

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<u>http://bmjopen.bmj.com</u>).

If you have any questions on BMJ Open's open peer review process please email <u>info.bmjopen@bmj.com</u>

# **BMJ Open**

# Poor prognosis of child and adolescent Musculoskeletal Pain

# a Systematic Literature Review

Journal:	BMJ Open					
Manuscript ID	bmjopen-2018-024921					
Article Type:	Research					
Date Submitted by the Author:	14-Aug-2018					
Complete List of Authors:	Pourbordbari, Negar; Research unit for general practice in Aalborg Denmark, Clinical medicine Riis, Allan; Department of Clinical Medicine at Aalborg University, Research Unit for General Practice in Aalborg Jensen, Martin; Department of Clinical Medicine at Aalborg University, Research Unit for General Practice in Aalborg Olesen, Jens; Department of Clinical Medicine at Aalborg University, Research Unit for General Practice in Aalborg Research Unit for General Practice in Aalborg Rathleff, Michael ; Department of Clinical Medicine at Aalborg University, Research Unit for General Practice in Aalborg					
Keywords: musculoskeletal pain, adolescents, children, prognosis, general practi						
Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.						
Systematic-review-animation-final.mp4						

SCHOLARONE<sup>™</sup> Manuscripts

1	
2	
3	
4	Poor prognosis of child and adolescent Musculoskeletal Pain -
5	a Systematic Literature Review
6	
7	
8	
9	Authors
10	Pourbordbari N <sup>1</sup> , Riis A <sup>1</sup> , Jensen MB <sup>1</sup> , Olesen JL <sup>1</sup> , Rathleff MS <sup>1</sup>
11	
12	Affiliation:
13	Research Unit for General Practice in Aalborg,
14	Department of Clinical Medicine,
15	Aalborg University,
16 17	Denmark.
17	Authors and contact information
19	
20	Corresponding author Negar Pourbordbari MD, Research Unit for General Practice in Aalborg,
20	
22	Aalborg University,
23	Denmark.
24	Email: negar@dcm.aau.dk.
25	
26	
27	
28	
29	
30	Word count: 2463
31	Department of Clinical Medicine, Aalborg University, Denmark. Email: negar@dcm.aau.dk. Word count: 2463
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42 43	
43 44	
44	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	For poor region only http://humionon.humi-region/state/should be a braid
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

# Abstract

#### Objectives

To identify baseline patient characteristics that are: (i) associated with a poor outcome on follow up regardless of which treatment was provided (prognosis); or (ii) associated with a successful outcome to a specific treatment (treatment effect modifiers).

#### 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 May 2017 without limitation in publication date.

#### Eligibility criteria

Prospective cohort studies reporting either prognostic factors or treatment effect modifiers on persistent musculoskeletal pain in 0- to 19-year-old children and adolescents.

#### **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 that investigated the prognosis or treatment effect modifiers of 0- to 19-year-old children and adolescents with self-reported musculoskeletal pain. Risk of bias assessment was conducted with the QUIPS tool.

#### Results

Twenty-five studies yielding a total of 109 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.

#### 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.

#### Registration

The protocol for this review was developed using the PRISMA-P 2015 statement, inspired by the Cochrane Central Register of Controlled Trials, and registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42016041378).

#### Strengths and limitations of this study

- 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 we developed a highly sensitive search for each of the eight databases 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.

#### Keywords

musculoskeletal pain; adolescents; children; prognosis; general practice

#### Introduction

General practice is often the point of first contact into the health care 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).

Musculoskeletal pain affects half of all children and adolescents, and increases exponentially in frequency around the age of 10 (2-6). A recent systematic review reported that 40% of an adolescent population had experienced pain during the past six 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 one year later (10, 11) and that 21% of 12-35-year-olds had persistent knee pain six 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. 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 (i) poor outcome on follow-up (prognosis) or (ii) 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 September 2017 without limitation on date. An experienced research librarian collaborated in the production of individual search strategies for each of the eight databases (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- to 19-years-old, with any type and location of musculoskeletal pain. Musculoskeletal pain was defined as pain in muscle, tendon, bone, and joint (12). 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

Study details and results were extracted using a pre-defined data extraction form inspired by The Cochrane Collaboration (13). We extracted the prognostic factors from the included papers and used the following estimates: odds ratios (OR), relative risks (RR), and/or P-values. If possible, we extracted the adjusted associations.

