledge: yes. -To clinical and health policy: yes. -To future research: yes.

Methods

Literature search to inform this study

Before commencing the planning of this cohort study, we conducted a systematic literature search to see if other prospective studies had investigated the same research question or were planning to do so. None specifically investigated childhood or adolescent prognostic factors for MSK pain in a general practice setting, nor did any of the included studies find any treatment effect modifiers(14). The systematic review in mention, has now been completed and this cohort study is based on the findings from that review. The prognostic factors found in our review, sparsely covered ethnicity, race, parental income, and residence, which will be investigated in this study. We furthermore limit our patient group to 8-19 years in order to preserve focus on an age group for which only limited knowledge on prognostic factors is available.

Design

This study is a prospective cohort study. We will use the STROBE guideline to report our study findings(29). Below is an illustration of the time line for our study process (figure 1), inspired by the guidelines of Prognosis Research, made by the PROGRESS Group(30). For validation of the prognostic screening, we will use the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement(31) and The TRIPOD Explanation and Elaboration document(32) (Appendix 4).

(NVK) National Scientific Ethics Committee

Figure 1 Illustration of the timing of our study up to the point of publication and sharing of results.

Study setting

General practice clinics in Denmark.

Eligibility criteria for participation of participants and parents

Participants

The children and adolescents must have self-reported MSK pain at the time of recruitment and consult the GP in relation to their MSK pain. The primary reason for consultation may not necessarily be listed as MSK pain, but to be eligible for inclusion, MSK pain must be mentioned during the consultation with the GP. We do not have a pre-defined minimum or maximum MSK pain duration as a eligibility criteria and patients are eligible whether or not they have previously consulted their GP for their current MSK complaint.

We define MSK pain according to the International Association for the Study of Pain, IASP as: "pain arisen from muscle, tendon, bone, and joint". Pain due to tumor, fracture, infection, or systemic and neurological cause will be excluded. Types of pain will be labelled according to the region affected, e.g. back pain, neck pain, shoulder pain, knee pain etc(33).

After consulting the GP in relation to MSK pain, inclusion and exclusion criteria will be applied as follows:

Inclusion criteria:

- 8 to 19 years
- Self-reported musculoskeletal pain

Traumatic pain caused by soft tissue damage, contusion or otherwise (excluding fracture), will be included.

Exclusion criteria:

- 0-7 or 20+ years
- Self-reported musculoskeletal pain due to tumor, fracture, infection, or systemic and neurological causes.

The inclusion and exclusion criteria will be determined at the following time-points:

1. During screening of the time schedule at the GP clinic
2. During the consultation with the GP
3. During a phone call made by the research assistant to either the participant or her/his parent, after retrieving their completed questionnaire from the GP clinic.

Parents

Parental participation will only be eligible after inclusion of their child. If a child is not eligible, or parental consent is not acquired on behalf of the child or adolescent <15 years of age, the parent will not be eligible for inclusion.

Declarations of consent

As mentioned in FINER, this study is approved by the National Ethics Committee (NVK). Declarations of consent, provided by NVK will be collected from included participants and parents(28). Below are listed, declaration and participant age groups on which the declarations apply to.

- *Participants 18 - 19 years of age*: declaration S1 (Danish, not included).
- *Participants 8 – 17 years of age*: declaration S5, (Danish, not included) deputy consent to be provided by the holder of custody of the participant. As we have no intervention or invasive testing in our study, one parental signature is sufficient.

Interventions

We have no interventions for this study.

Recruitment process

Recruitment of GP clinics

Our aim is to recruit a sample that represents the Danish child and adolescent population with musculoskeletal pain. For this purpose, we will invite GP clinics across Denmark through random recruitment procedure using random.org. Initially, we will recruit patients from a selected group of GPs, also representing the Danish child and adolescent population. Random recruitment will follow, and be based on experience from recruitment of the initial selected group. We recruit from an unselected list of GPs from across the country, and thereby invite a heterogeneous patient population in terms of mean income, mean life expectancy, and no. of GP visits etc.

Assuring optimal recruitment of GP clinics

According to Solberg LI *7 R-factors* are important in the recruitment process and obtaining data(34). We will apply these on our recruitment process as follows:

Relationship: between the first author NP (a medical doctor, GP-trainee and clinician) and her physician-peers. NP will make first contact to the GP clinics and offer to visit or meet on Skype, if necessary. A direct recruitment of clinicians by clinicians is a successful component of recruitment of clinicians(34).

Reputation: NP is among her physician-peers known as a clinician and a researcher.

Requirements: for participation in our project is at a tolerable and moderate level and the GP decides whether to recruit patients or have an employee doing this.

Rewards: We compensate the GPs for their participation as datacollectors, with a fixed amount per included patient. This according to regulation §3 by The Committee of Multipractice Studies in General Practice(35).

Reciprocity: A collaborative process of recruitment will take place, where the recruited clinics will contribute with participants and we will present our results to them in return. A short presentation of study results to the clinics will be offered after study completion.

Resolution: A mean number of 3-7 calls is the most effective number, when recruiting(34), why we will adjust and be patient in repeating calls in attempt of a successful recruitment.

Respect: In light of the first authors (NP) profession and clinical experience in GP, aware and respectful towards her fellow GPs work schedule, why participation will not be taken for granted, but appreciated.

Included GP clinics will receive a bulletin paper for display in the waiting rooms of the clinics. This piece of paper will depict concise and short information of the study in different languages, and be used as a recruitment tool. The patient still has to visit the GP, before recruitment in this study. When a patient reads the information written in her mother tongue, she/he will potentially feel that the study is addressing her in a more personal matter, than otherwise when written in a foreign language. The intention of the bulletin is to create curiosity and interest for this study, among patients or relatives at the GPs office. This applies to everyone who knows with a child or adolescent with MSK pain.

