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PROGNOSIS AND BIO-PSYCHOSOCIAL PROGNOSTIC FACTORS IN CHILDREN AND ADOLESCENTS WITH MUSCULOSKELETAL PAIN CONSULTING GENERAL PRACTICE

BY
NEGAR POURBORDBARI

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AALBORG UNIVERSITY
DENMARK

PROGNOSIS AND BIO-PSYCHO-SOCIAL PROGNOSTIC FACTORS IN CHILDREN AND ADOLESCENTS WITH MUSCULOSKELETAL PAIN CONSULTING GENERAL PRACTICE

PHD THESIS

by

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PREFACE AND ACKNOWLEDGEMENTS

My time working on this PhD thesis does not stand alone, but is undeniably interspersed between my time working as a GP-trainee. Shortly after choosing the specialty of general practice and embarking on my GP-trainee education I also chose research, as a way back to the academic school. Not having to choose one over the other; fast forward seven years to today, nearing the end of both processes, the opportunities for upskilling and professional success I have been given have been a source of abiding gratitude.

I want to thank the one hundred children and adolescents behind this PhD study. During the past years I have text messaged you all several times each with my private phone. I have as such taken you with me everywhere I went. You were all suffering from a pain condition. Still, you chose to help us with our research. Through our conversations your vulnerability has shown. Especially after our hour-long interviews, I am humbled by your personal and raw pain experiences. I wish that I as a clinician could gain the same insight in meeting pain patients.

Michael, my main supervisor and one year junior. I am the most pleased with how you have willingly watched me do this work shaped according to my own convictions and purpose. It is partly due to this, that I look through the pages of this thesis and think of it as my work, for better or worse. I hope the experience of working together on the studies in this PhD thesis has been a positive one for the books, considering this has been your first main supervisor gig. Thank you Martin and Jens for your co-supervision. In you three gentlemen I have had a strong foundation to do some good as a PhD student.

Negar Pourbordbari

September 2022

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LIST OF PAPERS

This PhD dissertation is based on the following four manuscripts:

Pourbordbari N, Riis A, Jensen MB, Olesen JL, Rathleff MS. Poor prognosis of child and adolescent musculoskeletal pain: a systematic literature review.
BMJ Open. 2019 Jul 18;9(7):e024921. PMID: 31324677; PMCID: PMC6661566.

Pourbordbari N, Jensen MB, Olesen JL, Holden S, Rathleff MS.
Bio-psycho-social characteristics and impact of musculoskeletal pain in one hundred children and adolescents consulting general practice.
BMC Prim Care. 2022 Jan 25;23(1):20. PMID: 35172756; PMCID: PMC8790922.

Pourbordbari N, Jensen MB, Olesen JL, Holden S, Rathleff MS.
The Child and Adolescent Musculoskeletal (ChiBPS) Pain cohort: 12 months prognosis and bio-psycho-social prognostic factors in children and adolescents with musculoskeletal pain in general practice.
Submitted to PLoS ONE.

Pourbordbari N, Johansen SK, Merrild CH, Jensen MB, Olesen JL, Rathleff MS.
”It was really frustrating that I just didn’t function.” A qualitative study on adolescent long-term musculoskeletal pain in general practice.
Submitted to The Clinical Journal of Pain.

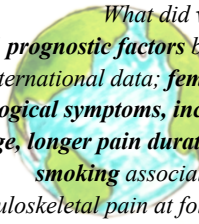
THESIS AT A GLANCE

WHAT IS THE PROGNOSIS AND THE PROGNOSTIC FACTORS IN CHILDREN AND ADOLESCENTS WITH MUSCULOSKELETAL PAIN CONSULTING GENERAL PRACTICE and how can we best explore this topic and in what best logical order?

We know from previous research that a significant proportion of adolescents report pain years after onset. We don't know who the children and adolescents with a particularly high risk of long-term musculoskeletal pain are. What is already published on this topic and how can we best investigate this?

We did a systematic literature review to explore baseline characteristics associated with musculoskeletal pain at follow-up[1]. *Why this method?* By doing a systematic review we were be able to identify, evaluate, and summarize findings of all relevant individual studies published on our topic. By doing so, we could access available evidence and build future research hereon. *What did we include in the review?* 0-19-year-olds with musculoskeletal pain at baseline and at follow-up.

What did we find?
Self-doubt, lack of accept, and **challenges in learning to live** with a long-term pain condition during adolescence underline an impact of musculoskeletal pain, that goes deeper than the pain sensation and the activity-limitation.



What did we find?
***111 prognostic factors** based on international data; **female sex, psychological symptoms, increasing age, longer pain duration** and **smoking** associated with musculoskeletal pain at follow-up.*

From our 3 studies we found that musculoskeletal pain is prevalent among children and adolescents[1,2,3], a significant proportion feel nervous or anxious[2], and more than half worry about their cause of pain[2,3]. Our understanding of adolescents' pain experience beyond worries was rather limited, however, if fear avoidance behavior persists it may facilitate transition towards chronic pain, indicating that pain cause more than just physical limitations[4]. We wanted to extract in-depth insights into the adolescents' experiences, thoughts, and beliefs on what influenced their prognosis.
How? Third, we did a qualitative semi-structured single-person interview study[4] and interviewed 13 adolescents from the ChiBPS cohort, all with pain at 6-months.

25% had pain, even **12-months after** consulting the general practitioner. Pain at 6 months follow-up was predicted most strongly by **pain episode duration longer than 7 days** and **using pain medication**, sometimes. **Feeling nervous** often/sometimes, **feeling tired during the day**, or **having difficulties falling asleep**, **carrying a schoolbag**, and **difficulties in bending to put on socks** all due to pain were all strongly associated with pain at 6-months[3].

We also found a complete knowledge gap from general practice despite the majority of adolescents consult their general practitioner, since previous studies had primarily been in secondary care or school-based populations with a strong focus on pain and a limited focus on psychosocial aspects of the pain experience. This implied further exploration of prognosis and prognostic factors for Danish children and adolescents consulting their general practitioner with musculoskeletal pain *with* selection criteria and data collection informed by the international based findings from our review.

How do we get data on an unexplored population?

We created our own cohort of 8-19-year-olds, consulting their general practitioner with musculoskeletal pain and named it the ChiBPS cohort.

How to do this?

We recruited Danish general practice clinics across the country[3]. We asked them to recruit children and adolescents consulting them with a musculoskeletal pain condition.

We recruited **100** Danish children and adolescents with musculoskeletal pain, providing data for 3 studies in this thesis.

First, we described our cohort in terms of demographics, pain features, psychosocial factors, physical activity, and expectations.

How? We did a cross sectional study using all data collected at baseline[2].

What did we find?

Knee and ankle were the two most common activity limiting pain sites. **53%** had **multi-site pain. 13%** used **pain medication** at least once a month. **1/3** were **nervous or worried/anxious.**

Second, we did a prospective cohort study.

Why a prospective cohort study design?

We used the prognostic factors we found in our systematic review and added more variables of interest and clinical relevance and measured these prior to a long-term musculoskeletal pain development. Thus gaining valuable information about long-term musculoskeletal pain incidence. We described the 3, 6, and 12-months prognosis. Our study was the first to provide evidence-based information on the prognosis of children and adolescents with musculoskeletal pain consulting the general practitioner.

What did we find?

ABBREVIATIONS

ACE:	Adverse childhood experience
BMI:	Body mass index
ChiBPS cohort:	The Child and Adolescent Musculoskeletal Pain Cohort
CI:	Confidence interval
COREQ:	Consolidated criteria for reporting qualitative research
GP:	General practitioner
HFAQ:	Hannover Functional Ability Questionnaire
IASP:	International Association for the Study of Pain
ICD:	International Classification of Diseases
IQR:	Interquartile range
MPU:	The Committee of Multipractice Studies in General Practice
MSK:	Musculoskeletal
NP:	Negar Pourbordbari
NRS:	Numerical rating scale
NSAID:	Non-steroidal anti-inflammatory drug
NVK:	The National Ethics Committee
PDI-DV:	The Pain Disability Index
OR:	Odds ratio
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-analysis
REDCap:	Research Electronic Data Capture
RoB:	Risk of bias
RR:	Relative risk
SD:	Standard deviation
SDI:	Subjective disability index
STROBE:	Strengthening the Reporting of Observational Studies in Epidemiology
QUIPS:	Quality In Prognostic Studies
WHO:	World Health Organization

FIGURES AND TABLES

1. INTRODUCTION

1.1. MUSCULOSKELETAL PAIN

Approximately 1.71 billion people have musculoskeletal (MSK) conditions worldwide[5]. According to the World Health Organization (WHO), up to one third of the world's population experience some form of chronic MSK pain[5]. Musculoskeletal pain is the biggest cause of disability internationally[6]. Overuse of imaging, surgery, and opioids are some of the common problems in MSK pain management, contributing to this major societal burden[7,8].

Many people experience persistent or recurrent MSK pain symptoms[5] and psychological and social factors play a major role in exacerbating the biological substrate of pain by influencing the perception of pain[9]. The physical, psychological, and socio-economic impact of MSK pain is supported[5] and MSK pain is as such due to a multi-factorial foundation best understood through a bio-psycho-social framework[8,10,11]. Identifying risk factors for long-term MSK pain is critical especially given that current Global Burden of Disease estimates may actually underestimate the prevalence, mortality, and morbidity of MSK pain[12].

Musculoskeletal pain as a concept is understood as pain arising from muscle, tendon, bone, and joint, as per the International Association for the Study of Pain (IASP) definition[13]. Within the International Classification of Diseases (ICD)-11 framework, chronic MSK pain is defined as persisting or recurring pain for longer than 3 months, is associated with significant emotional distress and/or significant functional disability[14]. Chronic MSK pain can be further divided in chronic primary MSK pain and chronic secondary MSK pain[15]. Chronic primary MSK pain is not better accounted for by another diagnosis[14,15] and chronic secondary MSK pain arises from an underlying disease classified elsewhere[15].

Musculoskeletal pain often concurrently affects more than one body site[16] and impacts daily functioning[17]. The bio-psycho-social framework for chronic MSK pain acknowledges that chronic MSK pain is always multifactorial[15]. This acknowledgment is the first pivotal step towards improved implementation of the bio-psycho-social model in person-centered care of musculoskeletal pain.[18]

1.2. THE CHILD AND ADOLESCENT MUSCULOSKELETAL PAIN EXPERIENCE

Acute and chronic MSK pain is common during childhood and adolescence[19-21]. Musculoskeletal pain affects half of all children and adolescents, increasing exponentially in frequency around age 10[20,22-25]. Between 8-32% of youth report weekly MSK pain and up to 39% experience monthly MSK pain[20]. Musculoskeletal pain in children and adolescents has previously been considered self-limiting[26].

However, the prognosis of adolescent MSK pain is not as favorable as once assumed. A significant proportion of adolescents report pain years after pain onset and chronic adolescent MSK pain is a serious developmental health concern[27-29]. One in every two adolescents with MSK pain continue to have pain 1-4 years after pain onset[30], thus predisposing adolescents with MSK pain to chronic pain and other chronic health conditions in adulthood[31]. Children with chronic pain are likely to report pain in adulthood[32,33] because adolescence is a life phase in which health habits are established[33] and chronic pain is furthermore a barrier for transferring positive health behavior into early adulthood[34,35]. Previous research highlights that cognitive-affective factors such as pain catastrophizing and pain-related fear, known to be associated with higher disability in youth with chronic pain are important even in the acute pain period[36].

Notwithstanding the ubiquity of pain and MSK pain primarily somatic in nature[37] it remains poorly understood in children and adolescents and as a result may be misinterpreted as inconsequential[31]. Despite children with idiopathic MSK pain have higher levels of family difficulties and stressful life events[27] little is known on characteristics among adolescents consulting their general practitioner (GP) with MSK pain[31].

As children's ability to introspect develops, they may learn to compartmentalize their experiences and the negative effects of pain on their physical, emotional, and social functioning[31]. Musculoskeletal pain in children and adolescents has previously been considered innocuous with limited long-term impact[26]. However, evidence indicates that MSK pain has a detrimental impact on the adolescents' quality of life and may cause withdrawal from school, social and athletic activities[38,39] and is associated with psychological distress[40]. Patients' own beliefs and self-management of MSK pain may predict the duration of pain as well as the impact of the pain[41,42]. Poor family functioning, stress and conflict are associated with child pain-related disability[43,44]. Potentially traumatic events during childhood and adolescence; adverse childhood experiences (ACEs) can radically and permanently disrupt a child's well-being, health, and prosperity[45]. This underlines the importance of exploring potentially traumatic experiences occurring within the first 18 years of life[46] since early life experiences are gaining more importance in health outcomes later in life[47].

The experience of chronic pain must be sufficiently concerning for the person to seek help for it[14]. Every individual's pain experience is unique[48] and a personal experience grounded in unique life experiences[49] embedded in cultural and historical context[50]. To study pain is therefore to understand the meaning of pain to those who live with it[51].

1.3. MUSCULOSKELETAL PAIN IN GENERAL PRACTICE

Musculoskeletal conditions are one of the most common causes of contact to general practice constituting up to one third of consultations and the most common reason for *repeated* consultations in general practice[52]. The management of MSK pain conditions in general practice is important. Low-value care, defined as health services that inflict little or no benefit to patients or where risk of harm exceeds probable benefit, according to best available evidence[53] is common across health systems globally, provided by all health professions and prevalent in the care of MSK conditions[54].

General practitioners are the first point of contact in many healthcare systems included for patients with pain[55]. The workload of MSK pain conditions in children and adolescents is an estimated 4-8% of UK general practice, where pain is the most frequent symptom[56]. Primary care in Denmark provide unlimited free usage of primary healthcare[57] and is positively associated with better health outcomes[58]. However, many GPs do not have adequate training and lack the skills and confidence in managing MSK conditions[59].

Previous research highlights that children, their parents, and clinicians take on different roles and responsibilities during a clinical encounter[60]. This underlines how factors important to children and caregivers like consequences on friendships, future career, finances, marital relationships of parents, and siblings are often overlooked in the assessment of pain and delivery of treatments[31].

Evidence of interventions for common MSK pain presentations point towards moderate-strong evidence for psychosocial interventions[61] however, our understanding of adolescents' pain experience beyond worries is rather limited. When assessing psychosocial symptomatology in care-seeking youth with acute MSK pain, identification of the individual's vulnerabilities in the chronic pain treatment is important[36]. As Toye et al. propose in their conceptual model; validation of the pain and self and reconnection with self and others has an empowering effect on an individual embarking a healing journey with pain[62].

Qualitative studies on coping with MSK pain reveal that adolescents experience negative emotions e.g. worry, frustration, sadness when confronted with limitations associated to their pain condition[63]. This is critical, since children exposed to environmental stressors or early adverse life events might have a higher risk of cognitive, emotional, and health problems[31]. These concerns are often not addressed during general practice consultations due to time limitation or reluctancy[64]. This leads to discrepancy between concern and elaboration[64]. Identifying and addressing negative pain beliefs becomes important in treating adolescents with MSK pain in general practice[65] to encourage acceptance and transition into self-management.

1.4. OBJECTIVES AND AIMS

The overall objective of this PhD thesis was to help fill in the knowledge gap in the literature on children and adolescents consulting general practice with MSK pain. Furthermore, we wanted to investigate the prognosis of child and adolescent MSK pain and the prognostic factors for long-term MSK pain among children and adolescents consulting their GP. We hypothesized, that by doing so, we could support the GP's assessment by offering evidence-based information on the likely prognosis and support the adolescents with the highest risk of a poor prognosis.

In **study 1** our aim was to identify baseline child and adolescent characteristics associated with a poor outcome on follow-up regardless of treatment provided (prognosis) or associated with successful outcome to a treatment (treatment effect modifiers)[1].

The aim of **study 2** was to describe characteristics of 8-19-year-old children and adolescents consulting their GP with MSK pain[2].

In **study 3** our aim was to investigate the 3, 6, and 12-months prognosis and prognostic factors of 8-19-year-old children and adolescents with MSK pain in general practice[3].

Closing with **study 4**, we aimed to extract in-depth insights into adolescents' own experiences of MSK pain and what influenced their prognosis[4].

2. METHODS

2.1. DESIGN

This thesis includes four study designs. A systematic literature review, study 1[1], a cross-sectional study, study 2[2], a prospective cohort study, study 3[3], and a qualitative interview study, study 4[4].

We wanted to inform general practice of prognostic factors in children and adolescents with MSK pain. We performed a systematic review, study 1 on the topic since the latest systematic review at that time, ended their literature search in 2015. We discovered a complete knowledge gap in general practice since previous studies had primarily been in general populations with a focus on biological prognostic factors and less on social and psychological prognostic factors. The review informed our selection criteria and data collection for the following studies 2 and 3. In these studies we aimed to explore the entire patient in terms of biological, psychological and social prognostic factors in creating the Child and Adolescent Musculoskeletal Pain (ChiBPS) cohort. This cohort was recruited entirely from general practice clinics. Having identified prognostic factors for MSK pain in a general practice clinical setting we wanted to gain insight into how the adolescents themselves experienced MSK pain and what they believed had influenced their prognosis. This leading to interviews with adolescents with MSK pain in our final study 4 of this thesis.

All children and adolescents included in studies 2, 3 and 4 were recruited from the same ChiBPS cohort consisting of 100 children and adolescents 8-19 years of age.

Below, literature search in study 1 and design and setting in study 4 is described, prior to a description of data collection in all studies. For studies 2, 3 and 4 questionnaires and interview guide were used for data collection. These tools are described further in 2.2. Data collection.

Literature search, study 1
We searched the databases Medline, Embase, Cinahl, Web of Science, Cochrane, SportDiscus, OT Seeker, and PsychInfo with individual search strategies produced in collaboration with an experienced research librarian (Appendix C, Appendix 1). All databases were searched from inception until February 2019 without limitation on date. Screening and selection of papers were performed independently by two reviewers.

Design and setting
Study 4 was conceptualized as a qualitative study. We performed semi-structured, single-person research interviews[66] designed in accordance with the seven-step guide for conducting semi-structured interviews by Kvale and Brinkmann[67]. Doing so, we considered thematization, intervention design, interviewing, transcription, analysis,

verification, and reporting of our findings. We used goal free analysis via the general inductive method described by Thomas[68]. We used NVivo coding software. Our study sample from the ChiBPS cohort was registered in ClinicalTrials.gov prior to recruitment, Identifier: NCT03678922. Our reporting followed the Consolidated criteria for reporting qualitative research (COREQ) guidelines for qualitative research[69].

We designed our interview setup to provide a comfortable environment, where adolescents could feel safe to engage with the interviewer and disclose their experiences on living with MSK pain, without judgement. Interviews were carried out between October 3rd and December 7th 2021. They ranged from 36-55 minutes with an average duration of 45 minutes, 9 hours and 46 minutes in total. The interviews were carried out at home of Negar Pourbordbari (NP), in the general practice clinic that the participant was a patient in or on Teams. All interviews were face to face and with only the adolescent and the interviewer NP present. Short breaks were practiced when needed, allowing post-rationalization. Snacks and drinks were provided, creating a nice atmosphere. Before and during the interviews, the adolescents were assured that there would be no wrong answers and explained that their answers would be considered as reflections of their experiences and therefore important[70].

2.2. DATA COLLECTION

In study 1 data extraction was performed by NP and divided into: study characteristics, participant characteristics, and prognostic factors with reported estimates: odds ratios (ORs), relative risks (RRs), 95% CI and/or p values (Table 2.1). Data extraction was done with a predefined form inspired by The Cochrane Collaboration[71].

Table 2.1. Included studies described by MSK pain type, baseline age, size of study population, and follow-up.

Study author (reference)	**Musculoskeletal pain location**	**Baseline age** (years)	**Study population** (n)	**Follow-up** (years)	**Persistent pain Female** (%)	**Persistent pain Male** (%)	**Persistent pain combined** (%)
Blaauw BA (18)	Headache	12 to 16	1586	4	45.7	22.7	35.1
Brattberg G 93 (19)	Back, Head	8, 11, 13	471	2	Back 15, Head 40	Back 4, Head 20	Back 9.3, Head 30.7
Brattberg G 04 (20)	Musculoskeletal(Back, Head)	10, 13, 16	597	11	59	39	20
El-Metwally A 04 (21)	Musculoskeletal	9 to 12	1756	1 and 4	4 year: 56.2	4 year: 43.8	1 year: 53.8, 4 year: 63.5
El-Metwally A 05 (11)	Lower limb	9 to 12	1756	1 and 4	1 year: 29.4, 4 year 31.9	1 year 55.8, 4 year 48.6	1 year: 32, 4 year 31
Flato B (22)	Musculoskeletal	2 to 17	37	9	13		59
Jones GT (23)	Low back	11 to 14	330	4			26
Jussila L (24)	Musculoskeletal	16 to 18	1773	2			
Laimi K (25)	Headache (tension type)	13	311	3	54	70.5	48
Lunde LK (26)	Low back	15 to 19	420	6.5			39
Mikkelsson M 97 (27)	Neck, Widespread, low back	9 to 12	1756	1			Neck 48.3, WSP 29.7, Low back 34.4
Mikkelsson M 98 (28)	Musculoskeletal	9 to 12	1756	1			52.9
Mikkelsson M 99 (29)	Neck, Widespread	9 to 12	464	1	Neck 70.4, WSP 62.5	Neck 41, WSP 62.5	Neck 29, WSP 28.6
Mikkonen P 08 (30)	Low back	16	2969	2			27.1
Mikkonen P 11 (31)	Low back	16	728	2	53	46	50.4
Mikkonen P 13 (32)	Low back	7 to 19	1660	2 and 3	2 year 68, 3 year 63	2 year 62, 3 year 47	
Paananen MV (33)	Musculoskeletal	16	1594	2		75	88
Rathleff CR (9)	Knee	12 to 15	768	1			48.8
Rathleff MS 16 Is (34)	Knee	16 to 18	504	2			55.9
Rathleff MS 16 Self (35)	Knee (PFP)	15 to 19	121	3 months			74.4
Sjolie AN (36)	Low back	14 to 16	88	3			39
Sperotto F (37)	Musculoskeletal	8 to 13	289	3			54.3
Stanford EA (39)	Head, Stomach, Back	10 to 11	2488	2			Head 29, Stomach 17.9, Back 21.7
Ståhl M (38)	Neck	9 to 12	1756	1 and 4			1 year: 48.2, 4 year: 33.5
Uziel Y (40)	Growing pain	10 to 16	35	5			48.6

Headache: non-migrainous. *Included stomachache participants. Grey background = not applicable[1].

In studies 2 and 3 data was collected and managed with Research Electronic Data Capture (REDCap) hosted by Aalborg University[72,73]. REDCap is a secure, web-based software platform designed to support data capture for research studies providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources[72,73]. The majority of the recruited general practice clinics elected the use of tablets provided for data collection. If this was opted out, NP would send the recruited participants a direct link to the questionnaires. All extracted data was handled in concurrence with The Danish Data Protection Agency[74].

Questionnaires, study 2 and 3

Two different questionnaires were used in the studies in this thesis. They served for data collection at four different time points (Appendix E, S2 and S3 Files). One baseline questionnaire and one follow-up questionnaire, the latter used at 3, 6, and 12 months follow-up. Data retrieved from these four questionnaires were used in studies 2 and 3. We developed the questionnaires based on our systematic literature review[1], discussions with a GP reference group, and questions used in previous work[1,25,39,75-84]. To ensure comprehension of the questions, the questionnaires were piloted on seven 8-19-year-old children and adolescents with recent MSK pain ensuring a final version without major difficulties in comprehension; two girls 11 and 17 years old and five boys 8, 9, 11, 14, and 19 years old. The general practice clinics and the children and adolescents recruited for the ChiBPS cohort were not given any specific information of the content of the questionnaires before entering the study.

The questionnaires contained descriptive characteristics and candidate prognostic factors covering measurements on demographics, pain characteristics, psychosocial measures, and physical activity (Appendix E, S1 Table). The questionnaires provided a mannequin shown with a frontal and posterior view of the female or male body depending on the sex of the individual completing the questionnaire. Following the mannequin was a list of 33 predefined body sites from which the children and adolescents were able to select more than one location. The list included head, neck, shoulder, chest, upper arm, elbow, lower arm, wrist, finger, hip, back, thigh, knee, shin, ankle, heel, foot, and toe. We included headache on the list because headache concurrently with neck pain was a previous identified prognostic factor for long-term neck pain. We did not consider headache a MSK pain site and headache without concurrent other MSK pain site would cause exclusion. More than one activity limiting MSK pain site was considered multi-site pain. If a child or adolescent reported having both activity limiting pain and non-activity-limiting pain, we used the number of activity limiting pain sites.

Our target audience for all our studies being GPs, we wanted the terminology of our prognostic factors when presented as results, to be applicable in a general practice setting. In order to gain recognition of this, NP created a temporary subgrouping, based on prognostic factors from our previous systematic review. She conveyed this

subgrouping to a focus group[81] consisting of 15 clinically experienced, Danish GP physician peers. She requested any concerns in comprehension including any suggestions towards an easy digestible language, in the context of general practice. Candidate prognostic factors were outlined in categories, based on literature, previous research[1], and on input from experienced clinicians during the development of the study (Appendix E, S1 Table).

We measured number of siblings in the household and requested which number in the row of siblings the individuals were. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Pubertal stage was measured using Tanner stages. We also measured age, gender, and post code. We included non-activity-limiting pain site(s). Multisite pain was based on number of pain sites reported as either activity limiting or non-activity-limiting pain. When a participant reported having both, we used number of activity limiting pain sites. Pain episode duration at baseline was determined using the following alternatives: 1) less than 3 hours, 2) less than 24 hours, 3) 1-7 days, and 4) more than 7 days. Frequency of pain episodes was reported using the following alternatives: 1) more than once a week, 2) less than once a week. Pain intensity was reported using numeric rating scale (NRS) 0 to 10. Being worried or anxious, having low self-esteem, believing in God were determined with the three alternatives: yes/no/I do not know. Feeling nervous was determined using the following alternatives: 1) often/sometimes or 2) seldom or never. Expectations of a pain free future was determined using the alternatives: 1) yes, in the near future, 2) yes, long-term, and 3) no. Having a job was determined with yes/no and physical demands of job stratified in 1) mostly sedentary work without physical demands, 2) mostly standing or walking work otherwise not physical demanding, 3) standing or walking work with mild lifts or exhaustion, 4) heavy or fast work which is physical demanding. Cause of pain, pain outside school hours, and pain impact on concentration was determined with yes/no. Reason for consulting the GP was determined using the following alternatives: 1) I want my pain to stop, 2) I am worried about the cause of my pain, 3) My family made me come, 4) I have a personal problem, 5) I cannot use my body as usual due to my pain, or 6) none of the above. Amount of sleep was determined using the alternatives: 1) 7 hours or less, 2) 8-10 hours, or 3) more than 10 hours. Alcohol, smoking, sleep, pain medication, and radiculopathy were also asked about. We measured screen time with hours per day. We used The modified Hannover Functional Ability Questionnaire (HFAQ)[77] to assess limitations in 9 daily activities: 1) reaching up to get a book from a high shelf, 2) carrying a schoolbag to school, 3) sitting on a school chair for a 45-minutes lesson, 4) standing in a line for 10 minutes, 5) sitting up in bed from a lying position, 6) bending down to put on socks, 7) standing up from an armchair at home, 8) running fast to catch a bus, and 9) sports activities at school. The limitations were summed and categorized as low (0-1 limitation), moderate (2-3 limitations), or high (4-9 limitations). We used the subjective disability index (SDI)[77,81], calculated from the answers to the following proposals (maximum 5 points): 1) I have difficulty in falling asleep because of pain, 2) I have difficulty in sitting during a lesson, 3) pain disturbs

me if I walk more than 1 kilometer, 4) pain disturbs me during physical exercise class, and 5) pain disturbs my hobbies. We previously identified SDI 1-2 and 3-5 compared to 0 as prognostic factor for long-term MSK pain[1]. We included the limitations included in HFAQ and the proposals in SDI in physical characteristics, because a majority of them described limitation in physical functioning and because of their clinical relevance. The amount of physical activity besides school hours was determined using yes/no, followed by the question: 'How many times a week do you do sport?'
Questionnaires were translated from English to Danish following the methodology of translation, back-translation, and verification[28]. All 100 children and adolescents in the ChiBPS cohort completed the Danish questionnaire except two, who mistakenly and reportedly unintentionally completed the English questionnaire despite Danish language abilities.