#### Outcomes and endpoints

Our primary outcome of interest was musculoskeletal pain at follow-up and identification of 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 (14). On the study level, NP and AR independently rated the 25 included studies and reached consensus on all risk of bias assessments (table 1). Prognostic factors from studies with a high risk of bias, were excluded from figure 3.

**Table 1** Risk of bias in included studies. With the Quality in Prognostic Studies (QUIPS) 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. Three studies were rated with high risk of bias, and hence excluded from the final results.

Study author year	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*	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

2	
2	
3	
4	
5	
6	
7 8	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
١ð	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	

Ståhl et al 2008	Prospective cohort	Low	Moderate	Low	Low	Moderate	Low
Uziel et al 2010	Prospective cohort	Moderate	Low	Low	Low	High	Moderate

\*Is knee pain during adolescence a self-limiting condition? Risk of bias in included studies. With the Quality in Prognostic Studies (QUIPS) 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. Three studies were rated with high risk of bias, and hence excluded from the final results

#### **Involvement of general practitioners**

With stakeholder involvement and input from a panel of general practice researchers experienced in musculoskeletal research, we sub-grouped our identified prognostic factors in accordance with the biopsychosocial model (15, 16):

Biological prognostic factors:

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

#### Psychological prognostic factors

- -General psychological factors
- -Depressive factors

Social prognostic factors:

- -General social factors
- -Sleep-related factors
- -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 odds ratios (OR), relative risks (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% confidence interval. As for P-value, a statistically significant association was defined as P < 0.05. We used the PRISMA checklist when writing our report (17).

#### Patient involvement

No patients or public were involved in the present study.

#### RESULTS

#### Included studies

Figure 1 reports the results of the search strategy. Of the 37,884 titles identified, 36,224 studies were screened, and 25 studies (9, 11, 16, 18-39) 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, stomach, lower limb, knee, and growing pain. No treatment effect modifiers were identified.

#### **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%).

#### Prognosis

Figure 2 highlights the persistence of musculoskeletal pain in all included studies at different follow-up time points. On average, 54% with general musculoskeletal pain, 49% with knee pain and 42% with neck pain also reported pain at follow-up. A complete report of all the identified prognostic factors is listed in supplementary table 1. Figure 3 depicts the majority of these prognostic factors, stratified in pain type, sex, study population size, and follow-up (please see web supplemental document for explanatory notes).

Very few prognostic factors were reported on back pain, growing pain, lower limb pain, and widespread musculoskeletal pain (supplementary table 1); consequently, they were excluded from figure 3. Table 2 condenses the results from 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 2 and figure 3 can be printed and used by a general

ge
-
veek
of life
erience
ractice
tly?
ling
1?
e

practitioner at time of initial consultation with a 0-19-year-old patient with musculoskeletal pain.

**Table 2** What to ask in clinical practice? *4* prognostic factors belonging to *4* frequent musculoskeletal pain types in general practice: General musculoskeletal-, Low back-, Neck-, and Knee Pain.

The questions are proposals towards assessment of prognosis on musculoskeletal pain.

\* to be evaluated by clinical examination

#### Prognostic factors associated with pain at follow-up

A total of 109 prognostic factors were associated with musculoskeletal pain at follow-up, of which most were on general musculoskeletal pain and low back pain (table 3). Supplementary table 1 includes these results and further detailed depiction of prognostic factors.

Study	Musculoskeletal	Baseline	Study	Follow-	Persistent	Persistent	Persistent
author	pain	age	population	up	pain at	pain at	pain at
(reference)	type	(years)	(n)	(years)	follow-up	follow-up	follow-up
					Female (%)	Male (%)	combined (%)
Blaauw BA (18)	Headache	12 to 16	1586	4	45.7	22.7	35.1
Brattberg G 93 (19)	Back,	8, 11, 13	471	2	Back 15,	Back 4,	Back 9.3,
	Head				Head 40	Head 20	Head 30.7
Brattberg G 04 (20)	General	10, 13,	597	11	59	39	20
	musculoskeletal	16					
El-Metwally A 04 (21)	General	9 to 12	1756	1 and 4	4 years: 56.2	4 years: 43.8	1 years: 53.8,
	musculoskeletal						4 years: 63.5
El-Metwally A 05 (11)	Lower limb	9 to 12	1756	1 and 4	1 year: 29.4,	1 year 55.8,	1 year: 32,
					4 years 31.9	4 years 48.6	4 years 31
Flato B (22)	General	2 to 17	37	9	13	N/A	59
	musculoskeletal						
Jones GT (23)	Low back	11 to 14	330	4	N/A	N/A	26
Jussila L (24)	General	16 to 18	1773	2	N/A	N/A	N/A
	musculoskeletal						