Recruitment of participants

The GP is suggested ways of recruitment, in order to choose which best suits the infrastructure of the individual clinic.

Recruitment by an employee:

The employee executes the recruitment process with a screen of all scheduled patients for that day. This prior to the first consultation of the day. The eligibility screening has two criteria: 1. Cause for consultation including a MSK pain complaint and 2. Age 8 to 19 years. The word **MSK** is written next to the names of all eligible patients to indicate and remind the employee or the consulting GP to hand out the questionnaire to the patient, before they leave the clinic.

Not to rarely, is the cause of consultation not mentioned on the schedule. In this case, the words **OBS MSK** is written next to the patients name, notifying the GP of unknown and potential eligibility of recruitment in the study. This, presumed that the patient is 8-19 years old. The GP will screen for eligibility during the consultation with the patient and hand out the questionnaire, if eligible.

Recruitment by the GP:

The GP screens the schedule for the day, and indicates eligibility with the word **MSK** written next to the patient name.

When consulting a patient with the indicated **MSK**, the GP is reminded to hand the patient the patient material. This can be done, prior, during or in the end of a consultation while the patient is getting dressed.

The patient hands in the completed questionnaire to an employee of the clinic, who stores it in a locked place. NP or her assistant will collect this in agreement with the clinic.

It is also possible for the GP to include a patient if MSK pain comes up during the consultation, without prior mentioning and hence unknown by the employee.

We will recruit patients from September 2018 to December 2019 and expect 500 participants in the ChiBPS cohort. If we are not able to recruit the number of participants according to our sample size calculations recruitment will continue until this number is reached.

Recruitment of parents

The child must first be included in the study in order for his/her parent(s) to be eligible. For included children, we will also request data from parents during a time window of two weeks from the time of Part-Quest receival. We are not selective as to if and how many of the parents wish to participate. Parents declining participation will not cause withdrawal of the childs' eligibility or inclusion.

Contingency plan for recruitment

A tracking data base will be developed to facilitate tracking and accurate reminders to the clinics included. In the process of initial contact with the clinics, a number of expected included participants will be estimated by each clinic. The clinic will make this estimate based on its patient demography,

which can be different across clinics e.g. some clinics will have a majority of young patients and others the opposite. This number will indicate a minimum for successful recruitment.
Upon agreement, the clinics will be approached with a friendly notification, in case recruitment falls below the self-anticipated number of participants. This notification can be followed by the achieved number of recruited participants for our study so far (from all clinics involved), with the intention of sharing our successful recruitment and providing the involved clinics with a sense of ownership and motivate further collaboration. The recruitment of GP clinics will be pilot tested in 1-2 Danish GP clinics and is expected to include two patients. We will be responsive toward any unaffordable planned proceedings and comments for improvement of the recruitment process.

Baseline data and data collection
The participant schedule of assessments consists of descriptive factors, measure through a questionnaire (table 1). The three questionnaires in this study cover all the assessments in table 1, without exception. The assessments are divided in both known and unknown significant prognostic factors, known similar significant prognostic factors and finally known significant prognostic factor which we don't consider feasible in a GP setting, including reason. The table furthermore displays study period and differentiate between which assessments are measured in consideration of prognosis and which as primary and secondary outcome variables.

Participant timeline and follow-up
Participants will be followed from their initial GP consultation initiating the inclusion and onwards. The pre-defined follow-up assessments are 3, 6 (primary), and 12 months, but the cohort will be followed continuously onwards every 1-5 years. At follow-up, a research assistant working together with and supervised by NP will contact the participants on phone, to remind them of the follow-up questionnaire they will receive by e-mail. A similar process will be repeated at all follow-up time points.

Table 1 displays a schedule of participant enrolment and assessments at 3, 6 and 12-months follow-up, according to the SPIRIT guidelines(36, 37). All included participants will be registered at eligibility screen, acquired written consent, and assessments, the latter collected at both baseline and follow-up time points.

Outcomes
With our primary outcome we aim to capture pain that interferes with their everyday lives and collect the location of pain. The patient characteristics (exposures) are based on results from our systematic review(14), used in other studies (when including references).
The specific wording in the outcomes and throughout the questionnaire has been piot tested among similar aged kids and adolescents.
Our secondary outcomes highlight the development or potential aggravated psychological and social factors related to musculoskeletal pain at follow-up.

<u>Primary outcome</u>
1) MSK pain influence

> *Q: Have you experienced pain in the past two weeks that have lead you to not being able to participate in play in the school yard or sparetime activities (ex. football or other sparetime activity)(38)?*

If yes, we ask them to draw the area where they have experienced this pain with the following question:

Q: Draw on your body the areas you have had pain during the past two weeks (39).

These two questions will form our primary outcome and will be collected at all endpoints.

Secondary outcomes

1) Problemfilled MSK pain.

*Q: Draw a circle around the area of your body, where you have had the **most** problems with pain. You may only draw **one** circle.*

2) Pain intensity depicted on Faces Pain Scale Revised (FPS-R) or a 10 cm VAS scale for 8-11 and 12-19 year olds respectively (9).

Exposures

3) Self-reported anxiety.

Q: "Do you feel anxious"?

4) Self-reported depression (16).

Q: "Do you feel depressed"?

5) Self-reported low self-esteem (16).

Q: "Do you think that you have low self-esteem"?

6) Duration of troublesome pain episode (40, 41).

Q: "How long does a pain episode usually last"? (see appendix 1 and 2 for the Q in full length).

7) Frequency of troublesome pain episode (10, 42, 43).

Q: "How often do have a pain episode?" (see appendix 1 and 2 for the Q in full length).

8) Nervousness (41).

Q: "How often do you feel nervous?" (see appendix 1 and 2 for the Q in full length).

9) Higher disability index (12, 44).