Activity limiting musculoskeletal pain
In our baseline questionnaire, we captured MSK pain sites experienced in the previous two weeks. We differentiated MSK pain in activity limiting defined as pain during the past 2 weeks leading to not being able to participate in play in the school yard or spare time activities and non-activity-limiting. When answering no to activity limiting MSK pain the following question was whether the child or adolescent had pain in other body sites than selected in the previous question. We used a short recall period of 2 weeks to limit the effect of recall bias.

Prognostic factors
We wanted to be able to convey the prognostic factors for long-term MSK pain found in study 3 to our target audience of GPs. We wanted the terminology used to be applicable in a general practice setting. We used a temporary subgrouping based on prognostic factors from our systematic review, study 1 and conveyed this to a focus group consisting of 15 clinically experienced Danish GP physician peers for comprehension and context purposes[81]. Our candidate prognostic factors in Tables 1 and 2 were categorized based on previous research and input from experienced clinicians[1,3]. The HFAQ limitations and SDI proposals were included in physical characteristics, due to the majority describing limitations in physical functioning.

Interview guide, study 4
NP made first contact with the entire sample frame upon recruitment for the ChiBPS study more than two years prior to study 4[2,3]. NP introduced the adolescents to study 4 without requiring a definite yes/no to participation, thus avoiding either 1) a quick and easy yes from someone who had not yet actually met the interviewer or 2) a defensive no because of too much initial pressure[85]. The adolescents were informed that they could decline to discuss any issues during the interview and withdraw from the study at any time entirely without consequences.
A semi-structured interview guide using open-ended questions was developed (Table 2.2). The guide was conceptualized via the framework for developing a qualitative

semi-structured interview guide by Kallio[84] as a four-step process including: 1. Identifying the prerequisites for using semi-structured interviews; 2. Retrieving and using previous knowledge; 3. Formulating the preliminary semi-structured interview guide; 4. Piloting the interview guide; and 5. Presenting the complete semi-structured interview guide. The questions in the interview guide were identified by all members of the research group and based upon previous research, the authors' clinical experience with treating adolescents with MSK conditions and with interviewing this patient group. The interview guide was piloted in interview 1 and 2 with changes applied accordingly, testing feasibility of the: (1) research design on children and adolescents 8-19 years old with MSK pain; (2) research design in the setting of the interviews; and (3) interview guide facilitated by the principal investigator NP, a female medical doctor with 12 years of experience as a physician of which four years as a consulting GP-trainee with experience in health-promoting conversations with children and adolescents.

Table 2.2. Semi-structured interview script.

Question 1	How did you first notice that you were in pain? Can you describe the situation in your own words?
	a. Where were you the first time you experienced the pain?
	b. What did you think caused the pain back then?
	c. When did you find out the pain was not going away?
	d. How did the pain affect you emotionally back then? (Were you scared, sad, or angry?)
Question 2	How do you experience your pain today?
	a. How has your experience of pain changed, since you noticed it the first time?
	b. Can you describe when you feel the best and the worst with your pain?
	c. What have you done to get better with the pain?
	c.1. Why do you think this has had an effect/no effect?
	d. Can you describe a situation where your pain suddenly felt different?
Question 3	Why do you think your pain has lasted?
	a. What do you think has made a difference in relation to your pain lasting?
	b. Do you think others could have done anything so you would not have pain now? Who and what?
	c. How long do you think your pain will last?
	d. If you were to advise other young people wo they would avoid chronic pain, what would that be?
	d.1. Why is this a good advice?
Question 4	What happened the first time you consulted the doctor with your pain?
	a. How long did you have pain before consulting the doctor?
	a.1. Why did you go to the doctor when you did?
	b. What did you expect the doctor would day or do?
	c. What did the doctor recommend for you to become pain free?
	c.1. What did you do when you came home from the consultation?
	d. How did what the doctor say impact your view of your pain?
Question 5	How did others react to your pain?
	a. When and in which situation did you choose to tell your parents or friends about your pain?
	b. How did your parents or friends react when you told them about the pain?
	b.1. How did this impact how you looked at your pain?
	c. Can you describe what your parents or friends have done to help you with your pain?

An overview of the final interview script with five open questions and 24 probing questions[1].

Interviews 1 and 2 were included in the analysis. The interviews began with an introduction and a "warm-up" question assumed that the respondent could easily answer, to make the interviewer and interviewee at ease with one another[87]. We asked five main questions to avoid too many questions pushing for insufficient depth of and because of lack of time[87]. Follow-up questions were used when something specific and interesting that spoke to our research problem was said; in trying to explore, clarify, and nuance answers and avoid the weak evidence entailed in inconsistent descriptions[87]. Probes were used to support the interviewee in keeping up the talk on the matter or ask for examples for particular points in order to fill in a missing piece

of what had been said[87]. This, to encourage for variety in answers and make the interviewee understand that depth and detail are okay[87]. The "closing" question provided closure to the interview leaving the respondent feeling empowered, listened to, and otherwise glad to have talked to the interviewer[88]. For the inconvenience of participation adolescents each received a voucher to the cinema. Interviews were transcribed verbatim by NP and three student workers. Transcription followed the guidelines by Brinkman and Tanggaard[66].

2.3. DATA SYNTHESIS AND MANAGEMENT

In study 1 the identified prognostic factors were sub-grouped in accordance with the bio-psycho-social model and with input from a panel of GP researchers experienced in MSK research[89,90]. Prognostic factors were divided in biological (female sex, older age, body measurement factors, physical functioning, pain characteristics), psychological (general psychological factors, depressive factors), social (general social factors, factors related to sleep/daytime tiredness, physical activity/inactivity, alcohol, smoking). We did not conduct a meta-analysis because of heterogeneity in patient population, setting, and time points of follow-up. Included prognostic factors were reported with estimates from their individual papers using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist[91] (Appendix C, Online supplementary appendix 2). Assessment of Risk of bias (RoB) in the included 26 studies was performed independently by two reviewers including NP, using The Quality In Prognostic Studies (QUIPS) tool[92] (Table 2.3). Studies were assessed on the overall RoB within each of the six domains and rated as low, moderate or high RoB. Prognostic factors yielded from studies with a high RoB were excluded from the results.

We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cross-sectional studies in reporting of study 2[93] and the guidelines of Prognosis Research and STROBE to report our study findings in study 3[93,94]. We uploaded the protocol for study 3 to ClinicalTrials.gov (Identifier NCT03678922) prior to recruitment. The Ethics Committee of the North Denmark Region (NVK)[95] waived the need for ethical approval of this study (date 090617) and approval prior to initiation was given by The Committee of Multipractice Studies in General Practice (MPU)[96] (ID: MPU 20-2017/date 100117, Appendix C). Declaration of consent was collected according to Danish standards and age (Appendix A).

Table 2.3. Risk of bias in included studies.

Study	Design	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and presentation
Blauuw et al 2015	Prospective cohort	Low	Moderate	Low	Low	Moderate	Low
Brattberg et al 1993	Prospective cohort	Moderate	Moderate	Low	Low	Moderate	High
Brattberg et al 2004	Prospective cohort	Low	Moderate	Low	Low	Low	Low
El-Metwally et al 2004	Prospective cohort	Low	Low	Low	Low	Low	Low
El-Metwally et al 2005	Prospective cohort	Low	Low	Low	Low	Low	Low
Flato et al 1997	Prospective cohort	Low	Low	Low	Low	Low	Low
Jones et al 2009	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Jussila et al 2014	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Laimi et al 2007	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Lunde et al 2015	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Mikkelsson et al 1997	Prospective cohort	Low	Low	Low	Low	Moderate	Moderate
Mikkelsson et al 1998	Prospective cohort	Low	Low	Low	Low	Low	Moderate
Mikkelsson et al 1999	Prospective cohort	Low	Low	Low	Low	Low	Low
Mikkonen et al 2008	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Mikkonen et al 2012	Prospective cohort	Moderate	Low	Low	Low	Low	Low
Mikkonen et al 2013	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Paananen et al 2010	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Rathleff et al 2013	Prospective cohort and nested case-control	Moderate	Low	Low	Low	Low	Low
Rathleff et al 2016 Is	Prospective cohort	Low	Low	Low	Low	Low	Low
Rathleff et al 2016	Prospective cohort	Low	Low	Low	Low	Low	Low
Sjolie et al 2001	Prospective cohort study with a cross sectional part	Low	Low	Low	Low	Low	Low
Sperotto et al 2015	Prospective cohort	Low	Moderate	Low	Low	High	Moderate
Stanford et al 2007	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Ståhl et al 2008	Prospective cohort	Low	Moderate	Low	Low	Moderate	Low
Uziel et al 2010	Prospective cohort	Moderate	Low	Low	Low	High	Moderate

With the Quality Prognostic studies tool, studies were assessed on the overall risk of bias within each of the six domains and rated as low, moderate, or high risk of bias[1].

In study 4 we analyzed the transcribed data via the General Inductive Approach for analyzing qualitative data according to an inductive analysis of data steps 1 to 5[68]. This approach allowed our findings to emerge from frequent or significant themes in the raw data, without restraints, confer a goal-free evaluation. Data collection and analysis ran simultaneously to allow the exploration of emerging themes. Interview transcripts were uploaded in NVivo software, Release 1.5 (QSR International, Cambridge, MA, USA) to facilitate data storage and coding. 1. Each interview as raw data was formatted according to a common format in terms of font size, margins, and questions. Coding of each line of data was done by NP, according to a coding framework developed by NP and the second author, based on preliminary reviews of the transcripts. New codes were added to the framework as coding preceded. 2. Every interview was read until the content became familiar and an understanding of the themes and events gained. 3. Categories were derived initially from phrases or specific segments of text as per inductive coding. This process was repeated for each transcript. To maintain rigor of analysis, a collaborative review of codes and themes was performed (see Rigor below for further details). 4. Overlap and redundancy among categories was reduced and segments of text could be coded into more than one category while other text segments could remain unassigned to any category at all, if not relevant to the evaluation objectives. 5. Categories were revised and searched among for subtopics. Quotations conveying the essence of a category were highlighted and categories linked when containing similar findings.

Rigor, study 4
Aiming for trustworthiness of data and analysis, NP and the second author discussed the coding of the first three transcripts. The second author an experienced qualitative researcher in the field of MSK pain. Hereafter, NP and the third author sampled and discussed the coding of a couple of transcripts. The third author an associate professor and anthropologist and experienced qualitative researcher outside the field of MSK pain. Thus eliciting different perspectives and ensuring agreement on developed themes. Second, we used visual methods (Appendix G, Supplementary file) to discuss identified themes with a multidisciplinary research team of a professor of general practice and experienced researcher in the field of MSK pain conditions, a professor of rheumatology with experience in research of MSK pain, and a professor in physiotherapy with extensive research experience in adolescent MSK pain. Translation of quotes was done by NP and read through by the last author.

2.4. STUDY POPULATION

Eligibility criteria
In study 1 we included prospective studies on children and adolescents aged 0 to 19 years with MSK pain. We excluded pain knowingly caused by tumour, fracture, infection, systemic and neurological conditions. We included studies independent of intervention and randomized trials including comparators. We excluded stomach pain, because of insufficient differentiation between MSK pain in the abdominal region and stomach pain due to other causes. We did not restrict our search to setting or language.

ChiBPS cohort
In studies 2 and 3 the ChiBPS cohort constituted our study population. The ChiBPS cohort of 100 adolescents[2,3] is a population of 8-19-year-old children and adolescents residing in Denmark with MSK pain. Inclusion criteria were age 8 to 19 years, self-reported MSK pain, and the ability to read and understand either Danish or English. Exclusion criteria were self-reported MSK pain due to tumour, infection, or systemic and neurological causes known by either the GP or the child/adolescent/their parent. To be eligible, patients consulting their GP had to have a MSK pain complaint mentioned to the GP as a current condition. However, it was not required to be their main reason for consulting their GP. Musculoskeletal pain was defined as pain arising from muscle, tendon, bone, and joint as per IASP definition[13].

Study sample, study 4
From the ChiBPS cohort, we chose a subgroup with poor prognosis i.e. MSK pain at six months follow-up, thus defining our study 4 sample frame of 36 adolescents. Inclusion and exclusion criteria were as such same as for the ChiBPS cohort (see above) but this sample frame had MSK pain at six months follow-up. The adolescents received verbal and written study information and written consent was obtained from the parent or the adolescent < 18 years or older respectively.

2.5. RECRUITMENT, STUDIES 2, 3 AND 4

Recruitment of general practice clinics
From October 2018 to August 2019, NP contacted and visited general practice clinics across Denmark for recruitment purposes to the ChiBPS cohort[2,3] (Appendix E, Supplementary File 1). The aim was to recruit a sample that represented the Danish child and adolescent population with MSK pain. A total of 24 rural and urban general practice clinics were included of which 17 recruited participants (Figure 3.1).

Recruitment of children and adolescents
Children and adolescents with self-reported MSK pain consulting their GP were recruited to the ChiBPS cohort. The recruitment was done in different ways among the clinics. In some clinics the GP recruited the participants and in others an employee did so. The employee was suggested to screen all scheduled patients for eligibility, prior to their consultations. The GP was suggested to screen the scheduled patients prior to the work day or during the consultation. Whichever suitable method in relation to the infrastructure of the clinic could be chosen. For study 4, NP contacted the group of children and adolescents with activity limiting MSK pain at 6 months follow-up in random order. Sixteen participants responded to the telephone calls made by NP. Thirteen agreed to participate. Based on the assumption that 84% of concepts are elicited by ten interviews[97] we aimed for ten interviews as a minimum. We interviewed 13 participants; an acceptable sample as thematic saturation was met as no novel codes were identified hereafter. Six adolescents remained not contacted; six females aged 10, 11, 11, 13, 13, and 16 at time of entry in ChiBPS.

2.6. OUTCOMES

In study 1 our primary outcome was MSK pain at follow-up. We identified baseline characteristics of 0-19-year-old children and adolescents with MSK pain that were associated with this outcome (prognostic factors).

In study 2 our primary outcome was self-reported activity limiting MSK pain upon consultation with the GP.

In studies 3 and 4 our primary outcome was self-reported activity limiting MSK pain at 6-months follow-up. Musculoskeletal pain was considered a poor prognosis if participants reported pain in the past two weeks, leading to not being able to participate in play in the school yard or spare time activities (Appendix F, S2 File). Children and adolescents were considered ‘recovered’ at follow-up if they did not report activity limiting pain at 6-months follow-up, regardless of the pain site or if they reported other pain which was not activity limiting.

2.7. STATISTICS

Sample size

In studies 2 and 3 we determined a sample size using two rationales: 1) a sample size large enough to test and replicate the analyses from previous studies 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, multi-site pain, and maximum HFAQ from our systematic review[1]. We gained an estimate of p-values according to sample size for all factors individually (Appendix B). Sample size of 500 participants 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 had yet tested any of the these potentially important prognostic factors and never in a general practice setting, we decided on 500 participants. This number was based on 250 cases (we assumed 50% would 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 was considered explorative as no studies had previously been conducted in a general practice setting. Assuming 50% had pain at follow-up and 20 events for each to be tested was needed. The low sample size of 100 participants lead to uncertainty of the estimates and hindered a stratified analysis and multivariable model as originally planned.

In study 4 we included thirteen participants. This was considered an acceptable sample size as 84% of concepts are typically elicited by ten interviews[97] and thematic saturation was met as novel codes were identified after our tenth interview.

Course and prognosis of musculoskeletal pain

In study 3 the proportion of knee, back, ankle, heel, and neck pain at all follow-up time points were presented as among only those who had knee, back, ankle, heel, and neck pain respectively at baseline (Figure 3.4). Data was exported from the questionnaires in REDCap to an Excel table and checked for misregularities. At all follow-up time points, the proportion of participants with activity limiting pain was based on the proportion responding at that specific time point.

Prognostic factors

In study 1 we defined a statistically significant association between a characteristic and an outcome as an RR or OR above or below 1 that did not include 1 in the 95% confidence interval (CI). For p value, we defined a statistically significant association as $p<0.05$.

In studies 2 and 3 we used descriptive statistics to summarize data and mean and standard deviation (SD) to describe normally distributed continuous data while non-normally data were described using median and interquartile range (IQR). Categorical data was described using percentages.

In study 3 we identified candidate prognostic factors as unfavorable outcome defined as activity limiting pain at 6-months follow-up. Descriptive analysis was used to report the course of MSK pain over the 12-month follow-up period. In this explorative study we were interested in baseline measures associated with our outcome. We qualitatively summarized our candidate prognostic factors focusing on a strong association based on the assumption of potential clinical relevance (defined in the author group) as OR > 3 and 1 excluded from the 95% CI. The analysis was presented with central estimates and appropriate measure of dispersion (95% CI). All prognostic factors were presented in association with pain at 6-months. The statistical analyses were conducted using STATA version 17.0.

Prognostic factors with low event rates

In study 3 the event rates of some of the prognostic factors were low and consequently these items were either pooled or excluded from Figure 3.7. We pooled the prognostic factors; 'alcohol less than once/month' with 'alcohol approximately once/month', 'pain medication more than once/week' with 'pain medication every day', and 'job, mostly sedentary' with 'job, standing/walking'. We did so due to their individual low event rates.

'Consulting the GP because of a personal problem' (n=1), 'cigarette smoking' (n=2), 'sleep >10 hours versus 8-10 hours/night' (n=2), and reporting no to all nine limitations in HFAQ (n=1) were excluded because of low event rates. Due to low event rates of 'being born outside Denmark', we did not include years lived in Denmark or nationality in our analysis.

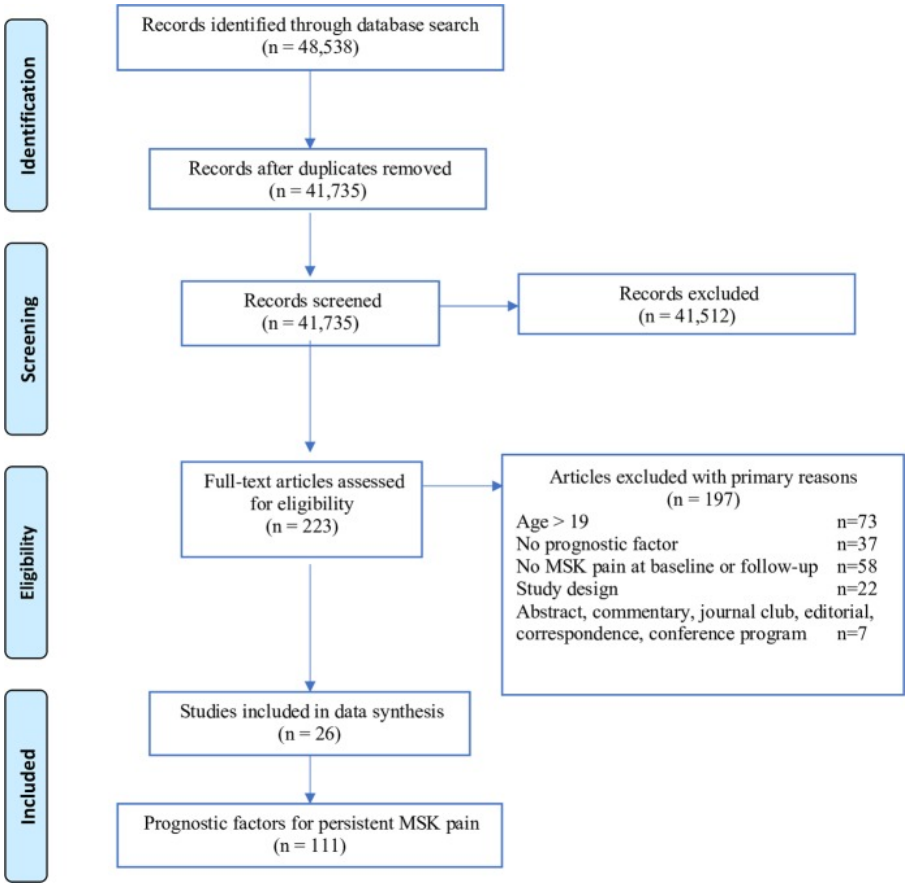
3. RESULTS

In this chapter, the results of the four studies included in this thesis are summarized. First a description of the included studies in our literature review, study 1, followed by a description of our ChiBPS cohort from study 2. Following this, a description of our findings on prognosis and prognostic factors – first from our study 1, then from study 3. Finally, our findings from study 4. A complete report of the results can be found in the respective papers in appendices.

Included studies, study 1

Our initial database search identified a total of 48,538 studies (Figure 3.1). We screened 41,735 studies and included 26 prospective studies[39,75-77,79-83,90,98-113]. Musculoskeletal pain types included in our search were general MSK, neck, back, lower back, lower limb, knee, and growing pain. We extracted MSK pain type, baseline age, recruitment setting, size of study population, follow-up and percentage of study participants who represented persistent pain at follow-up. The most common reasons for a moderate/high risk of bias were inadequately described study participation and statistical analyses (n=6, 23%), attrition rates (n=5, 20%) and poor adjustment for confounders (n=11, 42%). We rated three studies with high risk of bias and excluded these from the final results (Table 2-3).

Figure 3.1. PRISMA flowchart presenting the flow of citations reviewed in the course of the systematic review.



Forty-eight thousand five hundred and thirty-eight articles were identified through search in eight databases, resulting in 223 articles for full-text eligibility screen and a final number of 26 studies for inclusion yielding 111 prognostic factors on MSK pain[1].

Findings on prognosis and prognostic factors from study 1 is described in 3.2. Prognosis and prognostic factors for long-term MSK pain.

3.1. DANISH CARE-SEEKING CHILDREN AND ADOLESCENTS WITH MUSCULOSKELETAL PAIN IN GENERAL PRACTICE

From August 2018 to December 2020 124 children and adolescents were recruited from 17 general practice clinics. Of the 124, 100 were included in the ChiBPS cohort (Figure 3.2). Causes for exclusion were missing consent, incomplete/cloned questionnaires, or a lack of fulfillment of the eligibility criteria. The median age was 13 IQR [12-16.5] years and 55% were female. The most common MSK pain sites of our ChiBPS cohort were knee (56%), ankle (18%), back (14%), heel (12%), and neck (9%) (Figure 3.3). The median pain duration of the cohort was 5 months IQR [3 weeks-1 year]. Above half reported multi-site pain (53%). Figure 3.2 shows the common characteristics of a child or adolescent from our ChiBPS cohort. For a full description of characteristics, see Table 3.1 and Table 3.2.

Figure 3.2. Recruitment of general practice clinics and children and adolescents for study 2, 3 and 4.

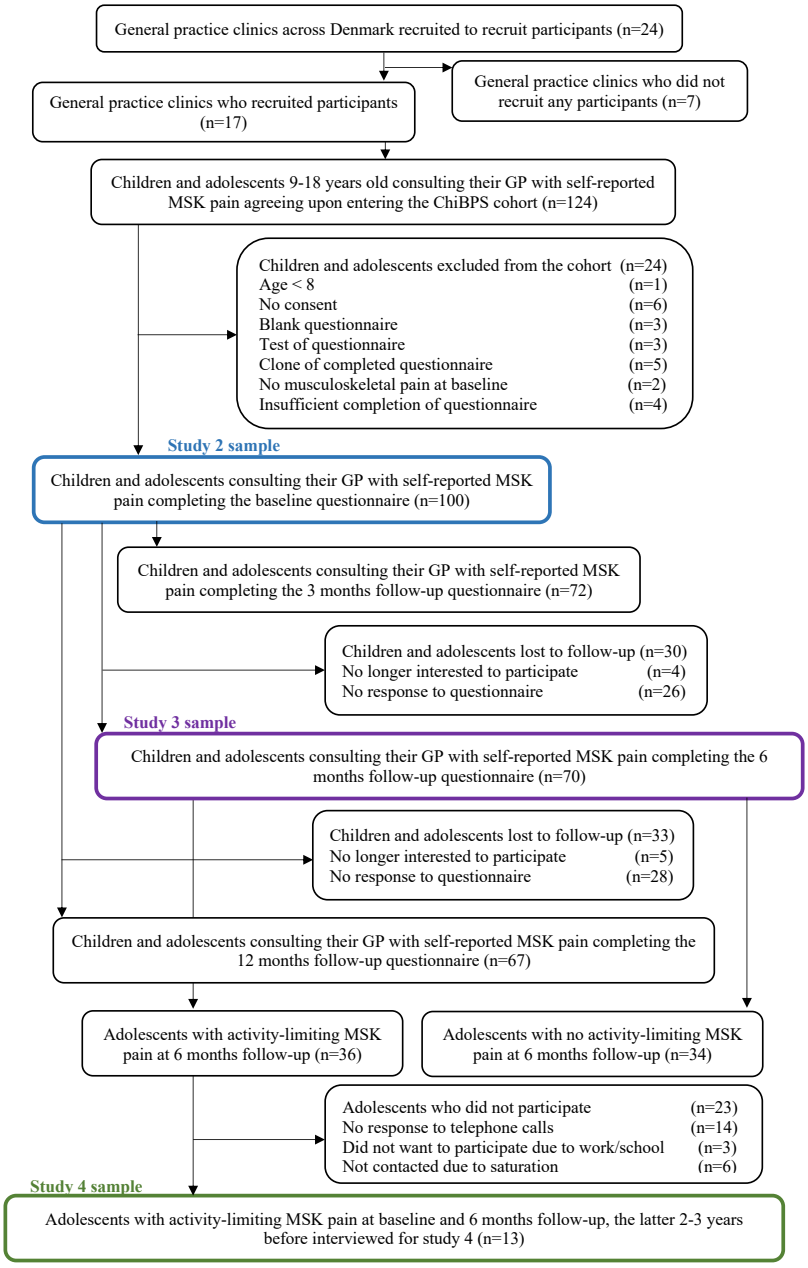


Figure 3.3. Common characteristics of a general practitioner care-seeking 8-19-year-old with musculoskeletal pain.

A typical Danish child/adolescent with musculoskeletal pain is a 12 or 13 year-old girl. She has knee pain and at least pain in one more body site. She consults her general practitioner because she cannot use her body as usual due to pain and she decides to do so after having had pain for one year. The pain episodes has been as frequent as once every week. In her household she is the youngest of two children. In school her concentration is affected by her pain, and she goes on with her day feeling tired. After school she is active in sports 2-3 times a week, even though her pain disturbs her spare time activities. During a typical day, she spends 3-6 hours looking at a screen. She believes in God. When her day is over and it is time for her to turn in she goes to bed knowing what causes her pain.

The figure is based on data from all participants, n=100 including both activity limiting and non-activity limiting pain. Cut off limit is defined at a minimum of 31% of all participants for inclusion of the characteristics included in this figure[2].