Laimi K (25)	Headache <sup>a</sup>	13	311	3	54	70.5	48
Lunde LK (26)	Low back	15 to 19	420	6.5	N/A	N/A	39
Mikkelsson M 97 (27)	Neck, Widespread, low back	9 to 12	1756	1	N/A	N/A	Neck 48.3, WSP <sup>b</sup> 29.7, Low back 34.4
Mikkelsson M 98 (28)	General musculoskeletal	9 to 12	1756	1	N/A	N/A	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	N/A	N/A	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 years 68, 3 years 63	2 years 62, 3 years 47	N/A
Paananen MV (33)	General musculoskeletal	16	1594	2	N/A	75	88
Rathleff CR (9)	Knee	12 to 15	768	1	N/A	N/A	48.8
Rathleff MS 16 (34)	Knee	16 to 18	504	2	N/A	N/A	55.9
Rathleff MS 16 (35)	Knee (PFP)	15 to 19	121	3 months	N/A	N/A	74.4
Sjolie AN (36)	Low back	14 to 16	88	3	N/A	N/A	39
Sperotto F (37)	General musculoskeletal	8 to 13	289	3	N/A	N/A	54.3
Stanford EA (39)	Head, Back, Stomachache	10 to 11	2488°	2	N/A	N/A	Head 29, Back 21.7
Ståhl M (38)	Neck	9 to 12	1756	1 and 4	N/A	N/A	1 year: 48.2, 4 years: 33.5
Uziel Y (40)	Growing pain	10 to 16	35	5	N/A	N/A	48.6

N/A = not applicable

A = Headache: non migrainous

b = Widespread pain

c = included stomachache participants

Extracted data from the Included studies were all musculoskeletal pain types investigated in the individual included studies together with baseline age, size of study population, follow-up and percentage of study participants who represented persistent pain at follow-up, -both stratified by gender and combined.

Female sex was the most frequently identified prognostic factor associated with musculoskeletal pain at follow-up. Eleven studies identified psychological factors (e.g. depression, anxiety, and low self-esteem) to be associated with pain at follow-up in seven out of nine musculoskeletal pain types (9, 16, 18, 20, 21, 23, 24, 28, 33, 34, 38).

Longer pain duration was associated with pain at follow-up across four musculoskeletal pain types: musculoskeletal, low back, knee, and back pain (20, 22, 23, 34).

Five studies identified sleep-related problems associated with outcome (21, 24, 28, 33, 38).

Other indicators for musculoskeletal pain at follow-up were increasing age (9, 21, 25, 28), smoking (30, 33), parental pain (16, 22, 39), and multisite pain (21, 22, 38).

Figure 3 summarises all identified prognostic factors for musculoskeletal pain at follow-up, stratified in 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 (supplementary table 1).

Increasing age (11, 20, 22, 27, 29, 34, 39, 40) 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 (22, 24, 40) and hypermobility (11, 28, 38).

#### DISCUSSION

#### **Principal findings**

Female sex was consistently associated with an increased risk of pain at follow-up across six different musculoskeletal pain types. Depressive symptoms (9, 16, 18, 21, 24, 28, 33, 34, 38), sleep-related factors (21, 24, 28, 33, 38), and parental pain condition (16, 22, 39) 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.

#### 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 (41). 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). Despite methodology differences, we did not identify additional studies from inception to 2015, but identified two new studies from January 2016 to 2017. These studies added important knowledge of female sex, pain frequency, and the prognosis of knee 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 i.e., female gender, older age, depression/anxiety, and long pain duration was 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 e.g. 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 (15, 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 (52 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 psycho-social 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 longterm 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. Health care practitioners should be cognisant not to assume that musculoskeletal pain during childhood or adolescence is transient or selflimiting.