Q's with yes/no answers:

1. is it difficult to fall asleep because of pain?
2. is it difficult to sit during a lesson?
3. does your pain disturb a walk longer than 1km?
4. does your pain disturb your physical exercise?
5. does your pain disturb your hobbies?

10) Higher HFAQ level (40).

Q: "Does your pain make any of the following acitivities difficult"?

1. reaching up to get a book from a high shelf
2. carrying your school bag to school
3. sitting on a school chair for a 45 min. lesson
4. standing in a queue for 10 min.
5. sitting up in bed from a lying position
6. bending down to put your socks on
7. standing up from an armchair at home
8. running fast to catch a bus
9. sport activities at school

11) Tired during the day (42, 45).

Sample-size

The sample-size in this study was determined using the two following rationales: 1) a sample-size large enough to test and replicate the analyses from previous studies on. Given the prior odds (0.5, 1, 2) of follow-up MSK pain for patients, using estimates for the prognostic factors female sex, high disability index, multisite pain, and maximum HFAQ from our systematic review(14). We gained an estimate of P-values according to sample size, for all factors individually (Appendix 8). Sample size of 500 patients, would result in an estimate of P-values below 0.05 for all prognostic factors and 2) investigate a range of new prognostic factors related to the sparsely investigated ethnicity and socioeconomic status. As no one has yet tested any of these potential important prognostic factors, and never in a general practice setting, we decided on 500 subjects. The 500 subjects was decided based on 250 cases (we assume 50% will continue to experience pain at our primary follow-up time) giving approximately 125 cases per prognostic factor (500/number of prognostic factors). The results from this analysis will be considered as explorative as no studies have previously been conducted in a general practice setting. Again, assuming 50% has pain at follow-up and 20 events for each to be tested factor are needed. The model should allow for 10-15 vairables in a multivariable logistic regression analysis. This would lead to a sample size of 480. Assumed, 5% is lost to follow-up and we have a sample-size of 504 included participants. Given the high prevalence of MSK pain at follow-up, this sample-size is feasible to include.

Questionnaires

We use three questionnaires in data collection of patient and parent characteristics: participant baseline questionnaire (Part-Quest-base) (Appendix 1), participant follow-up questionnaire (Part-Quest-follow-up) (Appendix 2), and the parent questionnaire (Pare-Quest) (Appendix 3).

In relation to our study, all these factors have an interest as to whether they present as prognostic factors in MSK pain at follow-up. We questioned whether it would be ethical to ask the question "Do you feel Danish?", why we conducted an intern survey among a group of seven immigrants and one descendant, representing five countries, from Europe and the Middle East. Among the immigrants, only one felt offended by this question. The rest did not, but two out of these said they would have felt offended, if they were born in Denmark. The descendant was not offended by the question. We decided to keep this question as part of our questionnaire and keep it applicable for all participants including the ethnic Danes, because we can't presuppose this patient groups' answer to this question. Hence the answer is a potential prognostic factor.

The questionnaires will be pilot tested among target participants; Part-Quest among 8-19-year-olds with MSK pain and the Pare-Quest among parents to children with MSK pain.

Translation of questionnaires

Our questionnaires wil be cross-cultural adaptive for participants with poor Danish language skills, insufficient to comprehend the original Danish questionnaires. In the process of translation and validation, we will translate our questionnaires both linguistically and culturally. Our three questionnaires and our bulletin will be translated from English to Danish, which is the mother tongue of the majority of our prospective participants.

The Part-Quest, Pare-Quest, and The Faces Pain Scale Revised (FPS-R) will be translated into Danish, following the general methodology of translation, back-translation, and verification (46):

1. English to Danish. Translation by a pool of 5-7 researchers fluent in English and Danish, with the latter as their mother tongue.
2. The Danish version will be read by 3-4 teachers, nurses, or physicians who are all familiar with young children's use of language, to ensure suitability for children 8-11 years of age.

3. The Danish version will be back-translated into English by a bilingual person who does not know anything about the questionnaires and has not see the original version. The original and the back-translated versions will be compared and needed adjustments will be made.
4. The Danish version will be pilot-tested with 2-3 children 8-11 years of age.

Some participants will be anticipated to have poor English and Danish language skills, insufficient to comprehend neither the original English or the Danish questionnaire.
To ensure cross-cultural adaptivity for these participants, we will translate our Danish questionnaires both linguistically and culturally by using professional, hired translators in translation of Danish to Farsi or Danish to Arabic. Translation by experienced authorized translaters with not only the target language as their mother tongue, but also familiar with the cultural aspects embedded in the target language.

Persian and Arabic FPS-R are available and will be applied in the Persian and Arabic Part-Quest versions respectively(46).

The questionnaires, will be handed to the participants and their parents in paper. If they are not able to complete the questionaires while still in the clinical setting (waiting room) and hand them to the secretary when completed, they may at a later point in time (no later than seven days) hand them in at the clinic. Seven days of response time, will be applicable also for follow-up questionnaires, before a reminder is sent out. In contrary to the baseline questionnaire, the follow-up questionnaires will be administered to the participants and parents through e-mail. If for some reason a participant do not respond within the given time limit, he/she will be reminded by e-mail or phone. This will be executed by the assistant, to ensure a satisfactory follow-up rate.

Data management
Retrieved data from both baseline and follow-up participant questionnaires and parent questionnaire will be handled as follows according to the Danish Data Protection Agency(47):
- All personal information is electronic kept in a brief dedicated to the ChiBPS study, on a server owned by Aalborg University (AAU).
- This study will be described in a secure web database, REDCap under AAU server, including who has access to the data and when data is to be deleted.
- To access AAU server and included briefs, a username and password is needed. Only involved researchers will have this access granted. The responsible author NP will store a key file and raw datafiles in a locked brief (passwords to this brief is kept on paper in an envelope in a locked cabinet in her affiliated address, which is also locked, and only researchers with relevant errand has access.