Table 3.1. Descriptive factors (demographics and pain characteristics) of study participants in the ChiBPS cohort at baseline (N=100*).*

Demographics	
Age, median [IQR]	13 y [12-16.5]
Female sex, n	55
Siblings, n, median [IQR]	1 [1-2]
Only child, n	7
Position in sibling line	
First	31
Second	36
Third/fourth	21
Youngest	41
BMI, kg/m^2, mean (SD)	19.88 (4.86)
Pubertal stage, n	
Prepubertal	32
Pubertal	67
Pain characteristics	
Activity limiting pain, n	
Knee	56
Ankle	18
Back	14
Non activity limiting pain, n	
Knee/neck pain	14
Back/ankle	10
Heel/foot	10
Pain duration, median [IQR]	5 mo [3 wk-1 y]
NRS, median [IQR]	7 [6-8]
Multi-site pain, n = 53	
2 sites	23
3 sites	14
4 sites	7
> 4 sites	9
Pain episode duration, n	
< 3 hours	34
< 24 hours	24
1-7 days	24
> 7 days	18
Pain episode frequency, n	
=/> Once/week	80
< Once/week	20
Radiculopathy, n	12

Data are based on 97%-100% replies. Position in sibling line, excluding only children and twins: fifth child, n=3, twins, n=2; pubertal status: one missing reply; multi-site pain: five participants reported only one pain site and this was non-activity limiting – as answer to pain question 3, of these one of the sites were the jaw. (ID 40, 42, 51, 57, 90); IQR, Interquartile range; NRS, pain numerical rating scale; y, years, mo, months, wk, weeks[2,3].

Table 3.2. Descriptive factors (psychosocial and physical activity characteristics) of study participants in the ChiBPS cohort at baseline (N=100).

Psychosocial characteristics	
Pain outside school hours, n	97
Nervous, n	
Often/sometimes	34
Seldom/never	66
Worried or anxious, n	
Yes	33
No	32
I don't know	35
Low self-esteem, n	
Yes	7
No	78
I don't know	15
I believe in God, n	
Yes	36
No	35
I don't know	29
Sleep per night, n	
</= 7 hours	22
8-10 hours	75
> 10 hours	3
Tired during the day, n	57
I have a job, n	33
I know the cause of pain, n	58
I expect the GP to prescribe pain medication, n	8
I expect a pain free near future, n	56
I expect a pain free long term future, n	38
Pain affects my concentration, n	58
Pain medication, n	33
Frequency of pain medication, n	
Once/month	13
Once/week	12
> Once/week	6
Every day	1
Paracetamol, n	17
NSAID, n	9
Reason for consulting the general practitioner, n	
I want the pain to stop	57
I am worried for the cause of pain	53
My family made me come	22
I have a personal problem	2
I cannot use my body because of pain	63
Alcohol consumption, n	31
Cigarette smoking, n	3
Physical activity characteristics	
Physical active besides school hours, n = 80	
1 time/week	11
2-3 times/week	39

4-6 times/week	16
> 6 times/week:	5
Screen time/other activity mostly sitting down, n	
1-2 hours/day	36
3-6 hours/day	49
>/= 7 hours/day	7
HFAQ, Pain makes it difficult to:, n	
Reach for a book on high shelf due to pain	10
Stand in a queue for 10 minutes	36
Carry my school bag to school	22
Sit on a chair for a 45 minute lesson	31
Bend down to put on my socks	33
Sit up in bed after a lying position due to pain	5
Do sport activities at school	79
Run fast to catch a bus	67
Stand up from a lean chair due to pain	18
SDI, n:	
Difficult to fall asleep due to pain	38
Difficult to sit during a lesson	49
Pain disturbs a walk > 1 kilometer	70
Pain disturbs physical exercise	88
Pain disturbs spare time activities	88

Data are based on 97%-100% replies; question concerning screen time had the lowest reply percentage. Pain medication: not mutual exclusive; physical activity: incl. one answer to: 'sometimes once other times 3', '1-2 times', '1-3 times', and '4-7 times', two answers '3-4 times', three answers: '3-5 times' and two answers to 0; screentime, outside school hours: excl. one answer of: '1-3 times', 'many times', and 'all the time', and three answers of: '2-3 times'; GP, general practitioner; NSAID, nonsteroidal anti-inflammatory drug. HFAQ, the modified Hannover functionalability Questionnaire (more than one limitation could be ticked) and SDI, Subjective disability index[2,3].

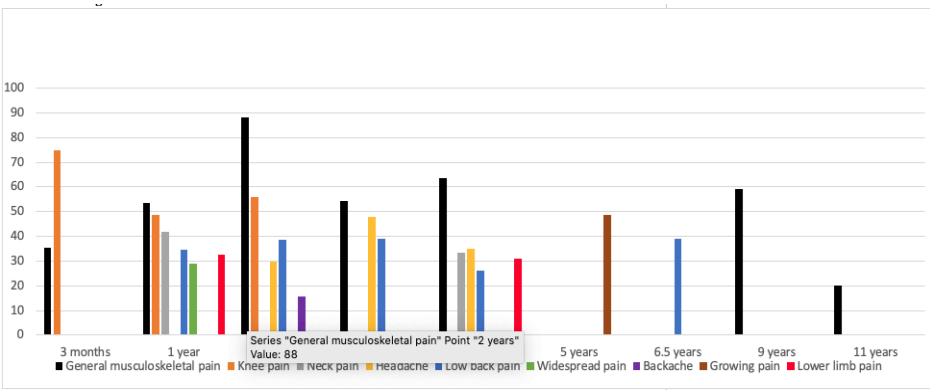
3.2 PROGNOSIS AND PROGNOSTIC FACTORS FOR LONG-TERM MUSCULOSKELETAL PAIN

We investigated prognosis and prognostic factors for long-term child and adolescent MSK pain in three studies. Our systematic review, study 1 with international data and our prospective cohort study, study 3 with national, Danish data.

Prognosis

We investigated prognosis of long-term persistent MSK pain in our systematic review and long-term activity limiting MSK pain in our cohort study. In our systematic review, study 1 we highlighted MSK pain persistence in our included studies at different follow-up time points (Figure 3.4). At 1 year follow-up an average of 54.4% with general MSK pain still had pain. At 4 year follow-up 63.5% with general MSK pain still had pain.

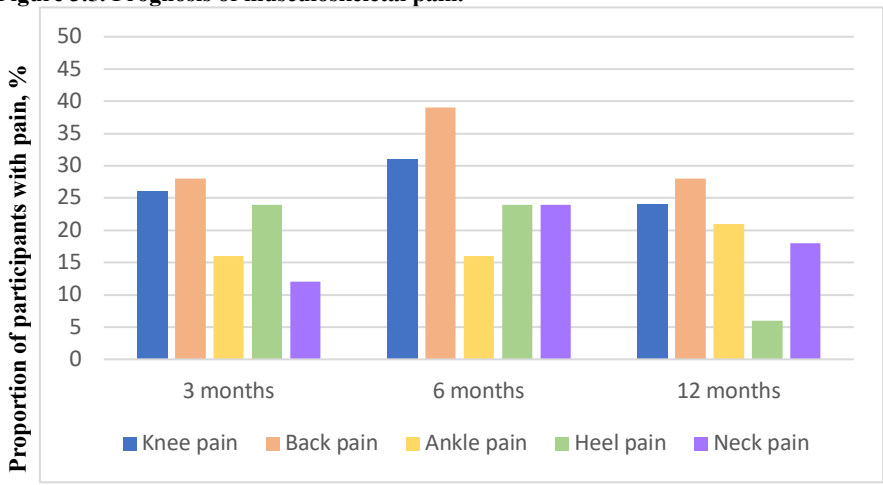
Figure 3.4. Persistent musculoskeletal pain stratified in pain type and follow-up.



The included studies investigate pain at follow-up time points ranging from 3 months to 11 years. General musculoskeletal pain (black columns) persisted in > 50% of participants after 1, 2, 3, 4, and 9 years follow-up[1].

In our ChiBPS cohort we found that the majority of the participants had knee pain with a trajectory showing 27% with activity limiting pain 3 months after inclusion and 32% with activity limiting pain 6 months after (Figure 3.4). Response rates of the follow-up questionnaires were 72%, 70% and 67% at 3, 6, and 12 months follow-up respectively.

Figure 3.5. Prognosis of musculoskeletal pain.



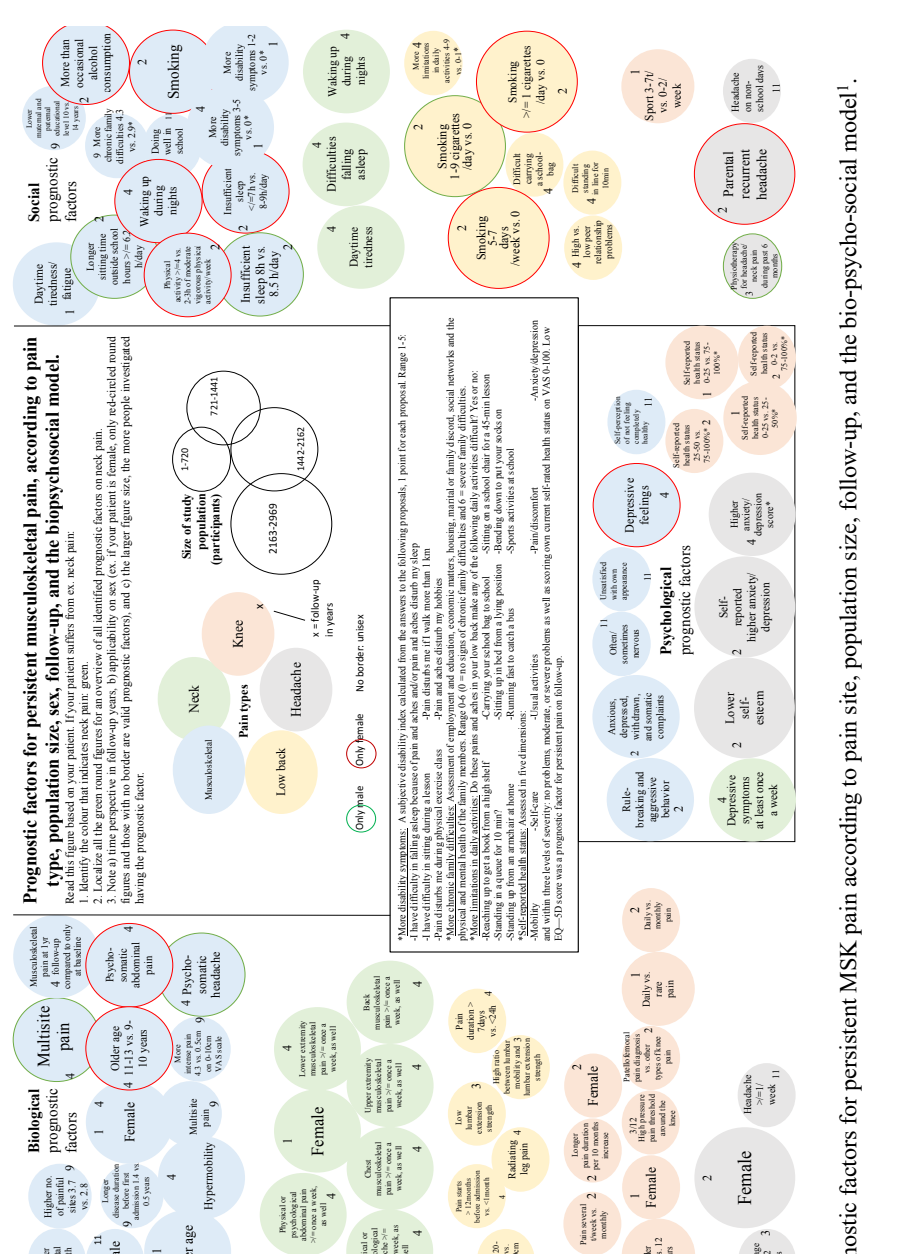
The proportion of 100 participants with baseline-activity-limiting MSK pain who had pain at 3, 6, and 12 months, stratified by pain site. The MSK pain depicted in Figure 3.2 includes activity limiting pain and non-activity-limiting pain at all three time points. Bilateral pain i.e. pain in two opposite body sites are considered mutual exclusive in the bars above. No mutual exclusivity for multi-site pain[2].

Prognostic factors for long-term musculoskeletal pain

We have identified prognostic factors for long-term MSK pain in two of our studies. In our systematic review we identified prognostic factors for long-term persistent MSK pain and in our cohort study we identified prognostic factors for long-term activity limiting MSK pain. In our systematic review, we found a total of 111 unique prognostic factors associated with MSK at follow-up. The majority of these were on participants with general MSK pain and second low back pain. Female sex was the most frequent identified prognostic factor associated with persistent MSK pain at follow-up. Longer pain duration[77,101,102,110], sleep-related problems[76,77,80,81,82], increasing age[39,81,82,104], smoking[80,107], parental pain[90,102,113] and multi-site pain[76,82,102] were also associated with long-term persistent MSK pain. Please see Figure 3.6 for a summary of all the prognostic factors identified in our systematic review, stratified by MSK pain site, study population size, sex, and follow-up.

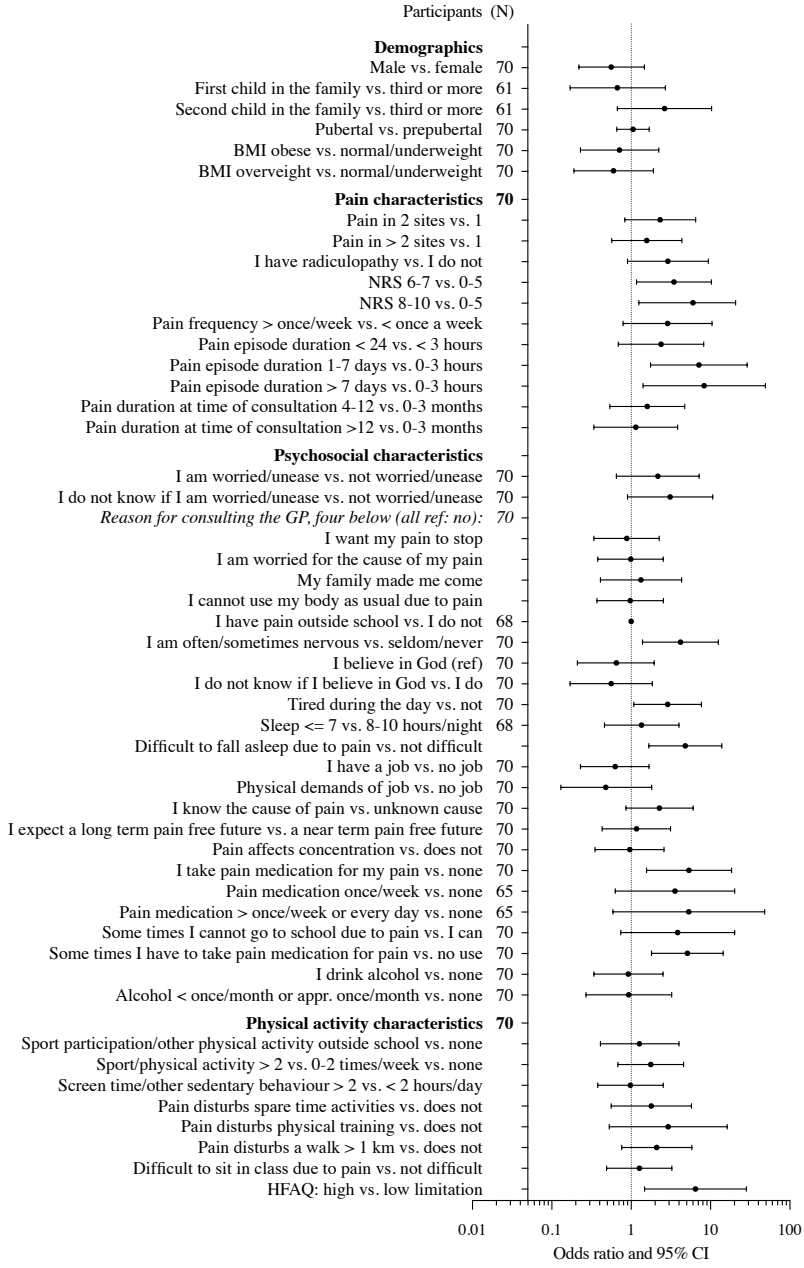
In our cohort study we identified prognostic factors associated with activity limiting MSK pain and divided them into demographic and pain characteristics, pain characteristics interfering with daily activities, psychosocial and physical activity characteristics. We found that pain intensity NRS 6-7 increased the risk of pain at 6 months follow-up (OR 3.5, CI 1.2-10.3) relative to NRS 0-5, pain episode duration of 1-7 days increased the risk of pain at 6 months follow-up (OR 7.1, CI 1.8-28.9) relative to pain duration of 0-3 hours, being nervous often or sometimes increased the risk of pain at 6 months follow-up (OR 4.2, CI 1.4-12.5) relative to not being nervous. We also found that having difficulties falling to sleep due to pain increased the risk of pain at 6 months follow-up (OR 4.8, CI 1.7-13.9) and using pain medication was associated with 5.4 higher odds (1.6-18.4) of activity limiting MSK pain at 6 months follow-up. Having difficulties with bending to put on socks increased the risk of pain at 6 months follow-up (OR 4.1, CI 1.3-13.2). Figure 3.7 shows the estimates and 95% confidence intervals of our candidate prognostic factors. Data was based on the 70 children and adolescents who responded to the 6-months follow-up questionnaire.

Figure 3.6. Prognostic factors for persistent musculoskeletal pain, according to pain site, population size, follow-up, and the bio-psycho-social model.



Prognostic factors for persistent MSK pain according to pain site, population size, follow-up, and the bio-psycho-social model[1].

Figure 3.7. Activity limiting musculoskeletal pain at 6 months follow-up.



Odds ratio and 95% confidence intervals for prognostic factors of MSK pain at 6 months. N = participants in the statistical analysis. When N is stated next to a group of characteristics and not below in the listed characteristics, N is the same for all listed characteristics in this group[3].

3.3 WHAT DO THE ADOLESCENTS HAVE TO SAY?

Participants, study 4

Participants in our study 4 consisted of 13 adolescents; 6 males and 7 females aged 13-21 years (Table 3.3). The majority (11 adolescents) had knee pain among other pain sites: hip, ankle, back, foot, shin, and heel.

Table 3.3. Participant characteristics and demographics (n = 13).

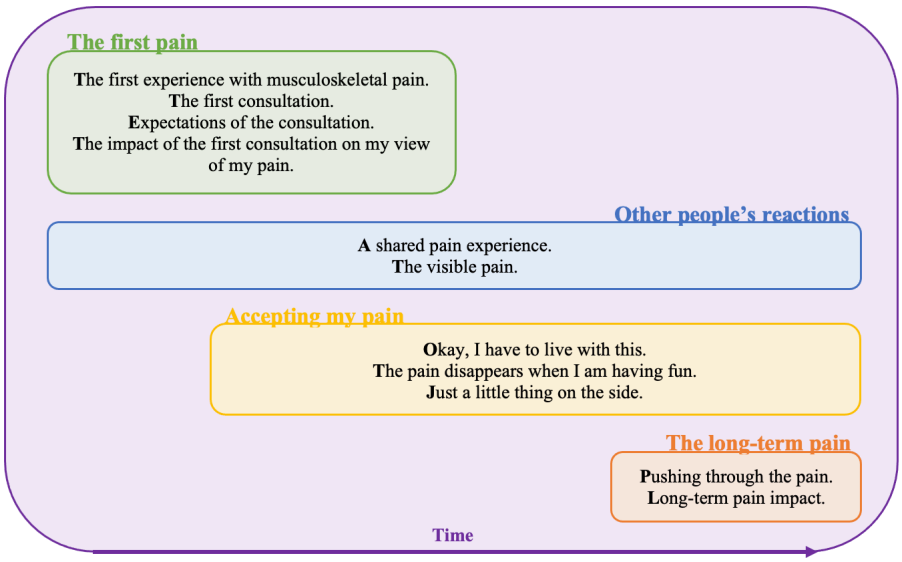
Pseudonym	Gender	Age at time of interview (years)	Age at time of entry in ChiBPS (years)	Pain site(s) at time of entry in ChiBPS	Interview length (minutes)
P1	Male	21	18	Hip, knee, ankle	40
P2	Female	18	16	Back, knee, feet	36
P3	Male	13	11	Thighs, shins, heel	54
P4	Female	13	11	Knees	45
P5	Female	18	16	Knees	41
P6	Female	15	12	Knees	49
P7	Male	15	12	Knee, shin	46
P8	Male	21	19	Knees	46
P9	Male	14	12	Knee, ankle, foot	40
P10	Female	21	19	Knee	44
P11	Female	16	13	Ankle	55
P12	Female	16	13	Knee	42
P13	Male	15	13	Knees	48

Pseudonyms were used to protect the identity of the adolescents. Pain sites indicated as unilateral (knee) or bilateral location (knees). All adolescents had self-reported MSK pain at time of entry in the ChiBPS cohort[4].

Overview of themes

Four superordinate themes emerged from our data analysis in study 4. The themes described the adolescents' experiences of their long-term MSK pain condition (Figure 3.8). The themes were 1. The first pain, 2. Other people's reaction, 3. Accepting the pain, and 4. The long-term pain.

Figure 3.8. Four themes and their designated categories according to time.



Four themes and their designated categories according to time. From the experience of the first pain, when other people's reactions started getting noticed, followed by acceptance of pain, and finally living with a long-term pain condition[4].

The first pain

This first theme described how the adolescents' experienced their MSK pain for the first time and the circumstances following; the expectations they had from the consultation with the GP, the first time they consulted the GP, and how the consultation had an impact on their view of their pain condition. Since this was their first experience with MSK pain, the adolescents appeared to be unfamiliar with the pain at first before acknowledging the pain at a later point in time. A prolonged pain episode, a pain provoked by physical activity or a persisting pain would push for acknowledgement of the pain as a long-term condition.

Longer pain duration or several consultations for the same pain condition appeared to result in a position of expectations towards the GP. The adolescents admitted and accepted the limitations that accompanied their pain in the consultation process. The limitation appeared as a belief in the GPs recommendation based on authority and a missing breakthrough in communicating the pain to the GP. One adolescent described his strategy in working around this limitation by bringing his mother to a follow-up consultation. His intention with bringing his mother was that her presence would catalyze the consultation into a serious matter. There was a sense of delegitimization of the pain, which lead to disappointment and feelings of not being taken serious. While some adolescents described entering the consultation with an expectation of

going to get information on an exact cause of their pain, others had a preconceived dual perception of the gravity of their pain.

Several adolescents described receiving pain medication as first line treatment. The adolescents also described receiving the 'wait-and-see approach'. Based on this recommendation, the GP was perceived to imply that the pain condition was not to be taken too seriously, since it was expected to soon pass. Depending on the circumstances after this initial consultation and whether they continued to have pain, the adolescents chose to consult the GP again in preference to accepting that their pain had not ceased. By doing so, the adolescents took ownership of their pain and furthermore displayed an act of trust in wanting to consult the GP yet another time. This, despite being told that their pain condition would unlikely continue.

Some of the adolescents applied the term whiney or making a fuss when characterizing their pain as something less than a condition or symptom worth acknowledging. Leaving the consultation without a name or a diagnosis, could lead to confusion. Why did they feel the pain that they did since 'nothing was wrong'? This implied a preconceived understanding that pain must come from 'something' or 'a problem' and if there was not 'something' - in this case a name or a diagnosis, then probably nothing was wrong and what they were feeling was equaled being whiney. However, leaving the consultation with a referral to other health care professionals supported their perception of the legitimacy of the pain. Adolescents described how they experienced receiving a referral as a recognition from the GP. This provided hope for remission. Being told by the GP that their pain condition was 'normal' considering their individual activity level or activity pattern preceding the pain would reassure and the adolescents would continue on worrying less about their pain. Furthermore, they would feel safe in continuing with their activities in spite of the felt pain. While expectations of the content of the consultation and the outcome was predicted by the adolescents, the impact of these were less predictable and, at times, made them question the pain that they were feeling. The doubt could then lead to re-evaluation of the pain and the extent of its validity.

Other people's reactions

This theme included the adolescents' experiences of their perceived reactions from friends, family, and other surroundings.

A significant reason underlying the perceived understanding of pain from others appeared to be a shared pain experience. Some of the adolescents shared a household with others with a current or previous experienced pain. The adolescents drew on the experiences of these family members and found comfort and felt instantly understood. It appeared to be difficult for the adolescents to explain to other people without personal pain experience. Because, the activities limited due to pain, were described as considered basic and something most people were able to do. The adolescents could pleasantly mirror their activity limitations in people with pain experience, because it would then be a shared experience between the adolescent and the other person with

pain experience. Being able to tell somebody, that they had pain after doing a simple task, because of the prenotion, that the other person understood mainly on the premise of their own pain experience. The adolescents appeared to end up not feeling alienated. Throughout the adolescents' descriptions lied a wanting for reassurance and respect of the pain condition. Other adolescents experienced the lack of a shared pain experience differently, saying that there was lack of respect and instead a reaction of wonder as to why the pain has not ceased, yet.

Some of the adolescents explained how having a pain perceptible to others or to themselves enabled a change in the reaction to their pain. This in comparison to the reaction they received at an earlier time when also in pain, but without a visible indicator of the pain i.e. a scar or a cast covered extremity. Not only the perceived reactions from their surroundings but also how they themselves perceived their pain. Assuming that the sensation of pain and the visible pain were two separate entities, most adolescents experienced other people began acknowledging their pain based on having witnessed a visible indicator of pain. The changed reaction increased the perceptibility of their pain from others as well as from themselves. The pain ceased to be a case of wonder and instead became acknowledged because of 'something' in the visual appearance of their body. From this realization emerged an allowed activity limitation, which was not present before. When the reaction changed, it left some adolescents irritated due to the mistrust from other people as the pain was not acknowledged before the event of a visible indicator. The visible indicator of pain was new, but they had actually felt pain for a long time. Furthermore, the adolescents described how visible pain became a proof of pain and a powerful card, because they now were able to say that something was wrong. Whilst generating reassurance and relief, it also made the adolescents question why they had to prove their pain through something visible. At the same time, they gained a sense of satisfaction in proving others wrong. There seemed to be another underlying condition of proving others wrong, in the sense of being able to overcome a temporary visible scar or a cast without this necessarily having a permanent impact on their functioning.

Accepting the pain

The adolescents described how they in time, felt challenged to view their pain through other people's reactions and accept how things were. This third theme described how the pain conditions were experienced over time in relation to acceptance of pain, the consequences induced by the pain impact, and the adolescents' attempted management of these.

The adolescents' described how they in the beginning of the pain experience believed they were able to do more about the pain. This belief seemed to decrease with time. Becoming familiar with which activities or intensities were pain inducing allowed the adolescents to avoid these and furthermore avoid the potential limitations caused by the pain. The adolescents employed preventative attitudes to enable continuation of what they were involved in, thus favoring accept over disappointment.

Some adolescents described how they had gained a greater tolerance to their pain condition. The pain stopped being the center of their attention and a hindrance and instead became something distanced from what otherwise might have taken place in their lives. The pain experience thus became less consolidated and a less mind consuming experience with time. When the pain stopped being an obstacle and shifted into something manageable, it enabled partial participation, instead of prevention of any participation at all. They did not feel completely outside of a joint activity.

Despite a long-lasting condition with several negative impacts on these adolescents, the long-term pain experience seemed to have a silver lining. With time, the adolescents described how they changed their view on their pain condition. It seemed, the adolescents began to reflect on the pain through the recognition of it being a long-term condition compared to what they otherwise thought in the beginning.

The long-term pain

All adolescents were asked why they believed they had a long-term pain condition. As they were asked this question approximately half-way through the interviews, most adolescents came to a halt. They stated never to have thought about this before. The process of reflection and understanding induced questioning the pain condition and why it had not ceased. Furthermore, how they believed it had had an impact on their lives.

What appeared to be associated to cause of long-term pain from the initial pain experience was a lack of accept of the pain condition. The pain was not accepted at first which in the case of many adolescents led to pushing through the pain. There was not always an intended purpose with pushing through the pain. In some instances, it was a natural continuation of doing sports, despite pain. The potential for future pain did not appear to prevent or limit the ongoing activity, even when the post activity pain could be intensified by the activity. Adolescents reasoned this with their joy of physical activity and how it seemed to provide a break or an escape from the pain. One of the reasons for pushing through the pain was to be able to partake in an activity, a competition in particular, or simply not being the cause of an unsuccessful team activity. There was a sense of responsibility toward others. This favored pushing through the pain. Since pain had been a long-time experience for the adolescents, they yearned to complete something without pain interfering on the process or the outcome. There appeared to be a notion of reluctancy toward withdrawal from a team activity due to pain. The non-participatory behavior of sitting on a bench or taking a break, while others were active together was overall deselected.