#### **Supplementary information**

Additional information accompanies this paper in the form of Appendix 1: Search string, Appendix 2: Completed PRISMA checklist, Appendix 3: Protocol, Figure 1: PRISMA Flow chart, Figure 2: Persistent musculoskeletal pain, stratified in pain type and follow-up, Figure 3: Prognostic factors for persistent musculoskeletal pain, according to pain type, population size, sex, follow-up, and the biopsychosocial model, Supplementary table 1: Estimates on prognostic factors specified according to musculoskeletal pain type, baseline age, and follow-up in the included studies, and an animation showing how our findings can be used in a clinical setting, go to: https://youtu.be/raltzsgkTHc

#### Author contributions

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 contributed with important reflections and revisions to both.

#### Funding

This work was supported by The Research Unit for General Practice in Aalborg, Denmark, without any further funders.

#### Ethical approval

Not applicable.

#### **Competing interests**

The authors have declared no competing interests.

#### Data sharing statement

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

## References

 1. Michaleff ZA, Campbell P, Protheroe J, Rajani A, Dunn KM. Consultation patterns of children and adolescents with knee pain in UK general practice: analysis of medical records. BMC Musculoskelet Disord. 2017;18(1):239.

2. Hofel L, Draheim N, Hafner R, Haas JP. Pain syndrome of the musculoskeletal system in children and adolescents. Zeitschrift Fur Rheumatologie. 2016;75(3):292-301.

3. King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. Pain. 2011;152(12):2729-38.

4. Auvinen JP, Paananen MVJ, Tammelin TH, Taimela SP, Mutanen POA, Zitting PJ, et al. Musculoskeletal pain combinations in adolescents. Spine. 2009;34(11):1192-7.

5. De Inocencio J. Epidemiology of musculoskeletal pain in primary care. Arch Dis Child. 2004;89(5):431-4.

6. Michaleff ZA, Kamper SJ, Stinson JN, Hestbaek L, Williams CM, Campbell P, et al. Measuring Musculoskeletal Pain in Infants, Children, and Adolescents. J Orthop Sports Phys Ther. 2017;47(10):712-30.

7. Smedbraten BK, Natvig B, Rutle O, Bruusgaard D. Self-reported bodily pain in schoolchildren. Scand J Rheumatol. 1998;27(4):273-6.

8. McGrath P. Psychological guidelines for helping children cope with chronic benign intractable pain. The Clinical journal of pain. 1986.

9. Rathleff CR, Olesen JL, Roos EM, Rasmussen S, Rathleff MS. Half of 12-15-year-olds with knee pain still have pain after one year. Danish Medical Journal. 2013;60 (11) (no pagination)(A4725).

10. Kastelein M, Luijsterburg PA, Heintjes EM, van Middelkoop M, Verhaar JA, Koes BW, et al. The 6-year trajectory of non-traumatic knee symptoms (including patellofemoral pain) in adolescents and young adults in general practice: a study of clinical predictors. British journal of sports medicine. 2015;49(6):400-5.

11. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Lower limb pain in a preadolescent population: prognosis and risk factors for chronicity--a prospective 1- and 4-year follow-up study. Pediatrics. 2005;116(3):673-81.

12. iasp. Acute Musculoskeletal Pain [Available from: <u>https://www.iasp-</u>

pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/MusculoskeletalPainFactSheets/Ac utePain\_Final.pdf.

13. Cochrane Training. Data collection form for intervention reviews 2014 [Available from: <u>http://training.cochrane.org/resource/data-collection-forms-intervention-reviews</u>.

14. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.

15. Engel GL. The Need for a New Medical Model: A Challenge for Biomedicine Science 1977;196(No. 4286):19-136.

16. Stanford EA, Chambers CT, Biesanz JC, Chen E. The frequency, trajectories and predictors of adolescent recurrent pain: A population-based approach. Pain. 2008;138(1):11-21.