Hereafter, data will be extracted from REDCap and transferred to a table similar table 1, which will then be anonymized through participant ID.

Statistical methods
Descriptive results will be stratified by sex and MSK pain type, presented with their central estimate and appropriate measure of dispersion (95% confidence interval CI). All descriptive statistics and test will be reported in accordance to the recommendations of the STROBE statement(29).
We will test the univariate association between each potential prognostic factor as well as combining the factors in a multivariable model to show the individual contributions.
The primary analysis will be done on those who has a first time consultation with their GP concerning their current MSK pain, but all consultations will be included.

The full statistical analysis plan will be developed concurrently and will be finalized before the last patient is enrolled. We minimize information bias by using identical questionnaires for all patients included, e.g. by asking both Danes and non-Danes whether they feel Danish or not.

Ethics and dissemination

The Ethics Committee of the North Denmark Region has waived the need for ethical approval of this study (date 090617). The Multidisciplinary Committee has approved the study and recommends Danish GPs to participate (ID: MPU 20-2017 / date 100117). We are currently applying their grant, to provide compensation to the included GPs for every recruited participant they provide to the study. The Danish Data Protection Agency has similarly granted access to the project (date 101717). All mentioned reviews are executed prior to protocol registration in ClinicalTrials.gov and to enrollment of the first participant (figure 1).

The adolescents included in the ChiBPS cohort will receive usual care, i.e. as usually administered at their GP. This study will not intervene in the diagnostic and therapeutic process.

The manuscript will be submitted for publication in an appropriate peer-reviewed journal. In addition to this we will produce material for distribution among general practitioners and other healthcare providers managing children and adolescents with MSK pain. This will be done by data visualization through social media, websites and patient associations. The included participants will also be offered knowledge sharing of study results, if interested.

Since our target audience is general practitioners, we want our prognostic factors to be applicable in a GP setting in relation to the terminology they are presented in as results of this study. In order to gain recognition of this, NP will create a temporary subgrouping, based on the prognostic factors from our recent systematic review. She will convey this subgrouping to a focus group[45] consisting of 15 clinically experienced, Danish GP physician peers for feedback on the suggested terminology in subgrouping of the prognostic factors. She will ask for any concerns in comprehension including any suggestions towards an easy digestible language, in the context of general practice.

Discussion

One of the strengths of our study is the setting of general practice, which is a sparsely researched in relation to adolescent MSK pain.

Among our variables we collect data on MSK pain type and consider the answer to this question as a potential prognostic factor for MSK pain at follow-up, but can patellofemoral pain (PFP) be considered as a prognostic factor for a child with knee pain? In our recent systematic review, we found PFP diagnosis compared to other types of knee pain among 16 to 18 year olds as a prognostic factor ($p=0.01$)(14).

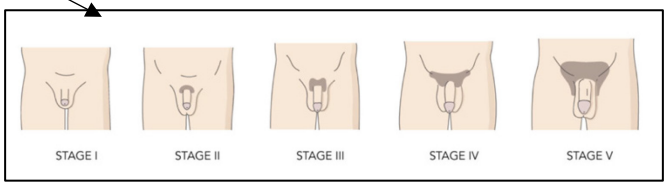
The PROGRESS Group differentiate between four types of prognostic research among which, more than one type fits our study; types one *(fundamental prognosis research)* and four *(stratified medicine research)* matches our short and long term goals, respectively(48, 49). The aim of this type of research is to identify specific biological or risk characteristics shared by subgroups of patients that predict an individual's response to treatment. This allows the clinician to tailor a treatment for the individual patient with the aim of gaining the most effective treatment benefit.

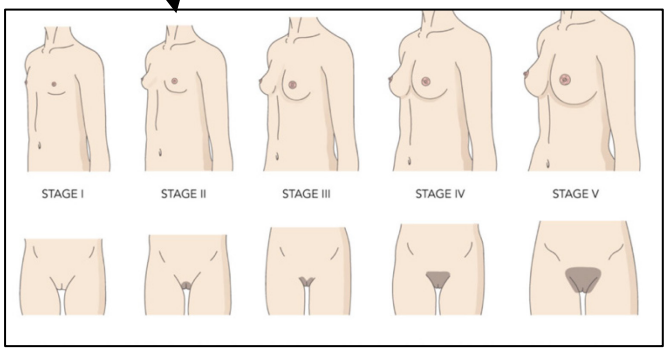
Appendix 1: Participant Baseline Questionnaire (Part-Quest-baseline)

1. Is this your first consultation with your general practitioner concerning your current musculoskeletal pain condition? Mark one answer.

o Yes o No, this is consultation number _____ with my current musculoskeletal pain condition

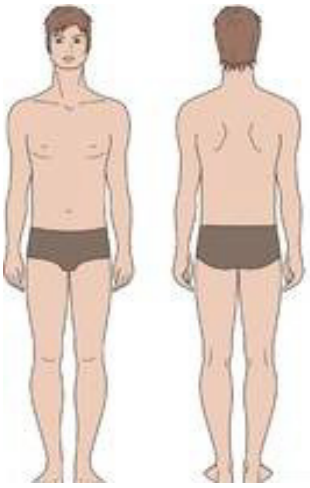
2. Draw a circle around the stage of your current physical features. Girls draw on the right figure and boys on the left.





3. How tall are you? _____ cm
4. How much do you weigh? _____ kg

Below is a drawing of **your** body.



5. Draw on your body the areas you have had pain or it has hurt, during the past two weeks. If you haven't felt hurt or pain during the past two weeks or currently, please write X here _____ (50)

6. Have you felt hurt during the past two weeks leading to not being able to participate in play in the school yard or sparetime activities (ex. football or other sparetime activity? yes _____ no _____

7. Draw a circle around the area of your body, where you have had the **most** problems with pain. You may only draw **one** circle.