There was a desire to complete something and several reasons for pushing through the pain. However, when the pain was recognized as a long-term condition and furthermore with an activity limiting impact, it had negative emotional consequences for the adolescents. The adolescents' main worry was that they would not be able to participate in physical activity alongside their peers, due to pain. Adolescents were left feeling uncertain as to what caused their pain and disappointment and that they

once again, were going to be singled out. The repetitiveness and the prolonged pain duration seemed to frighten and challenge hope for remission as one adolescent described. This level of activity limitation due to pain was described as difficult to tolerate and had a greater impact than what could initially be adapted to. The looking inward continued as the adolescents became aware of their declined level of function, due to pain. This decline appeared to be an unfamiliar, higher level of discomfort. According to the adolescents, the cause of their long-term pain covered varying levels of embracing the pain condition. Having a goal or an award in sight motivated a certain behavior in dealing with the pain.

4. DISCUSSION

4.1. PRINCIPAL FINDINGS

Our findings from study 1, 2 and 3 provide evidence-based knowledge of the prognosis and prognostic factors of long-term MSK pain in children and adolescents. Among Danish children and adolescents with self-reported MSK pain seeking care at the GPs clinical practice 53% reported multi-site pain and a median pain duration of 5 months. Among the five most common MSK pain sites; knee, ankle, back, heel, and neck, heel pain was the only pain site to show close to resolved cases at 12 months among all participants (Figure 3.2). At 6 months follow-up, up to one third of the Danish children and adolescents who consulted their GP with MSK pain still had pain. This pain at 6 months, was predicted most strongly by pain episode duration longer than 7 days and use of pain medication sometimes. Prognostic factors of long-term MSK pain in the literature span across the bio-psycho-social factors, but the majority were still biological factors. Across different MSK pain sites, female sex was consistently shown to be associated with increased risk of MSK pain at follow-up with estimates: OR and RR between 1.24 and 3.66. Among other prognostic factors strongly associated with 6 months pain among the Danish children and adolescents with MSK pain were feeling nervous often or sometimes, feeling tired during the day, and having difficulties falling to sleep.

Study 4 highlighted that adolescents with long-term MSK pain experienced the process of four themes from the first experience of MSK pain, to the beginning of the experienced reactions from other's, to their own acceptance of the pain and the experience of a long-term MSK pain condition.

Our findings suggest that while adolescents with long-term MSK pain have similar experiences, each of them has a unique story to tell.

4.2. STRENGTHS AND LIMITATIONS

In study 1, we developed a protocol using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement (Appendix D, Online supplementary appendix 3). We performed our literature search in eight databases with individual search strings constructed in cooperation with a skilled librarian (Appendix D, Appendix 1). Our searches were updated prior to final submitting of paper 1 without restriction on language or MSK pain duration[113]. We concluded no studies had been published based on child and adolescent populations recruited from a general practice setting. A strength is therefore that our ChiBPS cohort was solely recruited from general practice and that study 3 is the first study to explore the prognosis of adolescents with MSK pain consulting general practice. We used a sample size calculation prior to recruitment in study 2 and 3. However, we did not recruit according to these calculations. We recruited the ChiBPS cohort from

general practice clinics situated in rural and urban parts of Denmark consisting of a mix of single and multiple GPs of both genders and different ages. The cohort was recruited nationwide representative of the Danish child and adolescent population. There are several strengths related to our questionnaires. We differentiated MSK pain based on its limitation on activity from otherwise pain. This is particularly due to the commonality of pain important to distinguish and ensures differentiation of pain with and without an impact on the individual's self-reported activity level. We used identical questionnaires for all children and adolescents included i.e. both Danes and non-Danes were presented questions related to whether they felt Danish or not. This, to minimize information bias. We used a short recall period of 2 weeks to limit recall bias. We selected candidate prognostic factors based on our systematic review and on clinical relevance[1]. We used validates questions when possible and piloted them to ensure comprehension. The content of the questionnaires were not provided the children and adolescents prior to recruitment. Our results include modifiable factors associated with prognosis (psychosocial and interfering with daily activities). Most of these are identifiable in a general practice setting through examination and psychometric tests, the latter with financial benefits for the GP.

It is unclear how generalizable our findings from study 2 and 3 are to countries outside Denmark due to differences in health care, care-seeking behavior of patients, and culture. A small sample size of our ChiBPS cohort is a limitation that hindered stratified pain characteristics and pain impact in body sites in study 2 and 3 and a stratified analysis and multivariable model as originally planned for study 3. Leading to uncertainties of the estimates as well, future work is needed with larger sample sizes and formal hypothesis testing. Another limitation was the response rates of our questionnaires. The rates were 72% at 3 months follow-up, 70% at 6 months follow-up, and 67% at 12 months follow-up. Another limitation is that participants either completed the baseline questionnaire before (32%), after the GP consultation (76%), or started before and completed after (11%) within days after the consultation. This variation may imply an increase or a decrease in reported expectations of pain medication and future pain duration, since the consultation (which separates these three possible answers) might have had an impact on answering questions related to expectations.

In study 4 we interviewed 13 adolescents with experienced MSK pain on their own bodies. They were all recruited from the ChiBPS cohort and had a minimum of 6 months MSK pain duration. Our findings in study 4 were based on the adolescents' narratives in the dialogue with the interviewer NP. The interviews were with visual appearance of faces and non-verbal expression. Thus potentially causative for social desirability bias, denoting a mismatch between the genuine construction of the adolescents' reality and how this is presented to the interviewer[114]. All 13 adolescents had since their entry in the ChiBPS cohort 2-3 years prior to interview time to reflect and create meaning in an attempt to understand their pain condition. This potentially

leading to a differential response to the questions asked in the interview, predisposing to recall bias.

4.3. HOW DO WE DESCRIBE THE CARE-SEEKING CHILDREN AND ADOLESCENTS BESIDES HAVING MUSCULOSKELETAL PAIN?

The most common causes for consulting a GP in our study 2 and 3 were limitation in the habitual use of the body (64%), wanting the pain to stop (59%), and worrying about the cause of pain (55%). This is similar to previous research showing that pain intensity and activity limiting MSK pain were important drivers for seeking care among adolescents with pain complaints[76,113].

The most common MSK activity limiting pain body sites identified in our ChiBPS cohort were knee, ankle and back. Previous findings from UK general practice show the most common MSK pain body sites among a paediatric population as knee, back, and foot[56]. Our findings provide more detailed information on MSK pain through the relation to activity limitation including our most common non-activity limiting MSK pain sites of neck, back, and foot, our findings are similar to previous research. Compared to previous same-country findings from a school-based population of 3000 participants in Denmark; albeit not classified as pain related to activity limitation, our findings were similar to their most common pain sites of knee, back, and shoulder[39]. It has so far been unknown how large the impact of pain is among this primary care population. Previous research has mainly focused on secondary care or school-based populations. Studies generally observed a longer pain duration than our studies (often >12 months)[1], with a high proportion having previously contacted a health care practitioner[115]. Despite back pain affecting 33% of children in school-based populations, only six percent of them seek care for their back pain[116]. Care-seeking behaviour in children is uncommon and could indicate that years of pain duration push for a consultation rather than a wait-and-see approach. We found a shorter pain duration compared to previous cohorts of children and adolescents with MSK pain. This may suggest earlier contact to general practice. Despite this, we discovered that more than half of the sample experienced multi-site pain. Multi-site pain has consistently been identified as a prognostic factor for adult MSK pain[117,118] and our findings underline this association in adolescents. Adolescents seem to transition from single site pain complaints towards multi-site over time[119] and collectively these findings questions when we should intervene before development of multi-site pain. Konijnenberg et al. found approximately 50% school absence because of pain[120]. We found 22% reported difficulties in carrying their school bag to school, 31% had difficulties sitting for a 45-minute lesson, and 58% reported a negative effect of pain on their concentration.

4.4. WHAT INDICATES A POOR PROGNOSIS AT TIME OF CONSULTATION FOR MUSCULOSKELETAL PAIN?

Our findings in study 2 and 3 underline that MSK pain can persist up to 1 year for one third of care-seeking children and adolescents with MSK pain. This finding can support the GP in giving evidence-based advice to children and adolescents and their parents on the overall prognosis of MSK pain. Our findings furthermore suggest that the initial assessment of children and adolescents with MSK should include consideration of psychological and social as well as biological factors. The proportion of our Danish children and adolescents with MSK pain who have long-term pain are significantly lower compared to our results from our systematic review. At 3 months follow-up, 30% of the Danish participants had MSK pain and at 12 months, it was 24%. In our review the numbers were 35% and 54% 3 and 12 months follow-up respectively[1]. Whether the prognosis in our study 2 and 3 would be similar to study 1, when adjusted for the response rates of 72% and 67%, at 3 and 12 months respectively is possible but uncertain.

Female sex is suggested with a higher risk of long-term MSK pain followed by pain duration > one year, feeling anxious, daytime tiredness, > 6 non-school hours of sitting down/day and smoking all associated with an increased risk of a poor prognosis[1]. Most of the children and adolescents in our ChiBPS cohort were school children. Among all our prognostic variables, having pain outside school was the single factor reported by all participants with a poor outcome of pain at 6 months. This does not conflict with the assumption that most of schoolchildren's time is spent outside school. School hours consisting of learning as well as play may distract from pain. Pain medication is often first line treatment of MSK pain and easy accessible in most countries[121]. This together with the possibility to purchase over the counter Paracetamol may lead to self-management of MSK pain and furthermore longer pain duration before consulting the GP. Thus, supporting the indication that taking pain medication sometimes, is associated to a poor prognosis. Not surprisingly, reported pain duration longer than 4 months at time of consultation is weakly associated to pain at 6 months and an even weaker association is seen for pain duration longer than 12 months (also reported at time of consultation) (both ref: 0-3 months). This supports the assumption that even longer pain duration (years) push for a consultation rather than a wait-and-see approach and that that care-seeking behaviour in children and adolescents is uncommon[116].

Our prognostic factors differed in strength in their association to 6 months pain, but overall all presented wide 95% CIs, which could be generated by our small sample size or by variability herein. The 95% CI of some of our prognostic factors included 1. Future work is needed with larger sample sizes and formal hypothesis testing to provide definitive evidence on prognostic factors.

Previous research highlights sex differences in the response to pain. When assessing intensity of pain, threshold of pain, and pain-coping strategies females have a greater sensitivity to pain modalities and use social support, cognitive reinterpretation and positive self-statements, while males use behavioural distraction and problem-focused tactics to manage their pain[122-124]. This could partly explain female sex as a prognostic factor for long-term MSK pain. The prognostic factors that we report based on Danish children and adolescents; female sex, longer pain duration, sleep-related problems and multisite pain are similar to our previous findings based on international populations with persistent MSK pain[1]. However, daytime tiredness and difficulties falling asleep are known prognostic factors among neck pain participants and we identify a shorter pain duration than previously known[1] which could indicate that our population contacts general practice early in their course of pain. We also highlighted the association of feeling nervous and use of pain medication with long-term MSK pain, thus affirming previously identified psychosocial prognostic factors for long-term MSK pain[1]. Among previously identified prognostic factors that show no significant association with long-term pain in this population, were: sleep <= 7 vs. 8-9 hours/day and more than occasional alcohol consumption, compared to variables in this study (sleep <= 7 vs. 8-10 hours/day and alcohol consumption of varying frequency).

4.5. THE ADOLESCENT PAIN EXPERIENCE.

Family is believed to have a powerful influence on development and maintenance of chronic pain in pediatric populations[125]. This is corroborated by our findings showing how parental experienced pain facilitated to the adolescent's acceptance of their own pain. Having a home to bring their pain experience back to seemed to have a relieving effect on the pain experience. It allowed the adolescents to be more perceptible to open up and to share their pain experience. The adolescents reported how there were different demands from a person with personal pain experience. They did not demand the same level of explanation in terms of how and why the pain was there. There was a sense of shared understanding. The experience of pain was shared. Adolescents described how a lack of diagnosis was equal to nothing being wrong. They described feelings of confusion grounded in the inexplicability governed by the lack of a name connected to the pain. This caused a need to create a name. If they did not have a name they would tend to use the term whiney. These results support previous findings highlighting the meaning of a name in aiding the acceptance of a MSK pain condition[63] and the diagnosis as a step in the development of the adolescents' identity[32]. All the adolescents in this study were asked why they believed their pain had turned into a long-term pain condition. Being unable to embrace the pain, not having the tools or the knowledge to deal with their pain were self-reported causes for long-term pain. A lack of accept from peers as well as physicians were self-reported causes for long-term pain and as previously identified, lead to a sense of imprisonment in the pain condition and social disconnection[126]. The pain would intensify as a consequence[126].

In their descriptions of the MSK pain experience, the adolescents in study 4 first began identifying their pain at a point in time later than the time of first occurrence of pain. Witnessing that their pain did not cease supported their self-acknowledgement. At the same time of the long-term pain duration, they had expectations of the GP to take them seriously. This due to the longer pain duration or because of an increase in pain intensity. Because several had waited until a prolonged pain duration or frequent pain episodes before consulting the GP, this waiting period had created a level of expectation toward the GP. What seemed to push for a consultation (continuous or frequent pain) was suggested to be the grounds for the expectations as well.

Our findings highlight a wait-and-see approach as one of the most common recommendations provided by the GP. This corroborates previous findings[115]. The adolescents described how they perceived a wait-and-see recommendation as a sign of a good prognosis. There would be no further examination or treatment needed. Compared to adults with MSK conditions receiving a wait-and-see approach our findings resonate with feelings of disenfranchisement when in their experience, nothing was being done to the pain condition[127].

4.6. CLINICAL IMPLICATIONS

Our results underline that GPs need to be cognizant of the widespread bio-psycho-social impact and challenges these care-seeking children and adolescents experience. The GP should apply a multifactorial approach to the individual and the circumstances he/she surround themselves with. Co-occurring pain, psychological and social factors in general practice should be considered treatment-targets and we recommend questioning any recent events in the family or surroundings, that could potentially have an impact on the child since there is a lack of knowledge on the effect of these risk factors. They should also be taken into account when addressing the child or adolescents' coping behaviour and cognitive appraisal[128]. This due to acknowledgement of the potential multifactorial aetiology of the MSK pain in relation to their current wellbeing[89,129,130].

Our findings point toward both modifiable and non-modifiable factors associated with prognosis of long-term MSK pain. Most of these factors can be extracted from stored patient data, from performing psychometric tests and from examination, all in a clinical general practice setting and in an attempt to change the outcome for the better. The clinician may as such improve his/her understanding of a child or adolescents' risk of long-term MSK pain by asking questions at the initial MSK pain consultation to gather information on the individuals' present evidence-based prognostic factors for long-term MSK pain (Table 4.1). Most of the identified significant characteristics associated to prognosis are psychosocial, which is also the majority of our measured baseline characteristics. As such, we extended our previous knowledge into highlighting MSK pain interference on daily activities of children and adolescents with MSK pain. This may be of importance in the consultation of MSK pain

conditions in primary care setting, where psychological and social characteristics are not always included or prioritized during the MSK pain condition consultation.

Table 4.1. What to ask in clinical practice?

	General MSK pain	Low back pain	Neck pain	Knee pain
Prognostic factors	-Female sex and female smokers. -Day tiredness/fatigue. -Physical activity vs. none. -Depressive symptoms.	-Higher lumbar mobility[a]. -Longer pain duration. -Peer problems. -Smoking.	-Female sex. -Depressive symptoms. -Multisite pain vs. localized. -Day tiredness.	-Increasing age. -Daily pain. -Sport > 2t/week. -Low quality of life.
Questions	-Do you smoke? (F) -Do you feel tired during the day? -Do you do sport? -Are you feeling mentally well?	-Clinical examination. -How long have you had pain? -Do you have friends/do you experience bullying? -Do you smoke?	-Are you feeling mentally well? -Do you have pain in more than one MSK region? -Do you feel tired during the day?	-Do you experience daily pain? -Do you do practice sport frequently? -How are things at school and at home?[b]

Four prognostic factors belonging to 4 frequent MSK pain types in general practice. General musculoskeletal-, Low back-, Neck-, and Knee Pain. The questions are proposals towards assessment of prognosis on MSK pain. [a] to be evaluated by clinical examination. [b] suggested used in evaluation of quality of life. F, female patients[1].

Please see the supplementary animation on how our findings from our systematic review can be used in a clinical setting; access through link[1]:
https://www.youtube.com/watch?v=raltzsgkTHc

The knowledge of prognosis and prognostic factors may support the GP in offering evidence-based information on the likely prognosis and support the adolescents with the highest risk of a poor prognosis. Assuming that exposure to increased ACEs in childhood is associated to detrimental effects on long-term health[47,131], the highlighted psychosocial factors associated to the MSK pain experience and the prognosis of long-term MSK pain may have a significant negative impact on health. Exploration of these is something that most GPs are able to do based on their work function, since they in most cases are GPs for more than one generation of patients.

What an individual believes and does about their own MSK pain predicts how long the pain will last and to which extent it will be[41,42]. In study 4, we highlight that gaining an understanding of what an adolescent with MSK pain defines a hindrance of wellbeing might in turn improve the level of confidence in the GP. The GP may thus gain a more precise notion of where/what to manage and/or treat. To improve management of adolescent MSK pain an expansion in assessment from pain location and pain characteristics, to a wider range of focus on providing a safe space and time for the adolescents to inform and explain their current pain related challenges is needed. Knowledge of both the challenges and the strengths in terms of support from family or friends, may hold value in supporting the self-management of a MSK pain condition. Given that the beliefs of these individuals are modifiable, they are considered important targets for prevention and treatment of pain-related disability[132].

5. CONCLUSION

The overall objective of this PhD thesis was to help fill in the knowledge gap on children and adolescents consulting general practice with MSK pain.

With study 2, we described our ChiBPS cohort consisting of 100 8-19-year-old children and adolescents consulting their GP with MSK pain[2]. We found that two thirds of children and adolescents consult their GP with MSK pain because of limitations in the habitual use of their body due to pain. One third of children and adolescents are nervous or worried/anxious and more than half report their concentration is affected by their MSK pain.

Furthermore, our objective was to investigate the prognosis of child and adolescent MSK pain. With study 1 and 2, we highlighted the prognosis of long-term MSK pain among 0-19-year-olds in our systematic literature review (study 1) and 8-19-year-olds in our prospective cohort study (study 2). In our review, we found an average of 54.4% with MSK pain at 1-year follow-up[1] and among our ChiBPS cohort one in every four adolescents continued to experience MSK pain, even 12 months after they consulted their GP[2]. From our review we further found 63.5% with MSK pain at 4-year follow-up[1].

We wanted to investigate the prognostic factors for long-term MSK pain among children and adolescents consulting their GP. We explored this in study 1 and 3. With study 1, we identified baseline child and adolescent characteristics associated with a poor outcome on follow-up regardless of treatment provided (prognosis) or associated with successful outcome to a treatment (treatment effect modifiers). With study 3, we wanted to investigate the 3, 6, and 12-months prognosis and prognostic factors of 8-19-year-old children and adolescents with MSK pain in general practice. In study 1 and 3 we identified a range of factors that were associated with the risk of a poor prognosis. From our review, we found a total of 111 unique prognostic factors associated with MSK pain at follow-up[1]. Female sex, depression, anxiety, longer pain duration, sleep-related problems, and increasing age were al associated with MSK pain at follow-up[1]. We found that pain at 6-months follow-up was predicted most strongly by pain episode duration > 7 days, by pain medication use, sometimes, and by being nervous often or sometimes, being tired during the day, and having difficulties falling asleep[3].

Finally we aimed to extract in-depth insights into the adolescents' own experiences of MSK pain and what influenced their prognosis. Through interviews with 13 adolescents with long-term MSK pain experience, we identified a range of components of the adolescent long-term MSK pain experience. This included self-doubt, lack of accept, and challenges in learning to live with a long-term pain condition during adolescence[4].

We hypothesized, that by exploring our overall aim as described above, we could support the GP's assessment by offering evidence-based information on the likely prognosis and support the adolescents with the highest risk of a poor prognosis.

With this thesis we have highlighted a healthcare issue of significance. Our findings on bio-psycho-social factors are important in addressing children and adolescents with MSK pain as they represent co-occurring conditions. Our insight to the adolescents' own perspective on their long-term MSK pain condition help the GP to understand these care-seeking adolescents. The questioning and expectations of a certain performance level from other people led to feelings of insecurity and difficulties in living with the pain condition. This in contrast to the positive recognition from family, friends, and coaches. This adds to the current body of knowledge supporting the wide reaching impact of long-term MSK pain and show it goes beyond the pain experience and that there is a need to consider the complexity of the pain experience including a validation hereof.

SUMMARY

Eight percent of all child and adolescent general practice consultations are due to musculoskeletal (MSK) conditions with pain as the most frequent symptom. Despite the commonality of MSK pain limited knowledge exists about care-seeking children and adolescents with MSK pain. Studies from school populations studies show that up to 50% still experience pain 1-4 years later. Adolescents with MSK pain have an increased risk of health and social difficulties into adulthood. No studies have explored the prognosis of adolescents with MSK pain consulting general practice. The aim of this PhD thesis was therefore to investigate the prognosis of child and adolescent MSK and the prognostic factors of long-term MSK pain.

This PhD thesis was initiated by performing a systematic review searching for prospective cohort studies on prognostic factors or treatment effect modifiers on persistent MSK pain in 0-19 year old children and adolescents. Following the identification of prognostic factors based on international recruited data, we recruited a cohort of 8-19 year old children and adolescents consulting the general practitioner (GP) with self-reported MSK pain (ChiBPS cohort) from 17 general practice clinics across Denmark. The children and adolescents in the ChiBPS cohort completed a questionnaire at baseline, 3, 6, and 12-months follow-up providing data on demographics, physical activity, pain impact, psychosocial factors, and expectations towards the general practitioner. The data retrieved from the questionnaires lead to two studies; 1. cross sectional study describing characteristics of the ChiBPS cohort at time of consultation and 2. prospective cohort study investigating the 3, 6, and 12-months prognosis and prognostic factors of the ChiBPS cohort. We rounded off with the fourth and final study of this PhD thesis, where we drew on a sample of 13 adolescents from the ChiBPS cohort, of which all had a poor prognosis at 6-months follow-up. We performed semi-structured interviews to gain in-depth insights into the adolescent's experiences and beliefs on what influenced their prognosis. Data analysis was performed using a general inductive approach.

Our first study yielded a total of 111 unique prognostic factors on persistent MSK pain. Female sex and psychological symptoms were the most frequent investigated prognostic factors. We included 100 children and adolescents (54% female, median age 13 (IQR: 12-16.5 years) in our ChiBPS cohort. The most common pain site was the knee (56%) and the median pain duration at time of consultation was 5 months (IQR: 3 weeks-1 year). Sixty-three percent consulted the general practitioner due to the inability to use their body as usual, due to pain. After 6-months, 36% reported activity limiting pain and 42% reported multi-site pain. At 12-months follow-up, 26% reported activity limiting pain. Children and adolescents who felt nervous (OR 4.2 95% CI 1.4-12.5) or tired during the day (OR 2.9 95% CI 1.1-7.7), with 1-7 days pain episodes (OR 7.1 95% CI 1.8-28.9), who used pain medication (OR 5.4 95% CI 1.6-18.4), had difficulties falling asleep (OR 4.8 95% CI 1.7-13.9), carrying a schoolbag (OR 3.8 95% CI 1.1-13.1), or bending down to put on socks due to pain (OR 4.1 95%

CI 1.3-13.2) had a higher risk of pain after 6-months. In our fourth and final study we performed 13 interviews and derived four broad themes describing the experience of long-term MSK pain from: (a) the first pain, where adolescents report their expectations and experience of the first pain episode and consultation with the general practitioner; (b) other people's reaction, where adolescents describe the experience of sharing their pain and having a perceptible pain; (c) accepting the pain, where gaining a level of acceptance of pain could impact the experience of pain; to (d) the long-term pain, where the adolescents describe how pushing through the pain could be driven by the award of partaking in a shared experience or daily life activity.

In conclusion the studies of this PhD thesis have contributed with the identification of a number of components of the child and adolescent long-term MSK pain condition and experience. Our findings underline the commonality of long-term MSK pain in children and adolescents and the demands for a multidisciplinary bio-psycho-social approach. Behind the pain sensation and decreased functionality as often presented to the general practitioner, were self-doubt, lack of accept, and challenges in learning to live with a long-term pain condition. Supporting our hypothesis, our findings may help guide clinical practice and shared decision-making by offering evidence-based information on the likely prognosis and support the adolescents with the highest risk of a poor prognosis.

Last but not least, we have passed on the adolescents' own perspective on their MSK pain condition.

DANSK RESUME

Otte procent af alle børn og unge konsultationer i almen praksis er grundet muskelskelettilstande, hvoriblandt smerte er det hyppigste symptom. På trods af at muskelskeletsmerte er hyppigt er viden om lægesøgende børn og unge med muskelskeletsmerte begrænset. Studier baseret på skolepopulationer viser at op til 50% stadig oplever smerte 1-4 år efter. Unge med muskelskeletsmerte har en øget risiko for helbreds- og sociale vanskeligheder ind i voksenalderen. Ingen studier har eksploreret prognosen for unge med muskelskeletsmerte, der søger læge i almen praksis. Formålet med dette ph.d. studie var derfor at undersøge prognosen og prognostiske faktorer for langvarig muskelskeletsmerte hos børn og unge med muskelskeletsmerte.

Dette ph.d. studie blev initieret med en systematisk litteraturgennemgang, hvor vi søgte på prospektiv kohorte studier omhandlende prognostiske faktorer eller effektmodifikatorer for langvarig muskelskeletsmerte hos 0-19 årige børn og unge. Efterfulgt af denne identificering af prognostiske faktorer baseret på international data, rekrutterede vi en kohorte af 8-19 årige (ChiBPS kohorte) fra 17 almen medicinske klinikker på tværs af Danmark. Kohorten havde alle konsulteret deres praktiserende læge med selvrapporterede muskelskeletsmerte. Børn og unge i ChiBPS kohorten besvarede et spørgeskema ved baseline og 3, 6 og 12 måneder efter. Spørgeskemaet bestod af data om demografi, fysisk aktivitet, smertepåvirkning, psykosociale faktorer og forventninger til den praktiserende læge. Data fra spørgeskemaerne blev anvendt i to studier; studie 2; et tværsnitsstudie beskrivende karakteristika for ChiBPS kohorten på tidspunkt for konsultation og studie 3; et prospektivt kohorte studie undersøgende 3, 6 og 12 måneders prognose og prognostiske faktorer for ChiBPS kohorten. Vi rundede af med det fjerde og sidste studie af ph.d. studiet, hvor vi anvendte en stikprøve på 13 unge fra ChiBPS kohorten, der alle havde smerter ved 6 måneders opfølgning. Vi udførte semi-strukturerede interviews for at opnå et dybdegående indblik i de unges oplevelser og tro på hvad der ifølge dem selv influerede deres prognose. Vi anvendte general induktiv tilgang til data analyse.