17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

1	
2	
3 4	18. Blaauw BA, Dyb G, Hagen K, Holmen TL, Linde M, Wentzel-Larsen T, et al. The relationship
5	of anxiety, depression and behavioral problems with recurrent headache in late adolescence - a
6	Young-HUNT follow-up study. Journal of Headache and Pain. 2015;16(1):1-7.
7	19. Brattberg G. Back pain and headache in Swedish schoolchildren: A longitudinal study. Pain
8	Clinic. 1993;6(3):157-62.
9	20. Brattberg G. Do pain problems in young school children persist into early adulthood? A 13-
10 11	year follow-up. European Journal of Pain. 2004;8(3):187-99.
12	21. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Prognosis of non-
13	specific musculoskeletal pain in preadolescents: A prospective 4-year follow-up study till
14	adolescence. Pain. 2004;110(3):550-9.
15	22. Flato B, Aasland A, Vandvik IH, Forre O. Outcome and predictive factors in children with
16	chronic idiopathic musculoskeletal pain. Clinical and Experimental Rheumatology. 1997;15(5):569-
17	77.
18	23. Jones GT, Macfarlane GJ. Predicting persistent low back pain in schoolchildren: A
19 20	prospective cohort study. Arthritis Care and Research. 2009;61(10):1359-66.
20	24. Jussila L, Paananen M, Nayha S, Taimela S, Tammelin T, Auvinen J, et al. Psychosocial and
22	lifestyle correlates of musculoskeletal pain patterns in adolescence: A 2-year follow-up study.
23	European Journal of Pain (United Kingdom). 2014;18(1):139-46.
24	25. Laimi K, Vahlberg T, Salminen JJ, Metsahonkala L, Mikkelsson M, Anttila P, et al. Does neck
25	pain determine the outcome of adolescent headache? Cephalalgia. 2007;27(3):244-53.
26	26. Lunde LK, Koch M, Hanvold TN, Waersted M, Veiersted KB. Low back pain and physical
27 28	activity - A 6.5 year follow-up among young adults in their transition from school to working life.
29	Bmc Public Health. 2015;15.
30	27. Mikkelsson M, Salminen JJ, Kautiainen H. Non-specific musculoskeletal pain in
31	preadolescents. Prevalence and 1-year persistence. Pain. 1997;73(1):29-35.
32	28. Mikkelsson M, Salminen JJ, Sourander A, Kautiainen H. Contributing factors to the
33	persistence of musculoskeletal pain in preadolescents: A prospective 1-year follow-up study. Pain.
34 35	1998;77(1):67-72.
36	29. Mikkelsson M, Sourander A, Salminen JJ, Kautiainen H, Piha J. Widespread pain and neck
37	pain in schoolchildren. A prospective one-year follow-up study. Acta Paediatrica, International
38	Journal of Paediatrics. 1999;88(10):1119-24.
39	30. Mikkonen P, Leino-Arjas P, Remes J, Zitting P, Taimela S, Karppinen J. Is smoking a risk
40	factor for low back pain in adolescents? A prospective cohort study. Spine. 2008;33(5):527-32.
41	31. Mikkonen P, Viikari-Juntura E, Remes J, Pienimaki T, Solovieva S, Taimela S, et al. Physical
42 43	workload and risk of low back pain in adolescence. Occupational and Environmental Medicine.
43	2011.
45	32. Mikkonen PH, Laitinen J, Remes J, Tammelin T, Taimela S, Kaikkonen K, et al. Association
46	between overweight and low back pain: A population-based prospective cohort study of
47	adolescents. Spine. 2013;38(12):1026-33.
48	33. Paananen MV, Taimela SP, Auvinen JP, Tammelin TH, Kantomaa MT, Ebeling HE, et al. Risk
49	-
50 51	factors for persistence of multiple musculoskeletal pains in adolescence: A 2-year follow-up study. European Journal of Pain. 2010;14(10):1026-32.
52	34. Rathleff MS, Rathleff CR, Olesen JL, Rasmussen S, Roos EM. Is Knee Pain During
53	Adolescence a Self-limiting Condition? Prognosis of Patellofemoral Pain and Other Types of Knee
54	Pain. American Journal of Sports Medicine. 2016;44(5):1165-71.
55	ram. American Journal of Sports Medicine. 2010,44(5).1105-71.
56	
57	
58 59	
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml <b>11</b>

35. Rathleff MS, Roos EM, Olesen JL, Rasmussen S, Arendt-Nielsen L. Self-reported recovery is associated with improvement in localized hyperalgesia among adolescent females with patellofemoral pain: Results from a cluster randomized trial. Clinical Journal of Pain. 2016;32(5):428-34.