8. Mark the statements below, that are true about your pain. You may mark more than one.
- o it can easily be ignored
- o it affects my concentration
- o sometimes I have to take pain medication
- o sometimes I can't attend school because of the pain.

If you are 8 to 11 years old, please answer question 9.
If you are 12 to 19 years old, please *skip* question 9 and answer question 10.

9. These faces show how much something can hurt.
This face shows no pain.

The faces show more and more pain up to this one – it shows very much pain. Circle the face that shows how much you hurt (46).

10. On a scale of 0 to 10, where 0 is no pain and 10 is the worst possible pain, circle the number that best represents your pain (9).

0 1 2 3 4 5 6 7 8 9 10

Your name _____ Your phone no. _____ Your e-mail _____

Appendix 1: Participant Baseline Questionnaire (Part-Quest-baseline)

11. How long have you had your current pain? (50)_____

12. What is the cause for your current MSK pain (ex. a fall, a hit or other)? (If you are familiar with it) (50)_____

13. How long does a pain episode usually last (40)?
o Less than 3 hours
o Less than 24h
o 1-7 days
o More than 7 days

14. How often do have a pain episode?(51)
o At least once a weak
o Less than once a week

15. How often do you feel nervous?(52)
o Often/sometimes o Seldom/never

16. Which zipcode(s) do you live in? _____

17. If not born in Denmark, in which country were you born and how long have you lived in Denmark?
o Country of birth_____ o Months/years lived in Denmark_____

18. What do you feel the most as? (53) Please answer this question, no matter country of birth.
o Danish
o Danish with foreign background
o Foreigner
o I don't know

19. How large a part of your friends have immigrant background/not born in Denmark? (53) Mark one.
o None o Almost none o Almost all o All

20. Outside school hours, how many hours a day do you spend watching TV/tablet/mobile phone/computer or do other activities when mostly sitting down(39)? _____hours/day

19. How much do you sleep on average per night(43)?
- 7 hours or less
- 8-10h
- More than 10 hours

21. Are you physical active besides school hours? (10)
o Yes
If yes, how many times per week are you physical active besides mandatory physical education during school hours?_____ _____
o No

22. How often do you drink alcohol? (39, 54)
o More than once a month
o Approximately once a month
o Less than once a month
o I have only had alcohol one time
o I have never had alcohol

23. Do you smoke cigarettes(55)?
o Yes, less than 1 a day
o Yes, 1-4 a day
o Yes, 5-9 a day
o Yes, more than 9 a day
o No, I don't smoke cigarettes

24. How many siblings (including non-biological) do you have? _____
–What number are you in your group of siblings? _____

Your name _____ Your phone no. _____ Your e-mail _____

Appendix 1: Participant Baseline Questionnaire (Part-Quest-baseline)

25. Do you expect to be free of your current pain in the future?
o Yes, in the near future o Yes, in the long term future o No

26. Why did you come to your doctor today? You may choose more than one answer with circles.
o I want my pain to stop
o I am worried about the cause of my pain
o My family made me come
o I have a personal problem
o Because of my pain, I can't use my body as I used to

27. Do you take painkillers, and what do you take? (50)
o Yes, I take _____ .
If yes, how often do you take them?_____
o Yes, I take painkillers, but don't remember the name
o No, I don't take painkillers

28. Do you expect your doctor to give you medication for your pain?
o Yes, I would like that
o No

29. If you have a job, how would you generally describe your physical activity in your job? (56) Please choose one.
o Mostly sedentary work that does not require physical exertion
o Mostly standing or walking work, which otherwise does not require physical exertion
o Standing or walking work with some lifting or carrying work
o Heavy or fast work shich is physically strenuous
o I don't have a job
o I don't know

In the following last questions mark "x" in yes or no

	Yes	No
Is your pain radiating to your legs or arms(40)?		
Do you feel anxious(57)?		
Do you think that you have low self-esteem(57)?		
Do you believe in God?		
Is it difficult to fall asleep because of pain(44)?		
Is it difficult to sit during a lesson(44)?		
Does your pain disturb a walk longer than 1 km(44)?		
Does your pain disturb your physical exercise(44)?		
Does your pain disturb your hobbies(44)?		
Do you have pain outside school hours?		
Are you tired during the day(16)?		
Do you feel depressed(44, 57)?		

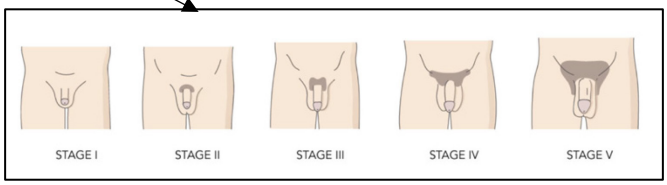
Does your pain make any of the following acitivities difficult(40)?	Yes	No
-reaching up to get a book from a high shelf		
-carrying your school bag to school		
-sitting on a school chair for a 45 min. lesson		
-standing in a queue for 10 min		
-sitting up in bed from a lying position		
-bending down to put your socks on		
-standing up from an armchair at home		
-running fast to catch a bus		
-sport activities at school		

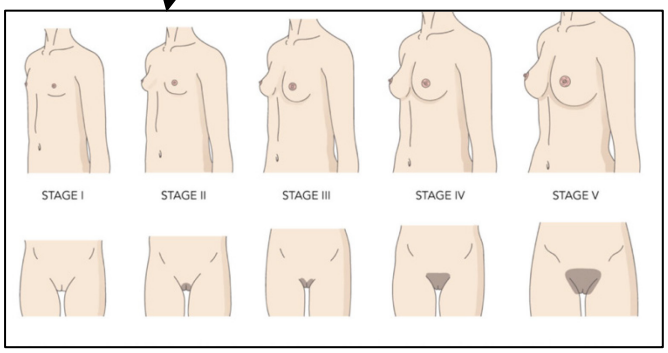
Your name _____ Your phone no. _____ Your e-mail _____