Vores studie 1 gav et udbytte på samlet 111 unikke prognostiske faktorer for langvarig muskelskeletsmerte. Hunkøn og psykologiske symptomer var iblandt de hyppigst undersøgte prognostiske faktorer. Vi inkluderede 100 børn og unge i vores ChiBPS kohorte (54% hunkøn, median alder 13 (IQR: 12-16.5 år)). Den hyppigste smertelokalisation var knæ (56%) og median smertevarighed på tidspunkt for konsultation hos egen læge var 5 måneder (IQR: 3 uger - 1 år). Treogtres procent konsulterede deres praktiserende læge, grundet manglende evne til at bruge kroppen som sædvanlig grundet smerten. Efter 6 måneder angav 36% aktivitetsbegrænsende smerte og 42% smerte flere steder på kroppen. Ved 12 måneders opfølgning angav 26% aktivitetsbegrænsende smerte. Børn og unge som angav sig nervøse (OR 4.2 95% CI 1.4-12.5) eller træt i løbet af dagen (OR 2.9 95% CI 1.1-7.7), med 1-7 dages

smerteepisodevarighed (OR 7.1 95% CI 1.8-28.9), som tog smertestillende medicin (OR 5.4 95% CI 1.6-18.4), havde vanskeligheder ved at falde i søvn (OR 4.8 95% CI 1.7-13.9), ved at bære en skoletaske (OR 3.8 95% CI 1.1-13.1) eller bukke sig for at tage strømper på grundet smerte (OR 4.1 95% CI 1.3-13.2) havde alle en højere risiko for smerte efter 6 måneder. Vores 13 interviews gav fire brede temaer, beskrivende oplevelsen af langvarig muskelskeletsmerte fra: (a) den første smerte, hvor de unge angav deres forventninger og oplevelser af den første smerteepisode og konsultation med den praktiserende læge; (b) andre menneskers reaktioner, hvor de unge beskrev oplevelsen af at dele deres smerte og have en synlig smerte; (c) acceptere smerten, hvor opnåelse af et niveau af accept af smerte kunne påvirke smerteoplevelsen til (d) den langvarige smerte, hvor de unge beskrev hvordan at presse igennem smerten kunne drives af en gevinst i deltagelse i en fælles oplevelse eller hverdagsaktivitet.

Studierne i denne ph.d. afhandling har bidraget med identificering af et antal af komponenter i børn og unges langvarige muskelskeletsmertetilstand- og oplevelse. Vores resultater understreger fællestræk af langvarig muskelskeletsmerte hos børn og unge og indbyder til en multidisciplinær bio-psyko-social tilgang. Bag smertesensationen og en nedsat funktionsevne som oftest præsenteres for den praktiserende læge fandt vi selv-tvivl, manglende accept og udfordringer i at lære at leve med en langvarig smertetilstand. Understøttende vores hypotese kan vores resultater hjælpe med at guide klinisk praksis og fælles beslutningstagende ved at tilbyde evidensbaseret viden om den sandsynlige prognose og ikke mindst støtte de unge med den højeste risiko for en dårlig prognose.

Sidst men ikke mindst har vi videreformidlet de unges eget perspektiv på deres muskelskeletsmertetilstand.

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APPENDICES

Appendix A. Informed consent.

DET VIDENSKABSETISKE KOMITÉSYSTEM

(S1)

Informeret samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel: Børn og unge med muskelskeletsmerte: prognose, etnicitet og langvarig smerte.

Erklæring fra forsøgspersonen:

Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet, og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: _____

Dato: _____ Underskrift: _____

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:

Ja _____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information: Negar Pourbordbari

Dato: _____ Underskrift: _____

Projektidentifikation: (Fx komiteens Projekt-ID, EudraCT nr., versions nr./dato eller lign.)

Standardsamtykkeerklæring udarbejdet af Det Videnskabsetiske Komitésystem, august 2016.

DET VIDENSKABSETISKE KOMITÉSYSTEM

(S5)

Samtykke fra forældremyndighedens indehaver til deres barns deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel: Børn og unge med muskelskeletsmerte: prognose, etnicitet og langvarig smerte.

Erklæring fra indehaveren af forældremyndigheden:

Jeg/vi har fået skriftlig og mundtlig information og jeg/vi ved nok om formål, metode, fordele og ulemper til at give mit/vores samtykke.

Jeg/vi ved, at det er frivilligt at deltage, og at jeg/vi altid kan trække mit/vores samtykke tilbage uden, at min/vores datter/søn mister sine nuværende eller fremtidige rettigheder til behandling.

Jeg/vi giver samtykke til, at _____ (barnets navn) deltager i forskningsprojektet. Jeg/vi har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Navnet eller navnene på forældremyndighedens indehaver(e):

_____ _____

Dato: _____ Underskrift: _____

Dato: _____ Underskrift: _____

Ønsker du/I at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for Dit/jeres barn?:

Ja ____ (sæt x) Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forældrene/barnet har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at forældrene kan træffe beslutning om barnets deltagelse i forsøget.

Navnet på den, der har afgivet information: Negar Pourbordbari

Dato: _____ Underskrift: _____

Projektidentifikation: (Fx komiteens Projekt-ID, EudraCT nr., versions nr./dato eller lign.)

Appendix B. Sample size calculations.

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

1

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). **W**hen 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
```

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

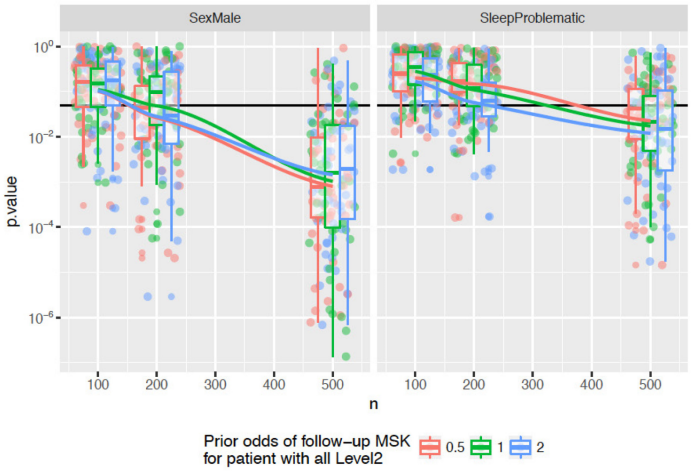
For $O = 1/2$ such that $p = P(\text{MSK at follow-up} \mid \text{Sex} = \text{Male}, \text{Sleep} = \text{OK}) = (1/2)/(1 + (1/2)) = 0.33$, we instead get:

```
## # 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 $O \in \{1/2, 1, 2\}$.


SexMale
SleepProblematic
p.value
10^{0}
10^{-2}
10^{-4}
10^{-6}
100
200
300
400
500
n
Prior odds of follow−up MSK
for patient with all Level2
0.5
1
2

Appendix C. MPU

PRAKTISERENDE LÆGERS ORGANISATION

UDVALGET FOR MULTIPRAKSISUNDERSØGELSER

dsam
Dansk Selskab for Almen Medicin

1. oktober 2017

Kære Negar Pourbordbari

Vedr. MPU 20-2017 Children and adolescents with musculoskeletal pain: prognosis, ethnicity and persistent pain

På baggrund af indstilling fra forskningsleder Martin Bach Jensen, Forskningsenheden for Almen Praksis, Aalborg Universitet har MPU-udvalget vurderet projektet og anbefaler praktiserende læger at deltage.

Det forudsættes, at den angivne finansiering til sekretær i praksis mhp. tidsforbrug er til stede.

Du bedes oplyse evt. deltagende praktiserende læger om indholdet af dette brev.

Vurderingen vil blive offentliggjort på DSAM's hjemmeside, www.dsam.dk, se under Forskning – Multipraksisudvalget – MPU-projekter.

MPU modtager gerne et eksemplar af eventuelle publikationer af undersøgelsen.

Med venlig hilsen

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Appendix D. Paper 1.

BMJ Open

Poor prognosis of child and adolescent musculoskeletal pain: a systematic literature review

Negar Pourbordbari, Allan Riis, Martin Bach Jensen, Jens Lykkegaard Olesen, Michael Skovdal Rathleff

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ABSTRACT

Objectives To identify baseline patient characteristics that are (1) associated with a poor outcome on follow-up regardless of which treatment was provided (prognosis) or (2) associated with a successful outcome to a specific treatment (treatment effect modifiers).

Design Systematic literature review according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.

Data sources Medline, Embase, Cinahl, Web of Science, Cochrane, SportDiscus, OT Seeker and PsychInfo were searched for prospective cohort studies up to February 2019 without limitation in publication date.

Eligibility criteria Prospective cohort studies reporting either prognostic factors or treatment effect modifiers on persistent musculoskeletal pain in 0-year-old to 19-year-old children and adolescents. Pain caused by tumours, fractures, infections, systemic and neurological conditions were excluded.

Outcome measures Our primary outcome was musculoskeletal pain at follow-up and identification of any baseline characteristics that were associated with this outcome (prognostic factors). No secondary outcomes were declared.

Method Two reviewers independently screened abstracts and titles. We included prospective cohort studies investigating the prognosis or treatment effect modifiers of 0-year-old to 19-year-old children and adolescents with self-reported musculoskeletal pain. Risk of bias assessment was conducted with the Quality in Prognostic Studies tool.

Results Twenty-six studies yielding a total of 111 unique prognostic factors were included. Female sex and psychological symptoms were the most frequent investigated prognostic factors. Increasing age, generalised pain, longer pain duration and smoking were other identified prognostic factors. No treatment effect modifiers were identified.

Conclusion Several prognostic factors are associated with a poor prognosis in children and adolescents with musculoskeletal pain. These prognostic factors may help guide clinical practice and shared decision-making. None of the included studies was conducted within a general practice setting which highlights an area in need of research.

PROSPERO registration number CRD42016041378.

Strengths and limitations of this study

- ► This review is highly updated with a search up to February 2019.
- ► No previous review has aimed to identify prognostic factors in children and adolescents with musculoskeletal pain with the purpose of informing clinical practice.
- ► In collaboration with a research librarian, a highly sensitive search for each of the eight databases was developed to ensure an inclusion of the totality of previous research.
- ► Two reviewers independently carried out the screening and data extraction was executed in the same manner for all included studies.
- ► No meta-analysis was conducted due to a heterogeneity of patient population, setting and endpoints.

INTRODUCTION

General practice is often the point of first contact into the healthcare system and musculoskeletal pain complaints are the most common cause of contact. The case workload due to musculoskeletal pain complaints in children and adolescents is estimated to be 4%–8% of the UK general practice[1] and musculoskeletal pain is known to affect half of all children and adolescents, increasing exponentially in frequency around the age of 10 years.[2–6] A recent systematic review reported that 40% of an adolescent population had experienced pain during the last 6 months.[3] The most common pain sites are the knee and back.[7] Musculoskeletal pain has a detrimental impact on the adolescents' quality of life and may cause them to withdraw from school, social and athletic activities.[8 9]

Musculoskeletal pain in children and adolescents has previously been considered a self-limiting condition without long-term impact.[10] Recent cohort studies show that 16%–32% of patients with knee pain still report knee pain 1 year later[10 11] and that 21% of 12-year to 35-year olds had persistent knee pain 6 years after initial contact to their general practitioner.[10] Collectively, these studies highlight that a significant proportion of adolescents will report pain even years later. Who are the

children and adolescents with a particularly high risk of long-lasting musculoskeletal pain? This is one of the most common questions from our stakeholder interviews with general practitioners (*unpublished stakeholder event*).

Knowledge of prognostic factors can inform the general practitioner of the prognosis of their patients and enable them to identify those with a poor prognosis to stratify care, address modifiable risk factors and better understand chronic pain conditions. The latest systematic review on prognostic factors for adolescents with musculoskeletal pain[12] ended their literature search in July 2015 which makes for a timely update. So far, no systematic reviews have aimed to inform clinical practice of prognostic factors in children, and adolescents with musculoskeletal pain. Therefore, we aimed to identify baseline patient characteristics associated with a (1) poor outcome on follow-up (prognosis) or (2) successful outcome of a treatment (treatment effect modifiers).

METHODS

Literature search

We searched in Medline, Embase, Cinahl, Web of Science, Cochrane, SportDiscus, OT Seeker and PsychInfo from their inception until February 2019 without limitation on date. An experienced research librarian collaborated in the production of individual search strategies for each of the eight databases (see online supplementary appendix 1).

Eligibility criteria

Study population and design

We included prospective studies that investigated prognostic factors or treatment effect modifiers in children and adolescents 0-year to 19-year olds, with any type and location of musculoskeletal pain. Musculoskeletal pain was defined as pain in muscle, tendon, bone and joint.[13] We included musculoskeletal pain types, reported in each of our included studies, without further definition of or changes in the designations chosen by the respective authors. We excluded pain knowingly caused by tumours, fractures, infections, systemic and neurological conditions, and stomach pain, because of insufficient differentiation between musculoskeletal stomach pain and stomach pain by other causes. Furthermore, we included all prospective studies, independent of intervention and randomised trials including all types of comparators. As expected, most studies did not use a comparator because they were prospective cohort studies. Similar to intervention, these studies were included independent of comparators. There were no restrictions on the type of setting or language.

Review process

Two reviewers (NP and AR) independently screened titles and abstracts for studies addressing the question: What are the prognostic factors and treatment effect modifiers for children and adolescents with musculoskeletal pain? Full-text articles were then screened, adding primary reasons for exclusion.

There was no blinding of the review authors to the journal titles, authors or institutions. Reference lists of all included studies were screened for eligible publications that may have been missed during the initial search. The study selection process was finalised without any disagreements on included studies. EndNote was used to remove duplicates and NP manually checked for duplicates afterwards.

Data extraction

Data for the included studies were extracted by NP in the form of: *study characteristics* (study design, recruitment setting and duration of follow-up), *participant characteristics* (musculoskeletal pain type, baseline age, study population and persistent pain at follow-up in females, males and combined) (table 1) and *prognostic factors* with their reported estimates: ORs, relative risks (RR), 95% CI) and/or p values. If possible, we extracted the adjusted associations.

Data were extracted with a predefined data extraction form inspired by The Cochrane Collaboration.[14]

Outcomes and endpoints

Our primary outcome of interest was musculoskeletal pain at follow-up. We wanted to identify any baseline characteristics that were associated with this outcome (prognostic factors). We used the term 'pain persistence' to describe participants who had pain at both baseline and follow-up, without applying restrictions on either pain measurement or on follow-up time points.

Risk of bias

Risk of bias was assessed using the Quality in Prognostic Studies (QUIPS) tool.[15] On the study level, NP and AR independently rated the 26 included studies and reached consensus on all risk of bias assessments (table 2). Prognostic factors from studies with a high risk of bias, were excluded from figure 1.

Involvement of general practitioners

With stakeholder involvement and input from a panel of general practice researchers experienced in musculoskeletal research, we subgrouped our identified prognostic factors in accordance with the biopsychosocial model[16 17]:

Biological prognostic factors

- Female sex.
- Older age.
- Body measurement factors.
- Physical functioning.
- Pain characteristics.

Psychological prognostic factors

- General psychological factors.
- Depressive factors.

Table 1 Included studies described by musculoskeletal pain type, baseline age, size of study population and follow-up

Study (reference)	MSK pain type	Baseline age (years)	Recruitment setting	Study population (n)	Follow-up (years)	Persistent pain at follow-up female (%)	Persistent pain at follow-up male (%)	Persistent pain at follow-up combined (%)
Blaauw[19]	Headache	12–16	School	1586	4	45.7	22.7	35.1
Brattberg[20]	Back, head	8, 11, 13	School	471	2	Back 15 Head 40	Back 4 Head 20	Back 9.3 Head 30.7
Brattberg[21]	General MSK	10, 13, 16	School	597	11	59	39	20
El-Metwally[22]	General MSK	9–12	School	1756	1 and 4	4 years: 56.2	4 years: 43.8	1 years: 53.8 4 years: 63.5
El-Metwally[11]	Lower limb	9–12	School	1756	1 and 4	1 year: 29.4 4 years: 31.9	1 year: 55.8 4 years: 48.6	1 year: 32 4 years 31
Flato[23]	General MSK	2–17	Clinical	37	9	13	N/A	59
Holley[24]	General MSK	10–17	Clinical	88	3 months	87.1	12.9	35.2
Jones[25]	Low back	11–14	School	330	4	N/A	N/A	26
Jussila[26]	General MSK	16–18	Community	1773	2	N/A	N/A	N/A
Laimi[27]	Headache*	13	School	311	3	54	70.5	48
Lunde[28]	Low back	15–19	School	420	6.5	N/A	N/A	39
Mikkelsson[29]	Neck, WSP, low back	9–12	School	1756	1	N/A	N/A	Neck 48.3 WSP 29.7 Low back 34.4
Mikkelsson[30]	General MSK	9–12	School	1756	1	N/A	N/A	52.9
Mikkelsson[31]	Neck, WSP	9–12	School	464	1	Neck 70.4 WSP 62.5	Neck 41 WSP 62.5	Neck 58.1 WSP 62.5
Mikkonen[32]	Low back	16	Community	2969	2	N/A	N/A	27.1
Mikkonen[33]	Low back	16	Community	728	2	53	46	50.4
Mikkonen[34]	Low back	7–19	Community	1660	2 and 3	2 years: 68 3 years: 63	2 years: 62 3 years: 47	N/A
Paananen[35]	General MSK	16	Community	1594	2	N/A	75	88
Rathleff[9]	Knee	12–15	School	768	1	N/A	N/A	48.8
Rathleff[26]	Knee	16–18	School	504	2	N/A	N/A	55.9
Rathleff[27]	Knee (PFP)	15–19	School	121	3 months	N/A	N/A	74.4
Sjölie[38]	Low back	14–16	Community	88	3	N/A	N/A	39
Sperotto[39]	General MSK	8–13	School	289	3	N/A	N/A	54.3
Stanford[17]	Head, back, stomachache	10–11	Community	2488†	2	N/A	N/A	Head 29 Back 21.7

Continued

Table 1 Continued

Study (reference)	MSK pain type	Baseline age (years)	Recruitment setting	Study population (n)	Follow-up (years)	Persistent pain at follow-up female (%)	Persistent pain at follow-up male (%)	Persistent pain at follow-up combined (%)
Ståhl[40]	Neck	9–12	School	1756	1 and 4	N/A	N/A	1 year: 48.2 4 years: 33.5
Uziel[41]	Growing pain	10–16	Clinical	35	5	N/A	N/A	48.6

*Headache: non-migrainous.
†Included stomachache participants.
MSK, musculoskeletal; N/A, not applicable; PFP, patellofemoral pain; WSP, widespread pain.

Social prognostic factors

- General social factors.
- Factors related to sleep/daytime tiredness.
- Physical activity/inactivity.
- Alcohol.
- Smoking.

Reporting of results

We were not able to conduct our a priori planned meta-analysis because of heterogeneity in terms of patient population, setting and time points for follow-up. The evidence on included prognostic factors was reported with ORs, RR and/or p values. As OR and RR may differ in interpretation, we reported them separately. A statistically significant association between a patient characteristic and an outcome was defined as an RR or OR above or below 1 that did not include 1 in the 95% CI. As for p value, a statistically significant association was defined as p<0.05. Average on pain at follow-up was calculated as average of individual studies reporting same musculoskeletal pain type at same follow-up duration (figure 2).

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist when writing our report[18] (see online supplementary appendix 2).

Patient and public involvement

No patients or public were involved in the present study.

RESULTS

Included studies

Figure 3 reports the results of the search strategy. Of the 48 538 titles identified, 41 735 studies were screened, and 26 studies[9 11 17 19–41] were included. All included studies were prospective studies. The included studies used a mix of different measures to capture pain at follow-up. Musculoskeletal pain types included in our search were general musculoskeletal pain, neck, back, lower back, lower limb, knee and growing pain. No treatment effect modifiers were identified.

Extracted data from the included studies: MSK pain type, baseline age, recruitment setting, size of study population, follow-up and percentage of study participants who represented persistent pain at follow-up, both stratified by gender and combined.

Risk of bias

The most common reasons for a moderate or high risk of bias were inadequately described study participation and statistical analyses (n=6, 23%), attrition rates (n=5, 20%) and poor adjustment for confounders (n=11, 42%). Three studies were rated with high risk of bias. With the purpose of filtering the results of prognostic factors, we excluded these studies from the final results depicted in figure 1.

Risk of bias in included studies. With the QUIPS tool studies were assessed on the overall risk of bias within each of the six domains and rated as low, moderate or

Table 2 Risk of bias in included studies. With the Quality in Prognostic Studies tool studies were assessed on the overall risk of bias within each of the six domains and rated as low, moderate or high risk of bias

Study author year	Design	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and presentation
Blauuw *et al* 2015[19]	Prospective cohort	Low	Moderate	Low	Low	Moderate	Low
Brattberg 1993[20]	Prospective cohort	Moderate	Moderate	Low	Low	Moderate	High
Brattberg 2004[21]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
El-Metwally *et al* 2004[22]	Prospective cohort	Low	Low	Low	Low	Low	Low
El-Metwally *et al* 2005[49]	Prospective cohort	Low	Low	Low	Low	Low	Low
Flatø *et al* 1997[23]	Prospective cohort	Low	Low	Low	Low	Low	Low
Holley *et al* 2017[24]	Prospective cohort	Low	Low	Low	Low	Low	Low
Jones and Macfarlane 2009[25]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Jussila *et al* 2014[26]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Laimi *et al* 2007[27]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Lunde *et al* 2015[28]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Mikkelsson *et al* 1997[29]	Prospective cohort	Low	Low	Low	Low	Moderate	Moderate
Mikkelsson *et al* 1998[30]	Prospective cohort	Low	Low	Low	Low	Low	Moderate
Mikkelsson *et al* 1999[31]	Prospective cohort	Low	Low	Low	Low	Low	Low
Mikkonen *et al* 2008[32]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Mikkonen *et al* 2012[33]	Prospective cohort	Moderate	Low	Low	Low	Low	Low
Mikkonen *et al* 2013[34]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Paananen *et al* 2010[35]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Rathleff *et al* 2013[9]	Prospective cohort and nested case–control	Moderate	Low	Low	Low	Low	Low
Rathleff *et al* 2016[36*]	Prospective cohort	Low	Low	Low	Low	Low	Low
Rathleff *et al* 2016[37]	Prospective cohort	Low	Low	Low	Low	Low	Low
Sjölie and Ljunggren 2001[38]	Prospective cohort study with a cross sectional part	Low	Low	Low	Low	Low	Low
Sperotto *et al* 2015[39]	Prospective cohort	Low	Moderate	Low	Low	High	Moderate
Stanford *et al* 2008[17]	Prospective cohort	Low	Moderate	Low	Low	Low	Low
Ståhl *et al* 2008[40]	Prospective cohort	Low	Moderate	Low	Low	Moderate	Low
Uziel *et al* 2010[41]	Prospective cohort	Moderate	Low	Low	Low	High	Moderate

*'Is knee pain during adolescence a self-limiting condition?'

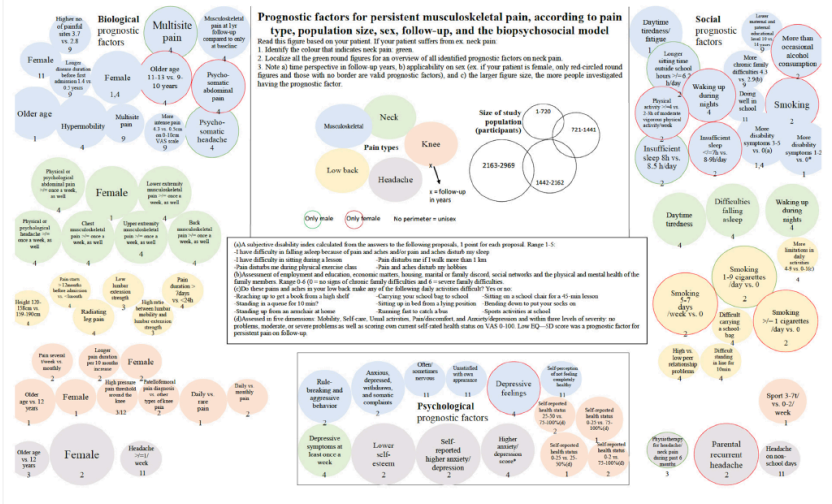

Figure 1 Prognostic factors for persistent musculoskeletal pain, according to pain type, population size, sex, follow-up and the biopsychosocial model.

high risk of bias. Three studies were rated with high risk of bias, and hence excluded from the final results.

Prognosis

Figure 2 highlights the persistence of musculoskeletal pain in all included studies at different follow-up time points and is calculated based on persistent pain at follow-up in table 1. At 1 year follow-up, an average of 54.4% with general musculoskeletal pain, an average of 41.8% with neck pain and 48.8% with knee pain reported pain. At 4-year follow-up, 63.5% with general musculoskeletal pain, 33.5% with neck pain and 26% with low back pain reported pain. At 9-year follow-up, 59% with general musculoskeletal pain reported pain. A complete report of all the identified prognostic factors is listed in online supplementary table 1. Figure 1 depicts the majority of these prognostic factors, stratified by pain type, sex, study population size and follow-up (please see online supplemental table 1 for explanatory notes).

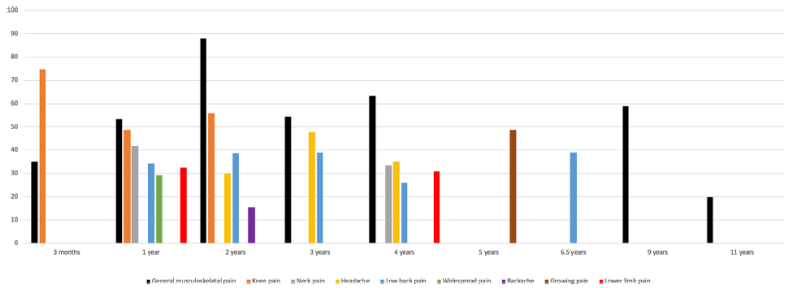

Figure 2 Persistent musculoskeletal pain, stratified in pain type and follow-up. The included studies investigated pain at follow-up time points ranging from 3 months to 11 years. General musculoskeletal pain (black) persisted in >50% of participants after 1, 2, 3, 4 and 9 years of follow-up.

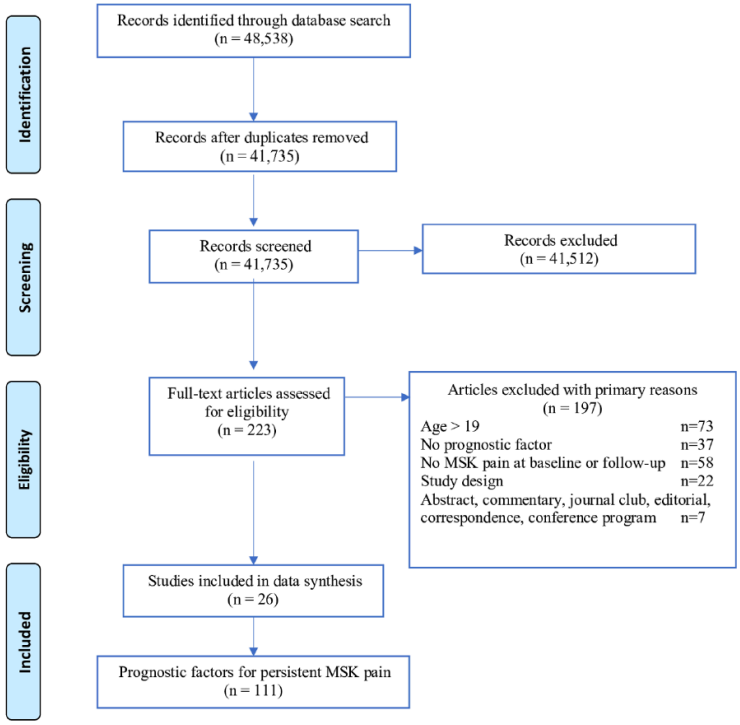

Figure 3 PRISMA flowchart presenting the flow of citations reviewed in the course of the systematic review. Forty-eight thousand five hundred and thirty-eight articles were identified through search in eight databases, resulting in 223 articles for full-text eligibility screen and a final number of 26 studies for inclusion yielding 111 prognostic factors on musculoskeletal pain.