36. Sjolie AN, Ljunggren AE. The significance of high lumbar mobility and low lumbar strength for current and future low back pain in adolescents. Spine. 2001;26(23):2629-36.

37. Sperotto F, Brachi S, Vittadello F, Zulian F. Musculoskeletal pain in schoolchildren across puberty: A 3-year follow-up study. Pediatric Rheumatology. 2015.

38. Stahl M, Kautiainen H, El-Metwally A, Hakkinen A, Ylinen J, Salminen JJ, et al. Non-specific neck pain in schoolchildren: Prognosis and risk factors for occurrence and persistence. A 4-year follow-up study. Pain. 2008;137(2):316-22.

39. Uziel Y, Chapnick G, Jaber L, Nemet D, Hashkes PJ. Five-Year Outcome of Children With "Growing Pains": Correlations With Pain Threshold. Journal of Pediatrics. 2010;156(5):838-40.

40. Lunde LK, Koch M, Hanvold TN, Waersted M, Veiersted KB. Low back pain and physical activity--A 6.5 year follow-up among young adults in their transition from school to working life. BMC public health. 2015;15:1115.

41. Huguet A, Tougas ME, Hayden J, McGrath PJ, Stinson JN, Chambers CT. Systematic review with meta-analysis of childhood and adolescent risk and prognostic factors for musculoskeletal pain. Pain. 2016;157(12):2640-56.

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

43. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. British journal of anaesthesia. 2013;111(1):52-8.

44. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL, 3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. The journal of pain : official journal of the American Pain Society. 2009;10(5):447-85.

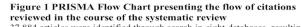
45. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choiniere M. A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? Pain. 2012;153(3):619-35.

46. Polatin P, Bevers K, Gatchel RJ. Pharmacological treatment of depression in geriatric chronic pain patients: a biopsychosocial approach integrating functional restoration. Expert Rev Clin Pharmacol. 2017;10(9):957-63.

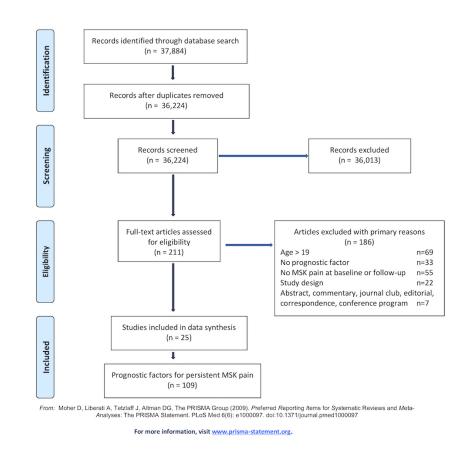
47. Amiri RS, Jouibari MF, Nejat F, El Khashab M. Iniencephaly: Clinical, Radiological and Surgical Findings. Pediatric Neurosurgery. 2010;46(4):290-3.

48. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007;133(4):581-624.

49. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Lower limb pain in a preadolescent population: Prognosis and risk factors for chronicity - A prospective 1- and 4-year follow-up study. Pediatrics. 2005;116(3):673-81.



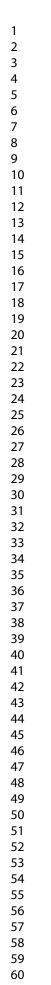
37,884 articles were identified through search in eight databases, resulting in 211 articles for full-text eligibility screen and a final number of 25 studies for inclusion yielding 109 prognostic factors on musculoskeletal pain.

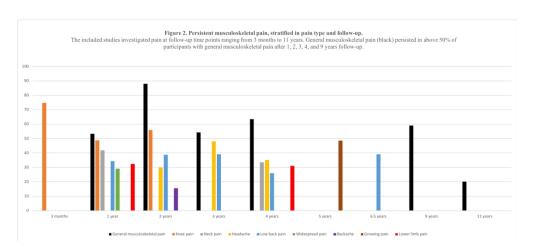


PRISMA Flow Chart presenting the flow of citations reviewed in the course of the systematic review.

37,884 articles were identified through search in eight databases, resulting in 211 articles for full-text eligibility screen and a final number of 25 studies for inclusion yielding 109 prognostic factors on musculoskeletal pain.