Appendix 2: Participant follow-up Questionnaire (Part-Quest-Follow-up)

1. How many consultations have you had with your general practitioner concerning your current musculoskeletal pain condition during the last 3 months(/3 months/6 months at respectively first, second, and third follow-up questionnaires)?_____

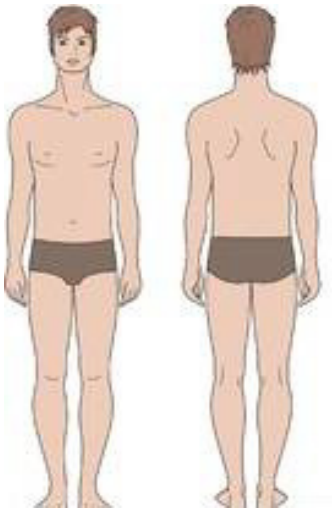
2. Draw a circle around the stage of your current physical features. Girls draw on the right figure and boys on the left.





3. How tall are you now? _____ cm
4. How much do you weigh now? _____ kg

Below is a drawing of **your** body.



5. Draw on your body, the areas you have had pain or it has hurt, during the past two weeks. If you haven't felt hurt or pain during the past two weeks or currently, please write X here _____

6. Have you felt hurt during the past two weeks leading to not being able to participate in play in the school yard or sparetime activities (ex. football or other sparetime activity? ? yes _____ no _____

7. Draw a circle around the area of your body, where you have had the **most** problems with pain. You may only draw **one** circle.

8. Draw circles around the statements that are true about your pain. You may choose more than one statement.
   - o it can easily be ignored
   - o it affects my concentration
   - o sometimes I have to take pain medication
   - o sometimes I can't attend school because of the pain

If you are 8 to 11 years old, please answer question 9.
If you are 12 to 19 years old, please *skip* question 9 and answer question 10.

9. These faces show how much something can hurt.

This face shows <u>no pain</u>.

The faces show more and more pain up to this one – it shows <u>very much pain</u>. Circle the face that shows how much you hurt.

10. On a scale of 0 to 10, where 0 is no pain and 10 is the worst possible pain, circle the number that best represents your pain (9).

0 1 2 3 4 5 6 7 8 9 10

Your name _____ Your phone no. _____ Your e-mail _____

Appendix 2: Participant follow-up Questionnaire (Part-Quest-Follow-up)

11. What is the cause for your current MSK pain (ex. a fall, a hit or other)? (If you are familiar with it)
_____

12. How long does a pain episode usually last?
o Less than 3 hours
o Less than 24 hours
o 1-7 days
o Longer than 7 days

13. How often do have a pain episode?
o I don't have breaks from the pain
o At least once a weak
o Less than once a week

14. How often do you feel nervous?
o Often/sometimes o Seldom/never

15. How large a part of your friends have immigrant background?
o None o Almost none o Almost all o All

16. Outside school hours, how many hours a day do you spend watching TV/tablet/mobile phone/computer or do other activities when mostly sitting down? _____hours/day

17. Are you physical active besides school hours?
o Yes - how many times per week are you physical active besides mandatory physical education during school hours?_____ _____
o No

18. Do you smoke cigarettes?
o Yes - how many cigarettes a day? o less than 1 o 1-4 o 5-9 o more than 9
o No

19. Do you expect to be pain free in the future?
- o Yes, in the near future
- o Yes, in the long term future
- o No

20. Why did you come to your doctor today? You may choose more than one answer with circles.
- o I want my pain to stop
- o I am worried about the cause of my pain
- o My family made me come
- o I have a personal problem
- o Because of my pain, I can't use my body as I used to

21. Do you expect your doctor to give you medication for your pain?
- o Yes, I would like that
- o No, I don't think so
- o I don't know

22. If you have a job, what do you do_____ and how many hours do you work on a weekly basis? _____

In the following last questions mark "x" in either yes or no

Does your pain make any of the following acitivities difficult?	Yes	No
-reaching up to get a book from a high shelf		

Your name _____ Your phone no. _____ Your e-mail _____

Appendix 2: Participant follow-up Questionnaire (Part-Quest-Follow-up)

	Yes	No
Is your pain radiating to your legs or arms?		
Do you feel anxious?		
Do you think that you have low self-esteem?		
Do you believe in God?		
Is it difficult to fall asleep because of pain?		
Is it difficult to sit during a lesson?		
Does your pain disturb a walk longer than 1 km?		
Does your pain disturb your physical exercise?		
Does your pain disturb your hobbies?		
Do you have pain outside school hours		
Are you tired during the day?		
Do you feel depressed?		

-carrying your school bag to school		
-sitting on a school chair for a 45 min. lesson		
-standing in a queue for 10 min		
-sitting up in bed from a lying position		
-bending down to put your socks on		
-standing up from an armchair at home		
-running fast to catch a bus		
-sport activities at school		

Your name _____ Your phone no. _____ Your e-mail _____

Appendix 3: Parent Questionnaire (Pare-Quest)

1. What is you relation to the child? (58)
   - o Mother
   - o Father
   - o Other

2. What is your biological relation to your child?
   - o Biological parent
   - o Stepparent
   - o Adoptive parent

3. How old are you? _____

4. What are your living arrangements with your child?
   - o My child does not live with me
   - o My child lives with me part time
   - o my child lives with me full time

5. What is your relationship status with your child's other parent?
   - o I am married to my child's other parent
   - o I live with my child's other parent outside marriage
   - o I am separated/divorced from my child's other parent/we don't live together