Very few prognostic factors were reported on back pain, growing pain, lower limb pain and widespread musculoskeletal pain (see online supplementary table 1); consequently, they were excluded from figure 1. Table 3 condenses the results from online supplementary table 1 and highlights four prognostic factors on four different musculoskeletal pain types. Below each factor are suggestive questions to provide the general practitioner with insight into the patient's prognosis. Table 3 and figure 1 can be printed and used by a general practitioner at time of initial consultation with a 0-year-old to 19 year-old patient with musculoskeletal pain.

Please see the online supplementary file-video for an animation showing how our findings can be used in a clinical setting.

Prognostic factors associated with pain at follow-up

A total of 111 prognostic factors were associated with musculoskeletal pain at follow-up, of which most were on general musculoskeletal pain and low back pain (table 3). Online supplementary table 1 includes these results and further detailed depiction of prognostic factors.

Female sex was the most frequently identified prognostic factor associated with musculoskeletal pain at follow-up. Eleven studies identified psychological factors (eg, depression, anxiety and low self-esteem) to be associated with pain at follow-up in seven out of nine musculoskeletal pain types.[9 17 19 21 22 25 26 30 35 36 40]

Longer pain duration was associated with pain at follow-up across four musculoskeletal pain types: musculoskeletal, low back, knee and back pain.[21 23 25 36]

Table 3 What to ask in clinical practice? Four prognostic factors belonging to four frequent musculoskeletal pain types in general practice: General musculoskeletal pain, low back pain, neck pain and knee pain. The questions are proposals towards assessment of prognosis on musculoskeletal pain

	General musculoskeletal pain	Low back pain	Neck pain	Knee pain
Prognostic factors	► Female sex and female smokers. ► Day tiredness/fatigue. ► Physical activity versus none. ► Depressive symptoms.	► Higher lumbar mobility.* ► Longer pain duration. ► Peer problems. ► Smoking.	► Female sex. ► Depressive symptoms. ► Multisite pain versus localised. ► Day tiredness.	► Increasing age. ► Daily pain. ► Sport >2 t/week. ► Low quality of life.
Questions	► Do you smoke?(F). ► Do you feel tired during the day? ► Do you do sport? ► Are you feeling mentally well?	► Clinical examination. ► How long have you had pain? ► Do you have friends/ do you experience bullying? ► Do you smoke?	► Are you feeling mentally well? ► Do you have pain in more than one musculoskeletal region? ► Do you feel tired during the day?	► Do you experience daily pain. ► Do you do practice sport frequently? ► How are things at school and at home?†

*To be evaluated by clinical examination.
†This question is a suggestion for use in evaluation of quality of life.
F, female patients.

Five studies identified sleep-related problems associated with outcome.[22 26 30 35 40]

Other indicators for musculoskeletal pain at follow-up were increasing age,[9 22 27 30] smoking,[32 35] parental pain[17 23 41] and multisite pain.[22 23 40]

Figure 1 summarises all identified prognostic factors for musculoskeletal pain at follow-up, stratified by pain type, study population size, sex and follow-up.

Non-significant prognostic factors

We identified a total of 134 patient characteristics across nine musculoskeletal pain types and different follow-up time points with a non-significant association with musculoskeletal pain at follow-up (see online supplementary table 1).

Increasing age[11 21 23 28 29 31 36 41] was the most frequently identified baseline factor with a non-significant association to musculoskeletal pain at follow-up. Multiple studies reported non-significant evidence on higher body mass index[23 26 28] and hypermobility.[11 30 40]

DISCUSSION

Principal findings

Female sex was consistently associated with an increased risk (OR and RR between 1.24 and 3.66) of pain at follow-up across six different musculoskeletal pain types. Depressive symptoms,[9 17 19 22 24 26 30 35 36 40] factors related to sleep/daytime tiredness[22 26 30 35 40] and parental pain condition[17 23 41] were all associated with a higher risk of pain at follow-up. Collectively, the identified studies included prognostic factors across all aspects of the biopsychosocial model, despite a main focus on biological factors. Increasing age was identified as both a significant and a non-significant prognostic factor in the included studies. This conflicting finding reflects the uncertainty surrounding the importance of age as a prognostic factor. A complete overview of strength of associations can be found in online supplementary table 1.

Strengths and limitations in comparison with existing literature

The latest systematic review on prognostic factors for children and adolescents with musculoskeletal pain ended their search in July 2015 which makes for a timely update.[12] In addition to adding newer studies, our review differs from the previous with search in more databases, no restriction on publication language and no restriction on pain duration.[41] Furthermore, this review is highly updated with a search up to February 2019 and the protocol for this review was developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement (see online supplementary appendix 3). Despite methodology differences, we did not identify additional studies from inception to 2015, but identified three new studies from January 2016 to 2017. These studies added important knowledge of female sex, pain frequency and the prognosis of knee pain and general musculoskeletal pain. Thereby, supporting the previous research. Despite the commonality of children and adolescents with musculoskeletal pain in general practice,[6] we did not identify a single study with a population of children or adolescents recruited from general practice.

A previous review on prognostic factors for adults with musculoskeletal pain in primary care was published in 2017[42] with findings similar to ours, that is, female gender, older age, depression/anxiety and long pain duration were found associated with an increased risk of

musculoskeletal pain at follow-up. This suggest that some of the prognostic factors function well across the age range and their use is not isolated to specific age groups.

Explanation of findings and implications for clinical practice

Our findings suggest that females are at higher risk of persistent pain. Previous research highlights potential sex differences in pain responses by assessing pain intensity and threshold and conclude that females display greater sensitivity to multiple pain modalities compared with males.[43] Importantly, pain-coping strategies have been found to differ between the sexes.[44 45] Females make use of social support, cognitive reinterpretation and positive self-statements, while males use behavioural distraction and problem-focused tactics to manage pain. This could partly explain the sex-difference in prognosis and may open new opportunities for targeted treatment to improve long-term outcomes of young females with musculoskeletal pain.

The current results point towards both modifiable (psychological factors, smoking and peer problems) and non-modifiable (sex, age and pain duration) factors associated with prognosis. Despite time constraints in general practice, most of these factors can be extracted from electronic stored patient data, psychometric tests and examination in a clinical general practice setting.

By asking your patient a few questions at the first consultation of musculoskeletal pain, the general practitioner may improve their understanding of their patients' risk of pain in the future. In the case of a present, baseline factor with a poor prognosis, for example, smoking among low back pain patients, the general practitioner now both has a scientific reason for and the clinical tool to modulate this factor. By prescribing cessation of smoking, thus, making an effort to improve the outcome for this patient.

Treatment of musculoskeletal pain requires the general practitioner to apply a multifactorial rather than a single-factor approach, hence, including the entire person and their life circumstances when treating patients with pain.[16 46 47] Clinicians must be aware of the multifactorial aetiology and consider biological, psychological and social factors of musculoskeletal pain when addressing patient's coping behaviour and cognitive appraisal.[48]

Implications for future research

Most of our included studies investigated biological prognostic factors (54 factors). Fewer investigated social (35 factors) and even fewer psychological prognostic factors (22 factors). Future research should include the entire patient, in terms of biological, psychological and social-related components and aim to study these prognostic factors in a general practice setting. There is a dearth of knowledge of how psychosocial factors are associated with prognosis and how general practitioners can harness this information to tailor treatment and information to their patients. Despite the potential importance of pain, 'who' the patient is should not be discounted. Geographical location of home, parental pain, profession and income, and social identity in terms of cultural differences, religious beliefs and relations could be important because we know from the biopsychosocial model that social background is important in relation to pain coping.

Only one study did follow-up after 4, 6.5, 9 and 11 years, respectively, which highlights the lack of long-term cohort studies on prognosis and impact of musculoskeletal pain in youth.

Almost one in every two children and adolescents still reported pain even years later.[10 11 49] This highlights the importance of prognosis of pain in children and adolescents. Healthcare practitioners should be cognisant not to assume that musculoskeletal pain during childhood or adolescence is transient or self-limiting.

Contributors NP conducted the systematic literature search. NP and AR independently carried out the screening, study inclusion and study bias assessment. NP and MSR led writing of both the protocol and manuscript and all authors NP, AR, MSR, MBBJ and JLO contributed with important reflections and revisions to both.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data and results presented within this systematic review can be obtained, on reasonable request, by contacting the corresponding author.

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Appendix 1. Search history.

Medline Ovid May 30th 2017

1	back pain/ or headache/ or exp musculoskeletal pain/ or Abdominal Pain/ or Back Pain/ or Low Back Pain/ or exp Arthralgia/ or Chest Pain/ or Facial Pain/ or Flank Pain/ or Metatarsalgia/ or Neck Pain/	110,274
2	Acute Pain/ or Chronic Pain/ or Breakthrough Pain/ or Pain, Intractable/ or Pain, Referred/	16,079
3	(musculoskeletal or back pain or backache or headache or joint or PFP or tendinitis 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 backache or back pain or headache or hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann).mp.	1,960,816
4	2 and 3	4,733
5	(backache or headache).mp.	78,052
6	((pain or ache) adj3 (musculoskeletal or back or joint or PFP or tendinitis 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 hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann)).mp.	103,970
7	1 or 4 or 5 or 6	217,985
8	limit 7 to "all child (0 to 18 years)"	41,139
9	(juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or teenager).mp.	3,721,647
10	7 and 9	54,465
11	8 or 10	55,016
12	(predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognostic or Mediator* or treatment effect modifier* or longitudinal*).mp.	4,208,880
13	11 and 12	20,363
14	(systematic reviews or meta analysis).pt.	80,495
15	case report/ or (case reports or letter or historical article or comment or editorial).pt.	3,595,207
16	limit 13 to (systematic reviews or meta analysis)	466
17	14 or 15	3,674,563
18	13 not (16 or 17)	17,183

EMBASE Ovid May 31st 2017

1	exp *musculoskeletal pain/	40,261
2	exp *"headache and facial pain"/	73,629
3	exp *abdominal pain/	10,492
4	*arthralgia/	4,782
5	*thorax pain/	9,691
6	*flank pain/	245
7	*metatarsalgia/	522
8	1 or 2 or 3 or 4 or 5 or 6 or 7	137,602
9	*chronic pain/	20,500
10	*breakthrough pain/	346
11	*intractable pain/	2,166
12	*referred pain/	233
13	or/9-12	23,135
14	(musculoskeletal or back pain or backache or headache or joint or PFP or tendinitis 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 backache or back pain or headache or hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann).mp.	2,678,325
15	13 and 14	8,147
16	(backache or headache).mp.	261,495
17	((pain or ache) adj3 (musculoskeletal or back or joint or PFP or tendinitis 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 hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann)).mp.	171,769
18	8 or 15 or 16 or 17	450,426
19	limit 18 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)	54,948
20	(juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or teenager).mp.	3,594,291
21	18 and 20	79,053
22	19 or 21	79,102

23	(predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognostic or Mediator* or treatment effect modifier* or longitudinal*).mp.	5,319,110
24	22 and 23	28,128
25	limit 24 to ("systematic review" or meta analysis)	497
26	case report/ or (letter or editorial or conference*).pt.	6,706,285
27	25 or 26	6,706,709
28	24 not 27	17,726

CINAHL Ebsco May 31st 2017

I	Search Terms	Search Options	Results
S18	S16 not S17	Search modes - Boolean/Phrase	3,716
S17	PT (Systematic Review or Meta Analysis)	Search modes - Boolean/Phrase	41,837
S16	S14 AND S15	Search modes - Boolean/Phrase	3,802
S15	(predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognostic or Mediator* or treatment effect modifier* or longitudinal*)	Search modes - Boolean/Phrase	530,171
S14	S11 OR S13	Search modes - Boolean/Phrase	11,516
S13	S10 AND S12	Search modes - Boolean/Phrase	11,425
S12	(juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or teenager)	Search modes - Boolean/Phrase	590,118
S11	S1 OR S7 OR S8 OR S9	Limiters - Age Groups: Infant, Newborn: birth-1 month, Infant: 1-23 months, Child, Preschool: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years Search modes - Boolean/Phrase	8,712
S10	S1 OR S7 OR S8 OR S9	Search modes - Boolean/Phrase	64,982
S9	((pain or ache) N3 (musculoskeletal or back or joint or PFP or tendinitis 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 hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann))	Search modes - Boolean/Phrase	37,883
S8	backache or headache	Search modes - Boolean/Phrase	16,417
S7	S5 AND S6	Search modes - Boolean/Phrase	4,707

S6	(musculoskeletal or back pain or backache or headache or joint or PFP or tendinitis 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 backache or back pain or headache or hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann)	Search modes - Boolean/Phrase	312,634
S5	S2 OR S3 OR S4	Search modes - Boolean/Phrase	12,235
S4	(MH "Referred Pain")	Search modes - Boolean/Phrase	284
S3	(MH "Breakthrough Pain")	Search modes - Boolean/Phrase	58
S2	(MH "Chronic Pain")	Search modes - Boolean/Phrase	11,921
S1	(MH "Back Pain") OR (MH "Low Back Pain") OR (MH "Facial Pain") OR (MH "Headache") OR (MH "Knee Pain+") OR (MH "Metatarsalgia") OR (MH "Muscle Pain") OR (MH "Neck Pain") OR (MH "Arthralgia") OR (MH "Shoulder Pain") OR (MH "Chest Pain") OR (MH "Elbow Pain") OR (MH "Heel Pain") OR (MH "Abdominal Pain")	Search modes - Boolean/Phrase	40,609

OT-seeker June 9th 2017

((pain or ache)
AND
(musculoskeletal or back pain or backache or headache or joint or PFP or tendinitis 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 backache or back pain or headache or hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann))
AND
juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or teenager

Cochrane June 9th 2017

Search Name:
Date Run: 09/06/17 10:28:15.152
Description:

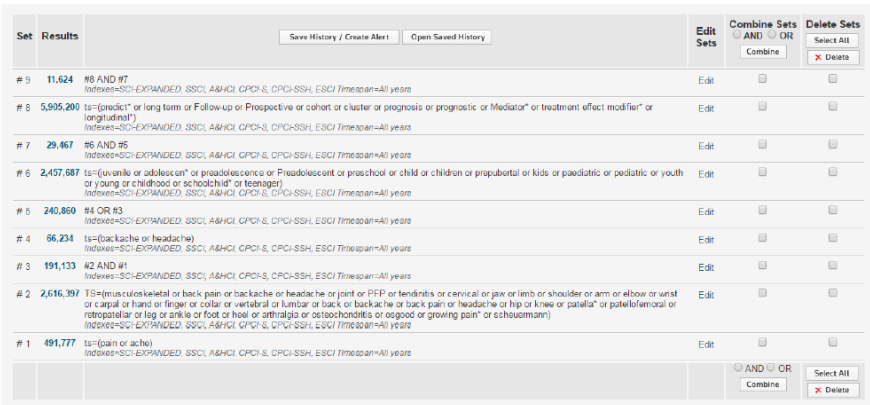
ID	Search Hits
#1	((pain or ache) next/3 (musculoskeletal or back pain or backache or headache or joint or PFP or tendinitis or cervical or jaw or limb or shoulder or arm or elbow or wrist or carpal or hand or finger or collar or vertebral or lumbar or back or backache or back pain or headache or hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann)) 7405
#2	(backache or headache) 26356
#3	#1 or #2 32236
#4	(juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or teenager) 243010
#5	#3 and #4 8870
#6	(predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognostic or Mediator* or treatment effect modifier* or longitudinal*) 399020
#7	#5 and #6 4430

All Results (4430)

- ○ Cochrane Reviews (1311)
  - ◉ All
  - ○ Review
  - ○ Protocol
- ○ Other Reviews (66)
- ○ Trials (3002)
- ○ Methods Studies (0)
- ○ Technology Assessments (4)
- ◉ Economic Evaluations (34)
- ○ Cochrane Groups (13)

Imported: Trial, Technology, Economic

Web of Science June 9th 2017



Set	Results	Save History / Create Alert / Open Saved History	Edit Sets	Combine Sets AND OR Combine	Delete Sets Select All Delete
# 9	11,624	#8 AND #7 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
# 8	5,905,200	ts=(predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognostic or Mediator* or treatment effect modifier* or longitudinal*) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
# 7	29,467	#6 AND #5 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
# 6	2,457,687	ts=(juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or teenager) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
# 5	240,860	#4 OR #3 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
# 4	66,234	ts=(backache or headache) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
# 3	191,133	#2 AND #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
# 2	2,616,397	TS=(musculoskeletal or back pain or backache or headache or joint or PFP or tendinitis 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 backache or back pain or headache or hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
# 1	491,777	ts=(pain or ache) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years*	Edit		
				AND OR Combine	Select All Delete

SportDiscus June 9th 2017

S7	((predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognostic or Mediator* or treatment effect modifier* or longitudinal*)) AND (S5 AND S6)	Search modes - Boolean/Phrase	843
S6	(predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognostic or Mediator* or treatment effect modifier* or longitudinal*)	Search modes - Boolean/Phrase	118,227
S5	S3 AND S4	Search modes - Boolean/Phrase	2,876
S4	(juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or teenager)	Search modes - Boolean/Phrase	200,385
S3	(S1 OR S2)	Search modes - Boolean/Phrase	25,984
S2	backache or headache	Search modes - Boolean/Phrase	12,066
S1	((pain or ache) N3 (musculoskeletal or back or joint or PFP or tendinitis 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 hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann))	Search modes - Boolean/Phrase	18,440

PsychInfo June 9th 2017

1	exp Musculoskeletal Disorders/	15,728
2	headache/ or muscle contraction headache/	7,110
3	myofascial pain/	317
4	back pain/	3,411
5	or/1-4	25,776
6	chronic pain/	11,631
7	pain/	22,243
8	6 or 7	33,184
9	(musculoskeletal or back pain or backache or headache or joint or PFP or tendinitis 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 backache or back pain or headache or hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann).mp.	220,772
10	8 and 9	9,266
11	(backache or headache).mp.	18,772
12	((pain or ache) adj3 (musculoskeletal or back or joint or PFP or tendinitis 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 hip or knee or patella* or patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis or osgood or growing pain* or scheuermann)).mp.	9,290
13	5 or 10 or 11 or 12	43,824
14	limit 13 to (100 childhood <birth to age 12 yrs> or 200 adolescence <age 13 to 17 yrs>)	5,603
15	(juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or teenager).mp.	895,379
16	13 and 15	5,465
17	14 or 16	7,676
18	(predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognostic or Mediator* or treatment effect modifier* or longitudinal*).mp.	723,493
19	17 and 18	2,119
20	(((systematic or method*) adj3 (review* or overview* or study or studies or search* or approach*)) or meta analy* or meta-analy* or metaanaly*).ti,ab,id.	142,307
21	limit 19 to ("0830 systematic review" or 1200 meta analysis)	36
22	21 or 20	142,310

23	19 not 22	1,971
1	exp Musculoskeletal Disorders/	15,728

Online supplementary appendix 2. Reporting checklist for systematic reviews and meta-analysis.

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Rationale	#3	Describe the rationale for the review in the context of what is already known.	3
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Protocol and	#5	Indicate if a review protocol exists, if and where it can be	3

registration		accessed (e.g., Web address) and, if available, provide registration information including the registration number.	
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	3
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	3
Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	3
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	4
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	4
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	4
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	5
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional	#16	Describe methods of additional analyses (e.g., sensitivity or	5

analyses		subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	5
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	5
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	5
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	5
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	5
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	7
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	8

Supplementary table 1. Estimates on prognostic factors specified according to musculoskeletal pain type, baseline age, and follow-up in the included studies.

Prognostic factors stratified in musculoskeletal pain type, sex, follow-up, and the biopsychosocial model		Musculoskeletal pain	Neck pain	Headache			
		Low back pain	Low limb pain	Stomachache			
		Knee pain	Back pain	Growing pain			
Baseline age	Prognostic factors subgrouped according to the biopsychosocial model	Study ID (Follow-up, yrs)	RR (95% CI)	OR (95% CI)	p-value	Adjusted for
	BIOLOGICAL PROGNOSTIC FACTORS					
	Female sex compared to male					
8 to 13		37 (3)			0.038	
10 to 16		20 (11)		M 1.8 (1.1-2.9)		
9 to 12		21 (4)	U 1.24 (1.07-1.44)			age
9 to 12		28 (1)		1.78 (1.18-2.69)	0.006	
9 to 12		27 (1)			0.001	
12 to 15		34 (2)	CR 1.29 (1.02-1.63)		0.08	
12 to 15		9 (1)		3.66 (1.09-12.33)	0.04	
10 to 11		39 (2)			M < 0.001	
10 to 11		39 (2)			M < 0.001	
10 to 11		39 (2)			U < 0.001	
	Older age					
9 to 12	Older age	28 (1)		1.24 (1.02-1.50)	0.031	
9 to 12 F	11 to 13 yrs vs. 9-10 yrs	21 (4)	M 1.40 (1.17-1.67)			
12 to 15	Older age, increase per year, 12 years as referent	9 (1)		M 1.45 (1.07-1.95)	0.01	
13	Older age	25 (3)			0.04	
	Body measurement factors					
8 to 13	Higher pubertal group (a) group 2 and 3 vs. group 1	37 (3)			0.022	
9 to 12 F	Beighton score 6-9 vs. score < 6	21 (4)	M 1.31 (1.18-1.46)			age
11 to 14	Height < 158cm	23 (4)	2.2 (1.2-3.8)			age, sex
9 to 12	Hypermobility score >/=6 vs. <6	11 (4)		M 2.93 (1.13-7.70)		
	Physical functioning					
14 to 16	Ratio flexion mobility (cm)/extension strength (min) (b)	36 (3)		1.9 (1.1-3.2)	0.02	gender, well being, physical
14 to 16	Ratio extension mobility cm/extension strength min (b)	36 (3)		3.2 (1.3-8.3)	0.02	gender
14 to 16	Ratio flexion + extension mobility (cm)/extension strenght (min) (b)	36 (3)		1.5 (1.1-2.2)	0.02	gender, well being, physical
	Pain characteristics					
2 to 17	Higher number of painful sites (mean 3.7 vs. 2.8) range 0-6	22 (9)			0.04	
2 to 17	More frequent generalised vs. localised pain (86 vs. 47%)	22 (9)		84.0 (2.1-3000)	0.02	
2 to 17	More intense pain (median 4.3 vs. 0.5cm) range 0-10cm VAS	22 (9)			0.03	
2 to 17	Longer disease duration before first admission (median 1.4 vs. 0.5 years)	22 (9)			<0.01	
9 to 12	Pain at both baseline and 1 year follow-up vs. only baseline	21 (4)		2.9 (1.9-4.4)		age
9 to 12 M	Multisite vs. localised pain	21 (4)	U 1.32 (1.04-1.66)			age
9 to 12 M	Headache (psychosomatic symptom (ci)	21 (4)	M 1.43 (1.12-1.83)			age
9 to 12 F	Abdominal pain (psychosomatic symptom (ci)	21 (4)	U 1.20 (1.03-1.40)			age
11 to 14	Radiating leg pain vs. no radiating pain	23 (4)	2.2 (1.4-3.6)			age, sex
11 to 14	Low back pain start > 12 month prior to admission	23 (4)	2.4 (1.3-4.4)			age, sex
11 to 14	Pain episode > 7 days vs < 24h	23 (4)	2.6 (1.4-4.9)			age, sex
15 to 19	Patellofemoral pain diagnosis vs. other types of knee pain	34 (2)	1.24 (1.04-1.49)		0.01	age, sex, BMI
15 to 19	High pressure pain threshold (PPT) around the knee	35 (3mo)			0.03	
12 to 15	Daily vs. rare pain	9 (1)		M 6.31 (1.21-33.01)	0.03	
12 to 15	Pain several times/week vs. monthly	34 (2)	CR 1.58 (1.15-2.17)		0.005	
16 to 18	Daily pain frequency vs. monthly	34 (2)	1.58 (1.17-2.14)		0.003	
16 to 18	Longer pain duration per 10-months increase	34 (2)	CR 1.04 (1.01-1.07)		0.01	
9 to 12 M	Also headache (d) at least once a week	38 (4)			<0.001	

The prognostic factors are divided primarily in biological, psychological, and social factors and secondary according to MSK pain site. The prognostic value were reported with RR, OR, and/or p-value.