6. Where were you born? (58)
   - o Denmark
   - o Other – where? _____and how many months/years have you lived in Denmark?_____

7. Do you smoke cigarettes? yes / no

8. Have you experienced chronic pain of more than 6 months, associated with arthritis, migraine, cancer, stomach ulcers or in your muscles, bones or tendons? (59) yes / no

9. Has one or more of your child's siblings had pain in their muscle, joint, bone or tendon? yes / no

10. Do you take pain killers, when you feel pain? yes / no

11. What do you feel the most as?
   - o Danish
   - o Danish with foreign background
   - o Foreigner

12. Are you religious?
   - o Yes
   - o No
   - o I don't know

13. What is your profession? _____ and how many hours do you work on a weekly basis? _____

14. How many years of education have you had? (58)
   - o < 10 years
   - o High school or other 10-12 years
   - o Bachelor or other 13-15 years
   - o University or other 15-17 years_
   - o PhD or other > 18 years

15. What is the total income of your household b. tax? (58)
   - o <200.000DKR
   - o 200.000-350.000DKR
   - o 350.000-750.000DKR
   - o >750.000DKR

16. Has a health care professional ever given your child the diagnosis hypermobility? yes / no

17. Does your child have a measured/known vitamin D insufficiency? yes / no

18. Has your child been vaccinated (once or more) against HPV (Human Papilloma Virus)? yes / no

19. Has your child received physiotherapy in the past 6 months for the current pain condition? yes / no

20. Do you believe your child feels anxious or depressed? yes / no

21. Do you believe your child has low self-esteem? yes / no

22. Have you accepted your child's pain condition? yes / no

23. Would you like the general practitioner to give your child pain medication? yes / no

24. Why did your child visit the doctor with his/her pain condition? You may circle more than one answer.
   - o For pain relief
   - o My child is worried for the cause of pain
   - o I am worried for the cause of pain
   - o Family pressure/encouragement
   - o The pain condition is a personal problem for my child
   - o The pain condition is my personal problem
   - o My child is due to the pain condition not able to use his/her body as usual

25. Is your child rather solitary? y/n Does he/she tend to play alone? y/n Does he/she have at least one good friend? y/n Is he/she generally liked by other children? y/n Is he/she picked on/bullied by other children? y/n Does he/she get on better with adults than with other children? Mark y or n to all.

Your name _____ Your phone no. _____ Your e-mail _____

Appendix 4: TRIPOD Checklist

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	
	5b	Describe eligibility criteria for participants.	
	5c	Give details of treatments received, if relevant.	
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	
	6b	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	Explain how the study size was arrived at.	
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	
Risk groups	11	Provide details on how risk groups were created, if done.	
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	
Model development	14a	Specify the number of participants and outcome events in each analysis.	
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	
	15b	Explain how to the use the prediction model.	
Model performance	16	Report performance measures (with CIs) for the prediction model.	
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	
Implications	20	Discuss the potential clinical use of the model and implications for future research.	
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	Give the source of funding and the role of the funders for the present study.	

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

Appendix 5: Sample size

Sample size calculations for prognostic factors of adolescents with musculoskeletal (MSK) pain

Mikkel Meyer Andersen

November 23, 2017

Introduction

We want to identify prognostic factors for adolescents with musculoskeletal (MSK) pain.

DISCLAIMER

These calculations are provisional and exploratory. Many assumptions are made and they may turn out not to hold. Please use with care.

Prognostic factors

These factors are believed to be prognostic for still having MSK pain at follow-up:

- Female sex compared to male sex OR 1.78 (1.18-2.69)
  - Study id 12, study id 2 comparable
- Sleeping < 7h/day vs. 8-9 h/day OR 1.68 (1.05-2.68)
  - Study id 17, females, 2 years follow-up

It is assumed that the confidence intervals are 95% and that the prognostic factors are independent.

Power calculations

The column `frac1` refers to the fraction of the population with this prognostic factor `Level1`.

The column `OR` refers to the OR for having prognostic factor at `Level1` (instead of `Level2`).

Type	Level1	Level2	frac1	OR	OR_L	OR_U	logOR
Sex	Female	Male	0.5	1.78	1.18	2.69	0.577
Sleep	Problematic	OK	0.2	1.68	1.05	2.68	0.519

It is natural to assume that a log odds ratio follow a normal distribution. The standard deviation is approximately `(log(OR_U) - log(OR_L))/4`.

We now assume that we have n individuals at baseline. Each individual will have a prognostic factor or not (according to `frac`). For example for $n = 10$:

Sex	Sleep
Male	OK
Male	OK

Appendix 5: Sample size

Sex	Sleep
Female	OK
Female	OK
Male	OK
Female	OK
Female	OK
Female	Problematic
Female	OK
Male	OK

For each individual, we could draw log odds ratios from a normal distribution with mean $\log \overline{OR}$ and variance $s^2_{\log \overline{OR}}$, $N(\log \overline{OR}, s^2_{\log \overline{OR}})$. Note, this corresponds to assuming that both the mean and variance is known (as oppose to estimated). When we assume that the mean and variance are unknown (and estimated), then we instead draw a log odds from the prediction distribution given by

$$\log \overline{OR} + s_{\log \overline{OR}} \cdot \sqrt{1 + \frac{1}{n}} \cdot T_{n-1},$$

where T_{n-1} is a random variable that follows a t distribution with $n-1$ degrees of freedom. This is if the patient has the level of the prognostic factor that was reported. If the other level of the factor is the one in question, then $\log OR$ is 0.