9 to 12 M	Also abdominal pain (d) at least a week	38 (4)				<0.001	
9 to 12 F	Also headache (d) at least once a week	38 (4)				<0.001	
9 to 12 F	Also abdominal pain (d) at least a week	38 (4)				<0.001	
9 to 12	Other musculoskeletal symptoms: upper extremities at least once a week	38 (4)				<0.001	
9 to 12 M	Other musculoskeletal symptoms: chest at least once a week	38 (4)				0.008	
9 to 12 F	Other musculoskeletal symptoms: chest at least once a week	38 (4)				0.001	
9 to 12	Other musculoskeletal symptoms: back at least once a week	38 (4)				<0.001	
9 to 12 M	Other musculoskeletal symptoms as well: lower extremities at least once a week	38 (4)				<0.001	
9 to 12 F	Other musculoskeletal symptoms as well: lower extremities at least once a week	38 (4)				0.003	
8, 11, 14	Headache >/= 1time/week	20 (11)		2.3 (1.1-4.5)			
10 to 16	Duration of pain episodes > 3 hours vs. < 3 hours	20 (11)		U 3.1 (1.1-8.2)			
10 to 16	Lower pain threshhold	40 (5)				<0.05	
10 to 16	Lower pain threshold at anterior tibial region (pressure level < 5kg/cm2)	40 (5)				<0.01	
	PSYCHOLOGICAL PROGNOSTIC FACTORS						
16 M	Internalization (e)	33 (2)		2.32 (1.23-4.37)			
16 M	Externalization (e)	33 (2)		2.17 (1.24-3.81)			
16 F	Internalization (e)	33 (2)		3.70 (1.88-7.27)			
9 to 12 F	Depressive feelings	21 (4)	U 1.21 (1.03-1.42)				age
10 to 16	Often/sometimes nervous	20 (11)		M 2.1 (1.3-3.4)			
16 to 18 M	Internalization (e)	24 (2)				< 0.001	
16 to 18 M	Externalization (e)	24 (2)				< 0.001	
16 to 18 F	Higher internalization score (e)	24 (2)				< 0.001	
16 to 18 F	Higher externalization score (e)	24 (2)				< 0.001	
10 to 16	Self-perception of not feeling completely healthy	20 (11)		U 1.7 (1.1-2.8)			
10 to 16	Unsatisfied with own appearance	20 (11)		U 1.6 (1.1-2.5)			
12 to 15	EQ-5D index score 0-25 vs. 75-100% quartiles (f)	9 (1)		U 0.08		<0.001	
12 to 15	EQ-5D index score 0-25 vs. 25-50% quartiles (f)	9 (1)		U 0.29		<0.001	
12 to 15	EQ-5D index score 25-50th % vs. 75th-100th % (f)	34 (2)	CR 1.81 (1.14-2.85)			0.01	
12 to 15	EQ-5D index score 0-25th % vs. 75th-100th % (f)	34 (2)	CR 2.00 (1.28-3.12)			0.002	
9 to 12 F	Depressive symptoms in a frequency of at least once a week	38 (4)				<0.001	
9 to 12 M	Depressive symptoms in a frequency of at least once a week	38 (4)				<0.001	
12 to 16	Higher score of anxiety and depressive symptoms (g)	18 (4)		1.4 (1.03-1.90)		0.032	
10 to 11	Self reported anxiety/depression	39 (2)				M <0.01	
10 to 11	Self reported low self esteem	39 (2)				U < 0.01	
10 to 11	Parent reported adolescent anxiety/depression	39 (2)				< 0.05	
10 to 11	Parent reported adolescent low self esteem	39 (2)				U < 0.01	
10 to 11	Self reported anxiety/depression	39 (2)				U < 0.01	
10 to 11	Self reported low self esteem	39 (2)				U < 0.01	
	SOCIAL PROGNOSTIC FACTORS						
	General social factors						
2 to 17	Lower paternal educational level (median 10 vs. 14 years education)	22 (9)			p<0.01		
2 to 17	Lower maternal educational level (median 10 vs. 14 years education)	22 (9)			p<0.01		
2 to 17	More chronic family difficulties (mean 4.3 vs. 2.9) (h)	22 (9)			p<0.01		
10 to 16	Doing well in school	20 (11)		U 1.8 (1.1-2.9)			
9 to 12	Higher disability index (i) 1-2 vs 0	28 (1)	1.72 (1.09-2.73)			0.005	
9 to 12	Higher disability index (i) 3-5 vs 0	28 (1)	3.17 (1.54-6.55			0.005	
9 to 12	Higher disability index (i) 3-5 vs. 0	21 (4)	U 1.23 (1.02-1.49)				age
11 to 14	High vs. low peer relationship problems	23 (4)	2.4 (1.3-4.2)				age, sex
11 to 14	Difficulty standing in line for 10 minutes	23 (4)	2.7 (1.5-4.9)				
11 to 14	Difficulties carrying a schoolbag	23 (4)	2.1 (1.1-4.0)				
11 to 14	High limitation level HFAQ (j) 4-9 vs. 0-1 limitations	23 (4)	4.1 (1.05-16.2)				
8, 11, 14	Headache on non-school days	20 (11)		3.1 (1.3-7.3)			
13 M	Use of physiotherapy for headache or neck pain during the past 6 months	25 [3]				0.004	

10 to 11 F	Parental recurrent headache	39 (2)			p<0.05			
8, 11, 14	Pain makes it difficult to concentrate, and I must take pain medication/sometimes miss school	20 (11)		2.9 (1.2-7.1)				
10 to 16	At least one parent with a pain syndrome	40 (5)			0.047			
	Sleep related factors							
9 to 12 F	Waking up during nights	21 (4)	U 1.18 (1.01-1.37)			age		
16 F	Sleep </= 7h vs. 8-9 h/day	33 (2)		1.68 (1.05-2.68)				
9 to 12	Day tiredness, fatigue	28 (1)		1.86 (1.16-3.00)	0.010			
16 to 18 M	Insufficient sleeping time h/day (mean 8 vs. 8.5 h/day)	24 (2)			0.001			
9 to 12 M	Difficulties falling asleep	38 (4)			<0.001			
9 to 12 M	Daytime tiredness	38 (4)			<0.001			
9 to 12 M	Walking up during nights	38 (4)			0.001			
9 to 12 F	Difficulties falling asleep	38 (4)			<0.001			
9 to 12 F	Daytime tiredness	38 (4)			<0.001			
9 to 12 F	Walking up during nights	38 (4)			<0.001			
	Physical activity / inactivity							
16 F	>/=4 vs. 2-3 hours of moderate-to-vigorous physical activity/week	33 (2)		1.63 (1.04-2.56)				
16 to 18 M	Longer sitting time outside school hours (mean 6.2 h/day)	24 (2)			0.004			
12 to 15	Sports participation 3-7 t/wk vs. 0-2 t/wk	9 (1)		M 2.01 (1.20-3.36)	0.008			
9 to 12	Exercise frequency 5-7 t vs. 0-2/week	11 (1)		M 2.43 (1.16-5.05)				
	Alcohol							
16 to 18 F	More than occasional consumption	24 (2)			0.038			
	Smoking							
16 F	Smoking vs. nonsmoking	33 (2)		1.89 (1.23-2.90)				
16 F	Smoking 5-7 days/week vs. nonsmoking	30 (2)		2.52 (1.40-4.53)		family's SES, physical activity, BMI, depressive mood		
16 F	Smoking 1-9 cigarettes/day vs. nonsmoking	30 (2)		2.39 (1.40-4.08)		family's SES, physical activity, BMI, depressive mood		
16 F	Smoking > 9 cigarettes/day vs. nonsmoking	30 (2)		2.57 (1.03-6.46)		family's SES, physical activity, BMI, depressive mood		
16 M	Smoking 1-9 cigarettes/day vs. nonsmoking	30 (2)		2.68 (1.35-5.32)		family's SES, physical activity, BMI, depressive mood		

Explanatory notes

F = prognostic factor only applicable for female participants, **M** = Male, when nonspecified = unisex

RR > 1 or < 1, OR > 1 or < 1, p < 0.05 indicate that the prognostic factor is associated with a higher risk of persistent MSK pain.

CI = confidence interval **M** = Multivariate analysis **U** = Univariate analysis CR = Crude

a = Group 1: prepubertal, group 2: became pubertal during 3 years follow-up, and group 3: pubertal at baseline. The pubertal stage was assessed by the presence of secondary signs of pubertal development. For females, puberty was defined by the stage of breast development (Tanner stage >/= 3) and menarche. For males, puberty was defined in presence of a testicles volume >/= 12 ml and presence of pubic and underarm hair.

b = Low lumbar extension strenght and high ratios between lumbar mobility and lumbar extension strenght predicts future low back pain

c = childhood abdominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed to be having a psychosomatic origin in the great majority of cases.

d = Classified as: other physical and psychological symptoms, without further definition

e = Internalizing score calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing from rule-breaking and aggressive behaviour.

f = EQ-5D assesses self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and within 3 levels of severity: no problems, moderate or severe problems as well as scoring own current self-rated health status on VAS 0-100.

g = Anxiety symptoms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive symptoms: felt hopeless when thinking of the future, felt down or sad.

h = Assessment of information about employment and education, economic matters, housing, marital or family discord, social networks and the physical and mental health of the family members. Score range 0-6, 6=severe family difficulties.

i = Subjective disability index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting during a lesson, pain disturbs a walk more than 1km, pain disturbs physical exercise, pain disturbs hobbies. Range 0-5.

j = The modified Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily activities difficult: 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, and sports activities at school. Low = 0-1 limitation, moderate = 2-3 limitations or high = 4-9 limitations (23).

k = Yunus criteria: pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swelling in hands and feet, fatigue, numbness in hands and feet, feeling excited and nervous. Yes to minimum 3 symptoms to meet the Yunus criteria.

l = SES: Socioeconomic status

m = CDI: Children's depression Inventory. Cut off point >/= 13 indicating depressive symptoms

Identified baseline factors without association to persistent musculoskeletal pain, divided in pain type (study ID).	
Musculoskeletal	Female: sitting h/day, sleep h/day, Male: physical activity MET-h/week and above occasional alcohol consumption, unisex: smoking pack years, body mass index (BMI) (24)
	Exercise frequency >3 vs. <3t/week, disability index 1-5 vs. 0 (i), waking up during nights (Male), day tiredness, difficulty falling asleep, depressive feelings (Male), headache (Female), abscence one day or more from school vs. never being asbcent due to pain, maximum volume O2 intake (per unit increase) measured during a shuttle run test (21)
	Headache, stomachache, depressive feelings, difficulty falling asleep, waking up during nights, Yunus criteria (k), increasing exercise amount, and hypermobility (28)
	Male: physical activity level, sitting >4 h/day, sleep </= 7 h/day, smoking and overweight. Female: externalization, sitting > 4h/day, overweight (33)

	Increasing age (20, 27)
	Increasing age, sex, family history of related diseases, VAS score assessed by physicians, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet count, lower score in psychosocial functioning reflecting mental health and functioning at school/work, within the family, with friends and in other social activities (Children's Global Assessment Scale, CGAS) (22)
Low back	Extension strength (minutes) and plain saggital mobility (36)
	Akward trunk postures, physically demanding job (working hands above shoulders, awkward trunk posture and standing or walking), working regularly or irregularly, duration of work, work with specific physical load factors (31)
	BMI (32)
	Male: smoking 5-7 d/week vs. no smoking, smoking <9 cigarettes/day (30)
	High emotional vs. low emotional problems, reaching to a high shelf, sitting up in bed, bending down to put on socks, high conduct problems, high hyperactivity, high prosocial behavior, widespread pain, headache, stomachache in the past month compared to none, daytime tiredness on a scale 0-10, 5-10 vs. 0-4, pain start < 12 months ago, pain lasts </= 7 days, pain today, pain severity on a scale 0-10, 4-10 vs. 0-3, Hannover 2-3 vs. 0-1 (23)
	Sex, increasing age, tobacco, profession: hairdresser and media/design compared to electrician, western ethnicity compared to non-western ethnicity, moderate/high vs. low socio-economic status (SES) (l), moderate/high vs. low physical activity level, BMI, moderate/high physical work demand vs. low (26)
Knee	Increasing age compared to 15, participation in sports, BMI, EQ-5D index score 50-75th percentile compared to 75-100th, weekly pain frequency compared to monthly (34)
	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a week pain frequency compared to rarely (9)
Lower limb	After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypermobility score >/= 6 vs. < 6. After 4 years follow-up: exercise frequency 5-7 t/week vs. 0-2 t, lower limb trauma at baseline. Common after both 1 and 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a week, multisite pain, female sex, headache, stomachache, depressive feelings, difficulty falling asleep, day tiredness, waking up during nights, school abscence due to pain vs. never abscent, disability symptoms >/=3 vs. </=2, volume ..O2 max average or above, exercise frequency 3-4 t/week vs. 0-2 t (11)
Neck	Joint hypermobility Beighton 6-9, physical activity at least half and hour more than 3 times a week (38)
Growing pain	Sex, ethnicity, increasing age (40)
Headache	Sex (19)
	Pain frequency, pain in daily activities, physiotherapy, relaxation therapy, sport activity, stress at home or in hobbies, pain on palpation, pain threshold measured by dolorimeter, depressive symptoms, temporomandibular disorder, stress at school, use of computer (25)
	Stress (20)
Widespread	Female sex, increasing age, tender point count, CDI > 13 (m), Yunus criteria >/=3, sleep score, disability index (f), psychosomatic symptoms (29)
Back	Stress (20)

Online supplementary appendix 3. Protocol.

PROSPERO
International prospective register of systematic reviews

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Systematic review

Please complete all mandatory fields below (marked with an asterisk *) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon
to see guidance on completing each section.
This record cannot be edited because it has been rejected

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Prognostic factors and treatment effect modifiers for children and adolescents with musculoskeletal pain: a protocol for a systematic literature review

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

21/06/2016

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/12/2017

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

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NHS National Institute for Health Research

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Negar Pourbordbari

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

7. * Named contact email.

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negar@dcm.aau.dk

8. Named contact address

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Fyrkildevej 7, 9220 Aalborg
Denmark

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

004527914224

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Research Unit of General Practice in Aalborg and Department of Clinical Medicine, Aalborg University, Denmark

Organisation web address:

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Negar Pourbordbari. Research Unit of General Practice in Aalborg and Department of Clinical Medicine, Aalborg University, Denmark
Mr Allan Riis. Research Unit of General Practice in Aalborg and Department of Clinical Medicine, Aalborg University, Denmark
Professor Martin Bach Jensen. Research Unit of General Practice in Aalborg and Department of Clinical Medicine, Aalborg University, Denmark
Dr Jens Lykkegaard Olesen. The Faculty of Medicine Department of Clinical Medicine, Aalborg University, Denmark
Dr Michael Skovdal Rathleff. Research Unit of General Practice in Aalborg and Department of Clinical Medicine, Aalborg University, Denmark

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Research Unit of General Practice in Aalborg and Department of Clinical Medicine, Aalborg University, Denmark

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

The aim of this study is to conduct a systematic review on children and adolescents with musculoskeletal pain with a view to determining which baseline patient characteristics are associated with a poor outcome in follow-up regardless of which treatment has been provided (prognosis) or are associated with a successful outcome to a specific treatment (treatment effect modifiers).
Review question: What are the prognostic factors and treatment effect modifiers for children and adolescents with musculoskeletal pain?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

This systematic review search will be conducted in the following electronic databases: MEDLINE, Embase, CINAHL, Web of Science, Cochrane and SPORTDiscus without limitations on dates.
Articles reported in English, German, Danish, Norwegian, Swedish, French, Spanish, Japanese, Chinese, Thai, Arabic, Persian, Turkish and Hindi will be included.
The search strategy will be divided into seven 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.
Additional details about the search strategy can be found in the attached PDF document (link provided

below).

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

https://www.crd.york.ac.uk/PROSPEROFILES/41378_STRATEGY_20170613.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Children and adolescents aged 0-19 years with musculoskeletal pain.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

The participants must all have some form of self-reported musculoskeletal pain at recruitment. Musculoskeletal 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: 0 to 19 years of age, self-reported musculoskeletal pain.
Exclusion criteria: Older than 19 years of age.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

All interventions used to treat musculoskeletal pain in children and adolescents are eligible, including 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 intraarticular, intramuscular and intratendinous injections with NSAID/glucocorticoid/steroid. We will also include studies that do not contain interventions.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

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

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Prospective cohort studies (including randomized trials) with a population of children and adolescents aged 0-19 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 the outcome).

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

There will be no restrictions on the type of setting.

24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

We will search for all baseline patient characteristics that are: (i) associated with a poor outcome on follow-up regardless of which treatment has been 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).

Timing and effect measures

We will include patient characteristics that are associated with both short- and long-term outcomes. These will be divided into three endpoints, i.e. short-term (3 months), medium-term (3-12 months) and long-term (more than 12 months).

25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state 'None' or 'Not applicable' as appropriate to the review

The proportion of patients that report themselves free of musculoskeletal pain at follow-up in the included studies.

Timing and effect measures

We will include patient characteristics that are associated with both short- and long-term outcomes. These will be divided into three endpoints, i.e. short-term (3 months), medium-term (3-12 months) and long-term (more than 12 months).

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

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 will screen the titles and/or abstracts that have relevance to the question: what are the prognostic factors for children and adolescents with musculoskeletal pain? Studies kept after the primary assessment will be screened by full text and then selected for a final inclusion.
Any excluded studies will be recorded, along with 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 additional eligible publications that may have been missed during the initial search.
Any disagreements inside the reviewer group will lead to the involvement of a third reviewer (MSR).
NP will extract data using a pre-defined data extraction form (see Appendix 1 in the full protocol), inspired by The Cochrane Collaboration, Data collection form for intervention reviews: RCTs and non-RCTs (3). All the extracted data will then 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 for information, if any data concerning the intervention or outcome is missing from an included study, the intention being to increase the thoroughness of the descriptions of interventions and outcomes in this study.

Studies examining children and adolescents with musculoskeletal pain aged 0 to 19 years will be included in this review. If a study reports on an age range that exceeds this, we will contact the corresponding author and ask for data on the 0-19 year olds. The requested data will be included if it can be retrieved within one month of the inquiry.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

The QUIPS risk of bias tool for prognostic studies will be used to assess the quality of each paper (4). 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 (see Appendix 2 in full protocol). 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.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

A narrative synthesis is planned, the reason being the 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.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

Data will be divided into two main separate groups: prognostic factors and treatment effect modifiers and then sub-grouped into regions of musculoskeletal pain, gender and age.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention

No

Meta-analysis
No

Methodology
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
Yes

Prospective meta-analysis (PMA)
No

Qualitative synthesis
No

Review of reviews
No

Service delivery
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education

No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Denmark

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

http://www.crd.york.ac.uk/PROSPEROFILES/41378_PROTOCOL_20160520.pdf

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

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 musculoskeletal 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.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

systematic review
children
adolescence
musculoskeletal pain
prognosis
treatment effect modifier

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

References:
1. http://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/MusculoskeletalPainFactSheets/AcutePain_Final.pdf
2. http://www.spine-health.com/glossary/conservative-treatment.
3. Cochrane Training, Data collection form for intervention reviews: RCTs and non-RCTs. http://training.cochrane.org/resource/data-collection-forms-intervention-reviews 2014.
4. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Appendix F. Paper 2

Pourbordbari *et al. BMC Primary Care* (2022) 23:20
https://doi.org/10.1186/s12875-022-01628-8

BMC Primary Care

RESEARCH Open Access

Bio-psycho-social characteristics and impact of musculoskeletal pain in one hundred children and adolescents consulting general practice

Negar Pourbordbari[1*], Martin Bach Jensen[1], Jens Lykkegaard Olesen[1], Sinead Holden[1,2] and Michael Skovdal Rathleff[1,2]

Abstract

Background: Eight percent of all child and adolescent general practice consultations are due to musculoskeletal conditions, with pain as the most frequent symptom. Despite the commonality of musculoskeletal pain, limited knowledge exists about care-seeking children and adolescents with musculoskeletal pain.

The purpose of this study was to describe characteristics of children and adolescents consulting their general practitioner with musculoskeletal pain.

Methods: This is a cross-sectional study based on baseline data from the child and adolescent musculoskeletal pain cohort study (ChiBPS), carried out in 17 Danish general practice clinics. Patients aged 8–19 years who had musculoskeletal pain when consulting their general practitioner were recruited. Participants completed a questionnaire on demographics, physical activity, pain impact, psychosocial factors, and expectations of their general practitioner. Descriptive statistics were used to summarize data. Normally distributed continuous data were described using mean and standard deviation while non-normally data were described using median and interquartile range (IQR).

Results: We included 100 participants (54% female, median age 13 [IQR: 12–16.5 years]). Frequent pain sites limiting activity were knee (56%), back (20%), ankle (19%), and neck (13%). Most participants (63%) consulted their general practitioner due to inability to use their body as usual, due to pain. Median pain duration at consultation was 5 months [IQR: 3 weeks-1 year]. More than a third were often/sometimes nervous (34%), worried or anxious (33%), and took pain medication (33%). Pain impeded ability to participate in sport activities at school (79%) and disturbed spare time activities (88%). Pain also made it difficult to concentrate for 58%, and to fall asleep for 38%. Only 38% expected a pain free long-term future.

Conclusion: This study demonstrates the bio-psycho-social impact of musculoskeletal pain in care-seeking children and adolescents. Demographics, pain characteristics, psychosocial characteristics, and physical characteristics should be included in addressing children and adolescents with musculoskeletal pain.

Trial registration: The ChiBPS study was pre-registered before participant recruitment (ClinicalTrials.gov Identifier: NCT03678922) date: 09.20.18.

Keywords: General practice, Musculoskeletal pain, Children, Adolescents, Characteristics

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Background

Each year, 8% of children and adolescents aged 3–17 years in the United Kingdom consult their general practitioner (GP) due to a musculoskeletal (MSK) problem [1]. Despite the ubiquity of pain, it remains poorly understood in children and adolescents and as a result may be misinterpreted as inconsequential [2]. Adolescent MSK pain has long been assumed to be innocuous with a limited impact beyond the pain experience. However, evidence indicates that adolescent MSK pain is associated with psychological distress [3], decreased quality of life [4], and a negative impact on sports participation and social activities [5, 6]. The prognosis of adolescent MSK pain is not as favorable as once assumed, and around one in every two adolescents with MSK pain continue to have pain even 1–4 years after onset [7]. This may predispose adolescents with MSK pain to chronic pain and other chronic health problems in adulthood [2].

The GP is the gatekeeper and the first point of contact in many health care systems. It is important to understand needs and impact of pain in adolescents who consult the GP for their pain. This may help support patient-centered care, which is one of the cornerstones of general practice.

Anxiety and coping among other patient characteristics may contribute to the development and maintenance of pain in children and adolescents [2]. Despite these could be relevant features to address during consultation, it is unclear how common these characteristics are among adolescents consulting general practice with pain, or the consequences on everyday lives.

We performed a systematic review investigating prognosis and prognostic factors for adolescent MSK pain [7], which informed our selection criteria and data collection. We discovered a complete knowledge gap on children and adolescents in general practice. Previous studies have primarily been in general populations, with a strong focus on pain with limited focus on psychosocial aspects of the pain experience.

The aim of this study was to explore demographics, pain features, psychosocial factors, physical activity, and expectations of children and adolescents consulting their GP with MSK pain.

Method

Study design and pilot work to inform the study

This cross-sectional study is based on baseline data within the child and adolescent musculoskeletal (ChiBPS) pain cohort study. The aim of the ChiBPS study is to describe prognostic factors associated to long term MSK pain among children and adolescents consulting their GP with MSK pain. The STROBE checklist for cross-sectional studies was used in reporting of the study [8].

Setting and recruitment

GP clinics

From October 2018 to August 2019, one author (NP) contacted and visited general practice clinics across Denmark to introduce them to the ChiBPS study [9]. Seventeen rural and urban area clinics were included with GPs of both genders (Supplementary file 1).

Participants

Potentially eligible participants were invited to participate either by an employee prior to consultation, or by the consulting GP prior to or during the consultation. In each clinic, an employee or GP screened all scheduled patients for eligibility, either prior to or during consultations. The GP could choose the most suitable method in relation to the infrastructure of the clinic. Once the study was explained to the children and adolescents by the GP or employee and the decision was made to participate, they were requested to complete an electronic questionnaire (outlined in detail below). The questionnaire was hosted on a secure server at University of Aalborg (AAU) and participants were not given any specific information of the content of the questionnaire beforehand.

To be eligible, patients had to have a MSK pain complaint and this had to be mentioned by either the patient/parent or the GP as a current condition during the consultation, but not required to be the main reason for consultation. Musculoskeletal pain included pain arising from muscle, tendon, bone, and joint as per the International Association for the Study of Pain (IASP) definition [10]. The lower age limit of 8 was based on the assumption of a child's ability to interpret/understand the questions included in our questionnaire. We did not include a pre-defined minimum or maximum pain duration as an eligibility criterion, and patients were eligible regardless of whether the current consultation was the first for their MSK complaint.

Inclusion criteria

- Age 8–19 years.
- Self-reported MSK pain (non-traumatic and traumatic caused by soft tissue damage, contusion or otherwise (excluding diagnosed fracture)).
- Ability to read and understand either Danish or English.

Exclusion criteria

- Self-reported MSK pain due to tumour, infection, or systemic and neurological causes known by either the GP or the patient/parent.

Data collection and management

Data was collected and managed using REDCap electronic data capture tools hosted at Aalborg University [11, 12]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [11, 12]. Most clinics elected to use study provided tablets to collect the data via the REDCap mobile app. If this was not possible, clinics could choose to have a link to the questionnaire sent directly to participants by a member of the research team (NP). Data was only shared with participant's consent and the appropriate data sharing agreements in place.

All extracted data was handled in concurrence with The Danish Data Protection Agency [13] and all data extracted from REDCap and transferred to an Excel table, in an anonymised format.

Questionnaire and measures

The questionnaire was developed based on our systematic review, discussions with a GP reference group, and questions used in previous work [7, 14–25] (Additional file 2: Appendix 1). Our measures are divided in four sections: demographics, pain characteristics, psychosocial measures, and physical activity measures.

To ensure comprehensibility, we first piloted the questionnaire with seven 8–19-year-old children and adolescents with recent MSK pain; two girls (11 and 17 years old) and five boys (8, 9, 11, 14, and 19 years old). We received feedback regarding three statements used in the questionnaire: 'mark the site', 'previous', and 'in what extent', and revised these to increase comprehensibility. Otherwise, there were no major difficulties in understanding the questions and the language was considered appropriate.

Musculoskeletal pain

We captured MSK pain sites that participants experienced in the previous 2 weeks. Participants were able to select where they experienced pain from 33 predefined sites on a mannequin (Additional file 2: Appendix 1), and whether pain caused activity limitations or not. Activity limiting pain was defined as pain during the past 2 weeks leading to not being able to participate in play in the school yard or spare time activities [14]. Patients were able to select more than one pain locations, with more than one location of activity limiting pain being considered multi-site pain. Pain intensity was rated on a 11-point numerical rating scale from 0 to 10. Headache was not included. Our questionnaire started with three questions that was intended to ensure eligibility (see pain questions 1, 2, and 3 in Additional file 2: Appendix 1). To limit the effect of recall bias, we used a short recall period of 2 weeks on questions related to pain.

Data handling and statistical methods

We exported data from our questionnaires in REDCap to an Excel table and checked for any potential errors (NP). Descriptive statistics was used to summarize data (Table 1 and Table 2). Normally distributed continuous data was described using mean and standard deviation

Table 1 Demographics and pain characteristics of 100, 8–19-year old care-seeking children and adolescents with MSK pain. $N = 100$. All numbers equals percentages because of the total population of 100

Demographics	
Age (median [IQR])	13 years [12–16.5]
Sex (n)	Female: 55, Male: 45
Number of siblings (median [IQR])	1 [1–2]
	Only child: 7
Position in sibling line[a] (excluding only children and twins, $n = 91$)	First: 31
	Second: 36
	Third/fourth: 21
	Youngest: 41
Pain characteristics	
Pain duration (median [IQR])	5 months [3 weeks-1 year]
Pain numerical rating scale (NRS) (median [IQR])	7 [6–8]
Multi-site activity limiting pain ($n = 53$[b])	2 sites: 23
	3 sites: 14
	4 sites: 7
	>/= 5 sites: 9
Pain episode duration (n)	< than 3 h: 34
	< than 24 h: 24
	1–7 days: 24
	> than 7 days: 18
Pain episode frequency (n)	=/> once a week: 80
	< once a week: 20

Data in Table 1 are based on 97–100% replies.

[a] fifth child, $n = 3$, twins, $n = 2$. [b] five participants reported only one pain site and this was non-activity limiting – as answer to pain question 3, of these one of the sites were the jaw. (ID 40, 42, 51, 57, 90)

Table 2 Psychosocial and physical characteristics of 100, 8–19-year old care-seeking children and adolescents with musculoskeletal pain. $N = 100$. All numbers equals percentages because of the total population of 100

Psychosocial characteristics	
Pain outside school hours (n)	97
Nervous (n)	Often/sometimes: 34
	Seldom/never: 66
Worried or anxious (n)	Yes: 33, No: 32, I don't know: 35
Low self-esteem (n)	Yes: 7, No: 78, I don't know: 15
Believe in God (n)	Yes: 36, No: 35, I don't know: 29
Difficult to fall asleep because of pain (n)	38
Tired during the day (n)	57
Have a job (n)	33
Know the cause of pain (n)	58
Expect the GP to prescribe pain medication (n)	8
Pain affects my concentration (n)	58
Take pain medication for pain (n)	33
Frequency of pain medication (n)	Once/month: 13
	Once/week: 12
	More than once/week: 6
	Every day 1
Know the name of pain medication, $n = 26$	Paracetamol: 17
	NSAID[a]: 1
	Paracetamol and NSAID: 8
Physical activity characteristics	
Physical active besides school hours times/week, $n = 80$[b]	0: 0
	1: 11
	2–3: 39
	4–6: 16
	> 6: 5
Screen time/other activities mostly sitting down outside school hours hours/day[c] (n)	0: 2
	1–2: 36
	3–6: 49
	>/= 7: 7
Pain disturbs (separate questions) (n):	a walk longer than 1 km: 70
	my spare time activities: 88
Pain makes it difficult to (more than one option could be ticked) (n):	stand in a queue for 10 min.: 36
	carry my school bag to school 22
sit on a chair for a 45-min. Lesson 31	bend down to put on my socks: 33
do sport activities at school 79	run fast to catch a bus: 67

Data in Table 2 are based on 97–100% replies; question concerning screen time had the lowest reply percentage.

[a] NSAID: non-steroidal anti-inflammatory drug. [b]incl. One answer to; sometimes once other times 3, 1–2 times, 1–3 times, and 4–7 times, two answers 3–4 times, three answers: 3–5 times. [c]Excl. one answer: 1-3 times, many times, and all the time and three answers: 2–3 times

while non-normally data were described using median and interquartile range. Categorical data was described using percentages.

Results

Study group characteristics

A total of 124 children and adolescents were recruited from 17 GP clinics. Of these, 24 were excluded; six due to missing consent, fifteen due to incomplete/cloned questionnaire, and three due to lack of fulfilment of eligibility criteria resulting in 100 participants (Table 1 and Table 2). The primary activity limiting pain sites were knee (56%), ankle (18%), back (14%), heel (12%), foot (12%), and neck (9%) with a median pain intensity of 7 (IQR 6–8). The median pain duration was 5 months [3 weeks-1 year].

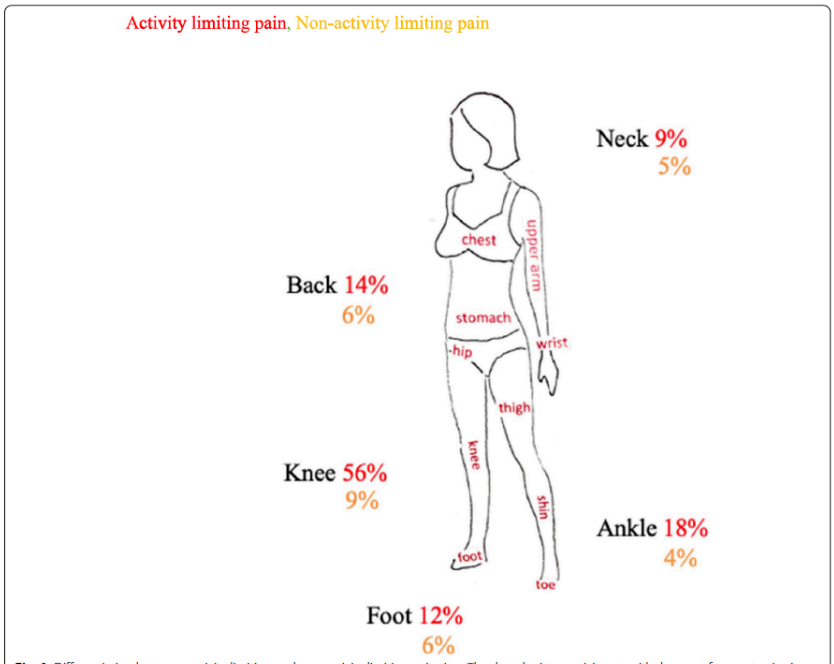

Fig. 1 Differentiating between activity limiting and non-activity limiting pain sites. The data depicts participants with the most frequent pain sites, stratified as activity and non-activity limiting pain. Data based on all participants, $n = 100$. Activity limiting and non-activity limiting pain are not mutual exclusive. One participant experienced activity limiting right sided knee pain and non-activity limiting left sided knee pain

Multi-site activity limiting pain was reported by 53%. Almost all children and adolescents had pain outside school hours (97%) and were disturbed by their pain during their hobbies (88%).

Figure 1 highlights the difference in activity limiting and non-activity limiting pain by pain sites, with knee pain the most frequent site of both. Figure 2 visualizes the common characteristics of a typical Danish child or adolescent with MSK pain, including demographics, physical activity, family pattern and pain impact on school.

Discussion

Main findings

Knee and ankle pain were the two most common activity-limiting pain sites among a care-seeking population of adolescents with MSK pain in general practice. Fifty-three percent experienced multi-site pain. Overall, 33% had used pain medication during the past 2 weeks and 13% used it at least once a month. Median pain duration was 5 months and a range of different functional and social limitations due to pain were reported.

Findings in relation to existing literature

Previous research from UK revealed that 8% of an adolescent population seek care from their GP due to MSK conditions each year [1]. It has so far been unknown how large the impact of pain is among this primary care population. Previous research is mainly in secondary care populations or in school-based populations. Studies generally observed a longer pain duration than the current study (often > 12 months) [7], with a high proportion who had previously contacted a health care practitioner [26].

Fig. 2 Common characteristics of a GP care-seeking 8–19-year old with musculoskeletal pain. A short story about a young girl with pain. A typical Danish child or adolescent with musculoskeletal pain is a 12 or 13 year-old girl. She has pain in her knee and in at least one more body part. She visits her general practitioner because she cannot use her body as usual due to pain and she decides to do so after having had pain for one year with pain episodes occurring as frequently as once every week. In her household she is the youngest of two children. In school her concentration is affected by her pain, and she goes on with her day feeling tired, but after school she is active in sports 2–3 times a week, even though her pain disturbs her spare time activities. During a typical day, she spends 3–6 h looking at a screen. She believes in God. When her day is over, and it is time for her to turn in she goes to bed knowing what causes her pain. Data is based on all participants, $n = 100$ including both activity limiting and non-activity limiting pain. Cut off limit is defined at a minimum of 31% of all participants for inclusion of the characteristics included in this figure

The proportion experiencing multi-site pain in our study was lower compared with previous studies [27]. Multi-site pain seems to develop over time with increasing pain duration [28]. This could indicate that our population contacts general practice early in the pain development. Early intervention has been proposed to improve long-term outcomes due to duration of pain complaints, multi-site pain and psychological symptoms associated with a poor prognosis [7]. Most of our sample suffered from either back or knee pain which aligns with the findings from UK general practice [1] and school-based populations in Denmark [29].

The impact of pain

Konijnenberg et al. [30] found approximately 50% school absence because of pain. We found 22% reported difficulties in carrying their school bag to school, 31% had difficulties sitting for a 45-min lesson, and 58% reported a negative effect of pain on their concentration. The most common causes for consultation in this study were limitation in the habitual use of the body (64%), wanting the pain to stop (59%), and worrying about the cause of pain (55%). This is similar to research showing that pain intensity and activity limiting MSK pain were important drivers for seeking care among adolescents with pain complaints [31, 32].

Explanation of findings

Our findings underline the need to consider psychological and social factors since female sex (55%), pain duration more than 1 year (24%), feeling anxious (33%), daytime tiredness (57%), more than 6 non-school hours of sitting down/day (7%) and smoking (2%) are associated with an increased risk of a poor prognosis [7]. Co-occurring pain, psychological and social factors in general practice should be considered treatment-targets and we recommend questioning any recent events in the family or surroundings, that could potentially have an impact on the child since there is a lack of knowledge on the effect of these modifiable risk factors.

Care-seeking behaviour

Despite back pain affect 33% of children in school-based populations, only 6 % of them seek care for their back pain [33]. Care-seeking behaviour in children is hence uncommon. This could indicate that years of pain duration push for a consultation rather than a wait and see approach.

Previous research suggest that 50–65% of children and adolescents have MSK pain 1–4 years after onset [7] whereas 14% of our population reported a pain duration of 1 year prior to the current consultation. Both numbers call for clinical implications, since long-term MSK pain condition can push toward a more progressive investigation by the GP. General practitioners commonly prescribe a wait and see treatment for MSK pain [34, 35].

Implications for practice and future research

Our results underline the bio-psycho-social impact of MSK pain in care-seeking children and adolescents. Importantly, the results reveal the wide-reaching impact on carrying a school bag, the concentration, and the negative impact on leisure time activities. MSK pain in adolescents was once considered a benign self-limiting condition with limited impact beside the actual pain experience. These results underline that GPs need to be cognizant of the widespread impact and challenges these young individual's experience.

Strengths and limitations of the study

Our study data was drawn from a nationwide cohort, representative of the Danish population in age, sex, and environment (Table 1, Table 2, Supplementary file 1). It is unclear if our findings are generalizable to other countries with different health care sectors, differences in care-seeking behaviour and cultural differences. We used validated questions when possible, and piloted the survey to ensure that children and adolescents understood the questions. Due to the commonality of pain, we collected data on pain that affected their typical activities and otherwise pain. This distinction is important and ensure we can differentiate pain with and without an impact on the individual. Self-report measures of pain and other factors may be affected by recall bias. To limit recall bias we used a short recall period of 2 weeks. Due to the small number of adolescents included, we did not stratify pain characteristics or pain impact into specific body sites. In this study we used "alcohol consumption" more than once per month, while previous studies have used the term "occasional use" [7]. This may make a direct comparison difficult. We did not collect data on NSAID intake for specifically MSK pain and are not able to exclude dysmenorrhea as a common pain condition among menstruating female adolescents.

Conclusion

Two thirds of children and adolescents consult their GP because of limitations in the habitual use of their body due to pain. One third of children and adolescents are nervous or worried/anxious and more than half report their concentration is affected by their pain. These findings and other bio-psycho-social factors are important in addressing children and adolescents with musculoskeletal pain as they represent co-occurring conditions.

Abbreviations

GP: General practitioner; MSK: Musculoskeletal.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12875-022-01628-8.

Additional file 1.

Additional file 2.

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Not applicable.

Authors' contributions

Authorship for this paper is based on criteria according to ICMJE (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). NP wrote the first draft of the paper and MSR helped with the final write-up. All authors contributed to the methodology and interpretation of included data. All authors improved the paper with critical review of content, a final approval of the version to be published and in agreement of accountability for the entire work and it's accuracy.

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Availability of data and materials

The datasets used in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The ChiBPS study was pre-registered before participant recruitment (ClinicalTrials.gov Identifier: NCT03678922) and submitted to The Committee of Multipractice Studies in General Practice receiving approval prior to initiation (ID: MPU 20–2017/date 100117). The study complied with the Declaration of Helsinki. The Ethics Committee of the North Denmark Region/The National Ethics Committee (NVK) waived ethical approval of the ChiBPS cohort study necessary due to the nature of the study. The STROBE checklist for cross-sectional studies was used in the reporting of the study [9].
Once the GPs were informed of the study at time of recruitment visits and decision was made to participate, statement of consent and data processor agreements were signed and the clinics were compensated for their part as intermediaries of contact to the children and adolescents, according to

regulation §3 by the Danish Committee of Multipractice Studies in General Practice. Written informed consent was obtained from the adolescent (18–19 years old) or from the guardian of participants 8–17 years old. Participation in this study did not interfere with the consultation and care provided by the GP nor did it include an intervention.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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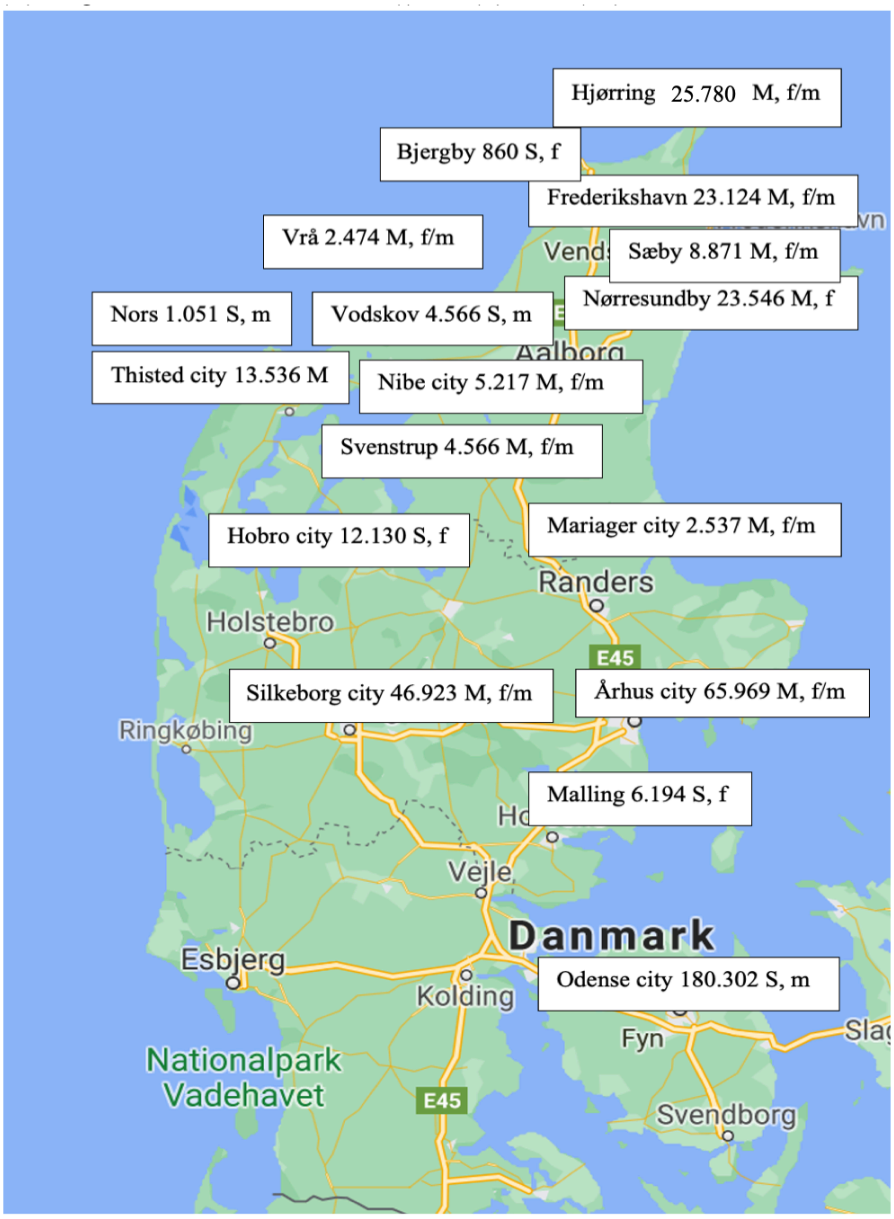
Publisher's Note

Supplementary file 1. Recruited general practice clinics.



Location of recruited general practice clinics in Denmark, who recruited participants for this study. Inhabitants in the communities where the clinics were located, recruitment done by one GP (s) or multiple (M), and gender of these indicated as female (f), male (m), or both (f/m).

Appendix 1. Questionnaire.

Confidential

Questionnaire for children and adolescents with musculoskeletal pain

Hi there,

thanks a lot for your participating in my research project:

Children and adolescents with musculoskeletal pain: prognosis, ethnicity, and long term pain (MPU 20-2017).

I appreciate it.

If you should have any questions, feel free to contact me on 27914224.

Best regards, Negar, medical doctor

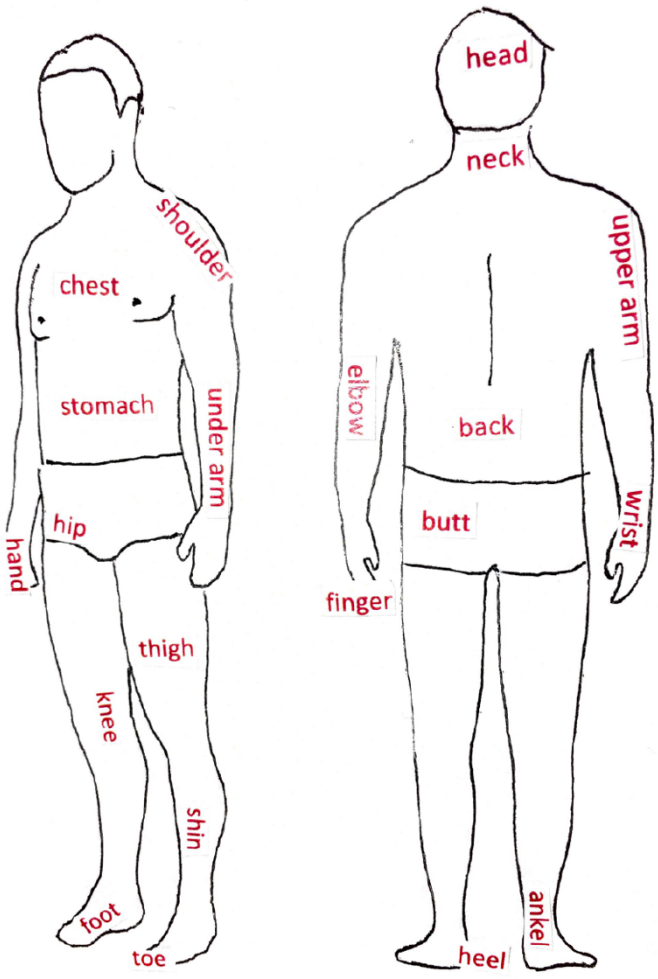
First, I would like to know whether you have turned 17 years old?	◯ Yes ◯ No
I consent voluntarily to my child's participation in this research project.	_____
I have received written and oral information of the project.	◯ Yes ◯ No
Name of the person custody lies with: (One name is sufficient).	_____
Do you wish to be informed of the results of the project and possible consequences for your child?	◯ Yes ◯ No
I consent voluntarily to participate as a participant in this research project:	_____
Do you wish to be informed of the results of the project and possible consequences for you?	◯ Yes ◯ No
Back to you (the patient). What is your name?	_____
What is your name?	_____
What is your CPR. no.?	_____

Confidential

Mobile phone no. Please write your parent's phone no. if you don't have one yourself	_____
What sex are you?	◯ Girl ◯ Boy
What is the name of your general practitioner or his/her clinic?	_____

The next questions concern your pain.

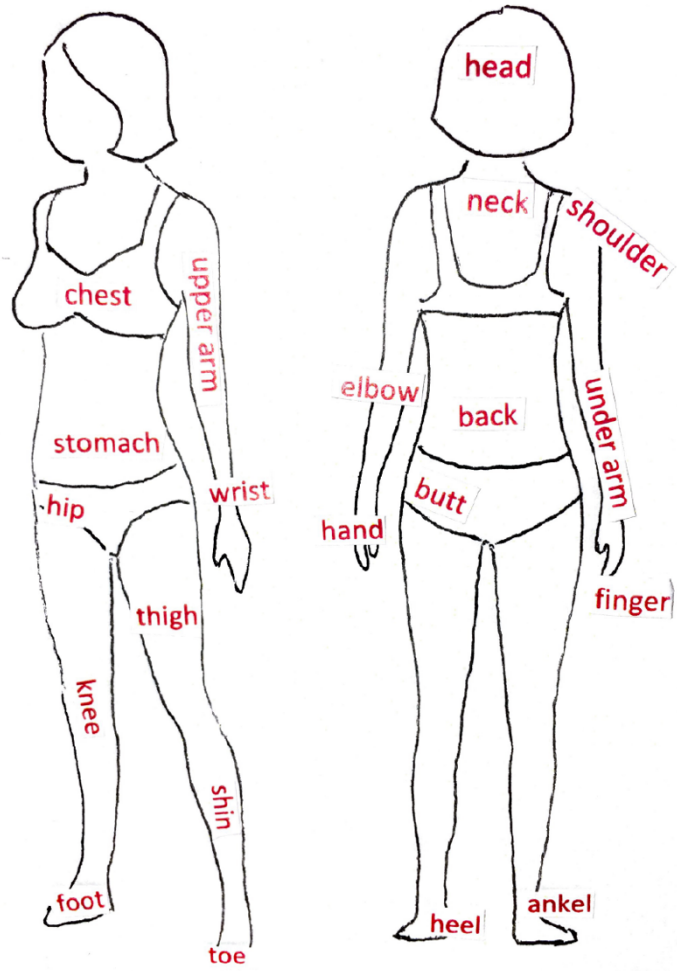
Below is a drawing of your body with names of the different parts of the body, where you can experience pain or feel hurt.



Confidential

Page 4

Below is a drawing of your body with names of the different parts of the body, where you can experience pain or feel hurt.



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 spare time activity)?	◯ Yes ◯ No
Please mark the areas of your body where you have pain during the past two weeks. If you have pain in more than one area of the body, it is important that you mark all the places with pain. Example: If you have pain in both the right knee and left foot, you must mark "right knee" and "left foot".	☐ Head ☐ Neck ☐ Right shoulder ☐ Left shoulder ☐ Right side of the chest ☐ Left side of the chest ☐ Right upper arm ☐ Left upper arm ☐ Right elbow ☐ Left elbow ☐ Right under arm ☐ Left under arm ☐ Right wrist ☐ Left wrist ☐ One or more fingers on the right hand ☐ One or more fingers on the left hand ☐ Right hip ☐ Left hip ☐ Back ☐ Right hip ☐ Left hip ☐ Right knee ☐ Left knee ☐ Right shin ☐ Left shin ☐ Right ankel ☐ Left ankel ☐ Right heel ☐ Left heel ☐ Right foot ☐ Left foot ☐ One or more toes on the right foot ☐ One or more toes on the left foot
The next question is whether you have pain in other areas of your body, different from the ones selected in previous question. Do you have pain in other areas of the body?	◯ Yes ◯ No

Confidential

Where?	☐ Head ☐ Neck ☐ Right shoulder ☐ Left shoulder ☐ Right side of the chest ☐ Left side of the chest ☐ Right upper arm ☐ Left upper arm ☐ Right elbow ☐ Left elbow ☐ Right under arm ☐ Left under arm ☐ Right wrist ☐ Left wrist ☐ One or more fingers on the right hand ☐ One or more fingers on the left hand ☐ Right hip ☐ Left hip ☐ Back ☐ Right hip ☐ Left hip ☐ Right knee ☐ Left knee ☐ Right shin ☐ Left shin ☐ Right ankel ☐ Left ankel ☐ Right heel ☐ Left heel ☐ Right foot ☐ Left foot ☐ One or more toes on the right foot ☐ One or more toes on the left foot
If you have pain in an area of the body, not named on the drawing above, please write it here:	_____
Mark the statements to the right, that are true about your pain. You may mark more than one.	☐ It can easily be ignored ☐ It affects my concentration ☐ Sometimes I have to take pain medication ☐ Sometimes I can't attend school because of the pain ☐ None of the above
On the scale of 0 to 10 to the right, where 0 is no pain and 10 is the worst possible pain, mark the number that best represents your pain.	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10
How long have you had your current pain?	_____
Are you familiar with the cause for your current pain?	◯ Yes ◯ No

What is the cause for your current pain (ex. a fall, a hit or other)?	_____
How long does a pain episode usually last?	◯ Less than 3 hours ◯ Less than 24 hours ◯ 1-7 days ◯ Longer than 7 days
How often do have a pain episode?	◯ At least once a week ◯ Less than once a week
Do you expect to be free of your current pain in the future?	◯ Yes, in the near future ◯ Yes, in the long-term future ◯ No
Do you take painkillers?	◯ No ◯ Yes, I take painkillers and know the name of them ◯ Yes, I take painkillers, but do not know the name of them
Please write the name of the painkillers that you take	_____
How often do you take painkillers?	◯ Once a month ◯ Once a week ◯ More than once a week ◯ Every day
Is your pain radiating to your legs or arms?	◯ Yes ◯ No

The next questions concern your doctors appointment today.

Why did you come to your doctor today? You may choose more than one answer.	☐ I want my pain to stop ☐ I am worried about the cause of my pain ☐ My family made me come ☐ I have a personal problem ☐ Because of my pain, I can't use my body as I used to ☐ None of the above
Do you expect your doctor to give you medication for your pain?	◯ Yes, I would like that ◯ No
Is this your first visit to your general practitioner concerning your current musculoskeletal pain condition?	◯ Yes ◯ No
This is visit number:	_____
Do you feel worried or anxious?	◯ Yes ◯ No ◯ I don't know
Do you believe, that you have low self-esteem?	◯ Yes ◯ No ◯ I don't know

Confidential

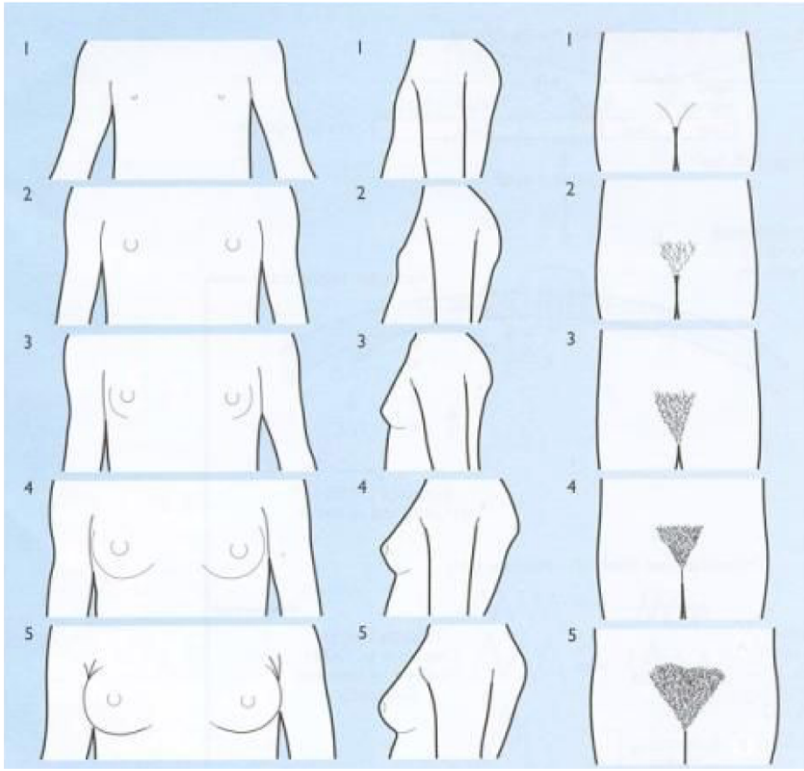
How many cigarettes do you smoke a day?	◯ I don't smoke cigarettes every day ◯ 1-4 cigarettes a day ◯ 5-9 cigarettes a day ◯ More than 9 cigarettes a day
Do you have a job?	◯ Yes ◯ No
How would you generally describe your physical activity in your job?	◯ Mostly sedentary work that does not require physical exertion ◯ Mostly standing or walking work, which otherwise does not require physical exertion ◯ Standing or walking work with some lifting or carrying work ◯ Heavy or fast work which is physically strenuous ◯ I don't know

The following questions are general questions about you.

How often do you feel nervous?	◯ Often or sometimes ◯ Seldom or never
Which zip code(s) do you live in? If you live in several places please write both zip codes.	_____ (If you live more than one place, please write both zip codes)
In which country were you born?	◯ Danmark ◯ Other country
In which other country were you born?	_____
How many years have you lived in Denmark?	_____
How many siblings do you have (including non-biological or siblings with a different mother or father than yours)?	◯ I don't have any siblings / I am an only child ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ More than 6
Which number are you in your group of siblings?	_____
What do you feel the most as?	◯ Danish ◯ Danish with foreign background ◯ Foreigner ◯ I don't know (Please answer the question, whatever your country of birth.)
How large a part of your friends have immigrant background or were not born in Denmark?	◯ None ◯ Almost none ◯ Almost all ◯ All

The last questions concern the development of your body.

Below is an image of the girl's body, and how it can look from the age 8 to 19 years.



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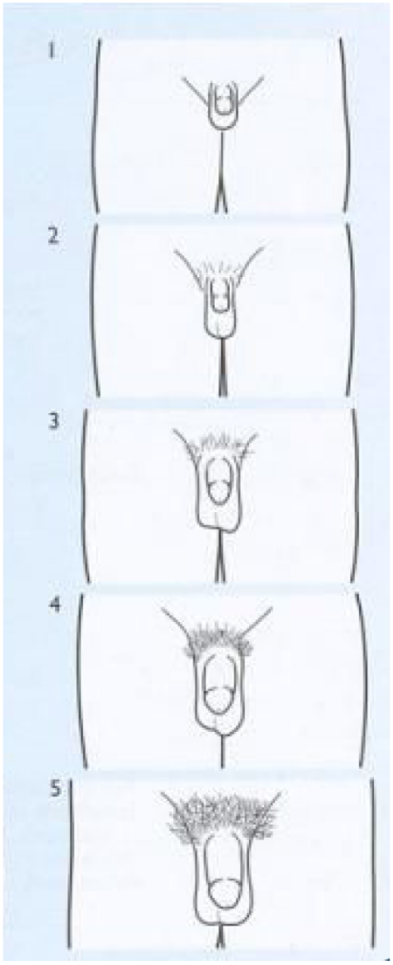
Below is an image of the boy's body, and how it can look from the age 8 to 19 years.



Which image represents your current physical features?

Please write one number.

_____

How tall are you? Please answer as best as you know your height	_____
How much do you weigh? Please answers best as you know your weight	_____
When was your visit at the doctor's with the above mentioned pain?	◯ Today ◯ About a week ago ◯ 2-4 weeks ago ◯ More than a month ago
Now we have reached the last question: When are you completing this questionnaire? You may now press: submit.	◯ Before seeing the doctor ◯ After having seen the doctor ◯ I started completing the questionnaire before seeing the doctor, but competed it after having seen the doctor

Appendix G. Paper 3

Not published.

Appendix H. Paper 4

Not published.

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