Adding such random variation gives:

```
## # A tibble: 10 x 4
##       Sex       Sleep     logORs     logOR
##     <chr>       <chr>      <chr>     <dbl>
##  1   Male          OK       0, 0 0.0000000
##  2   Male          OK       0, 0 0.0000000
##  3 Female          OK 0.53, 0.00 0.5258238
##  4 Female          OK 0.68, 0.00 0.6823795
##  5   Male          OK       0, 0 0.0000000
##  6 Female          OK 0.57, 0.00 0.5736114
##  7 Female          OK 0.74, 0.00 0.7404807
##  8 Female Problematic 0.75, 0.75 1.5014547
##  9 Female          OK 0.61, 0.00 0.6106082
## 10   Male          OK       0, 0 0.0000000
```

The unknown intercept in a logistic regression is the log odds of having MSK at follow-up given all prognostic factors are at `Level2` is unknown. For notation, let $p = P(\text{MSK at follow-up} \mid \text{Sex} = \text{Male}, \text{Sleep} = \text{OK})$. Then $O = p/(1-p)$ and the unknown intercept is $\log O$. Given O, the $p = O/(1+O)$.

For odds $O = 1 = 0.5/(1-0.5)$ such that $p = P(\text{MSK at follow-up} \mid \text{Sex} = \text{Male}, \text{Sleep} = \text{OK}) = 1/2 = 0.5$:

```
## # A tibble: 10 x 4
##       Sex       Sleep     logOR         p
##     <chr>       <chr>     <dbl>     <dbl>
##  1   Male          OK 0.0000000 0.5000000
##  2   Male          OK 0.0000000 0.5000000
##  3 Female          OK 0.5258238 0.6285086
##  4 Female          OK 0.6823795 0.6642696
##  5   Male          OK 0.0000000 0.5000000
##  6 Female          OK 0.5736114 0.6395961
##  7 Female          OK 0.7404807 0.6771010
##  8 Female Problematic 1.5014547 0.8177913
```

Appendix 5: Sample size

```
##  9 Female          OK 0.6106082 0.6480795
## 10   Male          OK 0.0000000 0.5000000
```

For $O = 1/2$ such that $p = P(\text{MSK at follow-up} \mid \text{Sex} = \text{Male}, \text{Sleep} = \text{OK}) = (1/2)/(1 + (1/2)) = 0.33$, we instead get:

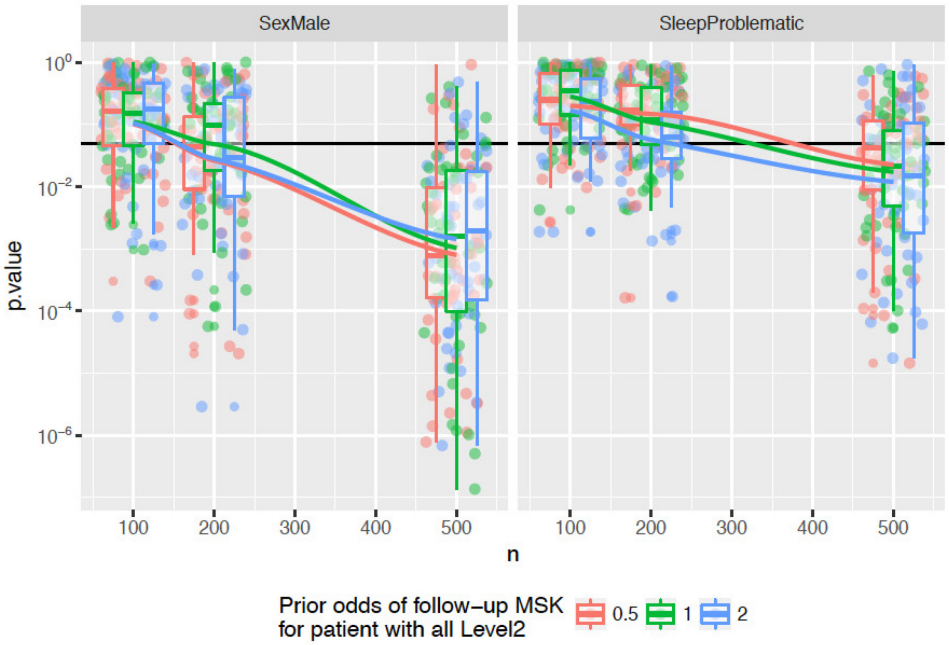
```
## # A tibble: 10 x 4
##       Sex       Sleep     logOR         p
##     <chr>       <chr>     <dbl>     <dbl>
##  1   Male          OK 0.0000000 0.3333333
##  2   Male          OK 0.0000000 0.3333333
##  3 Female          OK 0.5258238 0.4582665
##  4 Female          OK 0.6823795 0.4973081
##  5   Male          OK 0.0000000 0.3333333
##  6 Female          OK 0.5736114 0.4701516
##  7 Female          OK 0.7404807 0.5118312
##  8 Female Problematic 1.5014547 0.6917487
##  9 Female          OK 0.6106082 0.4793770
## 10   Male          OK 0.0000000 0.3333333
```

Using p, we can then further simulate an outcome:

```
## # A tibble: 10 x 5
##       Sex       Sleep     logOR         p FollowUpMSK
##     <chr>       <chr>     <dbl>     <dbl>       <dbl>
##  1   Male          OK 0.0000000 0.3333333           0
##  2   Male          OK 0.0000000 0.3333333           0
##  3 Female          OK 0.5258238 0.4582665           1
##  4 Female          OK 0.6823795 0.4973081           1
##  5   Male          OK 0.0000000 0.3333333           1
##  6 Female          OK 0.5736114 0.4701516           1
##  7 Female          OK 0.7404807 0.5118312           0
##  8 Female Problematic 1.5014547 0.6917487           1
##  9 Female          OK 0.6106082 0.4793770           1
## 10   Male          OK 0.0000000 0.3333333           0
```

This is now being done 10 times for each $n \in \{100, 200, 500\}$ and $O \in \{1/2, 1, 2\}$.

Appendix 5: Sample size



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