90x116mm (300 x 300 DPI)

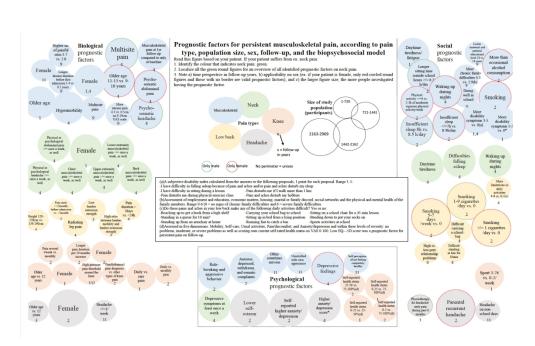




Persistent musculoskeletal pain, stratified in pain type and follow-up.

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

203x90mm (300 x 300 DPI)



Caption and legend embedded in figure.

337x206mm (300 x 300 DPI)

Table	2. Estimates on prognostic factors specified according to	Musculoskeletal pain	Neck pain					
musculoskeletal pain type, baseline age, and follow-up in the included studies		Low back pain	Low limb pain	Headache				
		Knee pain	Back pain	Growing pain				
aseline 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			$\rightarrow$
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)		2 24 (1 24 4 20)	M < 0.001			+
8, 11, 14		20 (11)		2.24 (1.24-4.20)				+
	Older age Older age	28 (1)		1.24 (1.02-1.50)	0.031			+
	11 to 13 years vs. 9-10 years	21 (4)	M 1.40 (1.17-1.67)	1.24 (1.02-1.50)	0.031			
	Older age, increase per year, 12 years as referent	9 (1)	IVI 1.40 (1.17-1.07)	M 1.45 (1.07-1.95)	0.01			+
	Older age	25 (3)		W 1.45 (1.07 1.55)	0.01			+
	Body measurement factors	23 (3)			0.04			+
	Higher pubertal group (a) group 2 and 3 vs. group 1	37 (3)			0.022			+
	Beighton score 6-9 vs. score < 6	21 (4)	M 1.31 (1.18-1.46)		0.022	age		+
	Height < 158cm	23 (4)	2.2 (1.2-3.8)			age, sex		-
	Hypermobility score >/=6 vs. <6	. ,	2.2 (1.2 5.6)	M 2 02 (1 12 7 70)		age, sex		
	Physical functioning	11 (4)		M 2.93 (1.13-7.70)				
	Ratio flexion mobility (cm)/extension strength (min) (b)	36 (3)		1.9 (1.1-3.2)	0.02	gender, well being, physical	activity	-
	Ratio extension mobility cm/extension strength (min) (b)	36 (3)		3.2 (1.3-8.3)	0.02	gender	activity	+
	Ratio flexion + extension mobility (cm)/extension strength (min) (b)	36 (3)		1.5 (1.1-2.2)	0.02	gender, well being, physical	activity	+
	Pain characteristics	00 (0)		1.5 (1.1 2.2)	0.02	gender, wendenig, prijsted	activity	+
	Higher number of painful sites (mean 3.7 vs. 2.8) range 0-6	22 (9)			0.04			+
	More frequent generalised vs. localised pain (86 vs. 47%)	22 (9)		84.0 (2.1-3000)	0.02			十
	More intense pain (median 4.3 vs. 0.5cm) range 0-10cm VAS	22 (9)			0.03			十
	Longer disease duration before first admission (median 1.4 vs. 0.5 years)	22 (9)			< 0.01			T
	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		
	Headache (psychosomatic symptom (c))	21 (4)	M 1.43 (1.12-1.83)			age		
	Abdominal pain (psychosomatic symptom (c))	21 (4)	U 1.20 (1.03-1.40)			age		$\Box$
	Radiating leg pain vs. no radiating pain	23 (4)	2.2 (1.4-3.6)			age, sex		
	Low back pain start > 12 month prior to admission	23 (4)	2.4 (1.3-4.4)			age, sex		
	Pain episode > 7 days vs < 24h	23 (4)	2.6 (1.4-4.9)			age, sex		-
	Patellofemoral pain diagnosis vs. other types of knee pain	34 (2)	1.24 (1.04-1.49)		0.01	age, sex, BMI		+
	High pressure pain threshold (PPT) around the knee	35 (3mo)		M C 24 /1 24 22 24	0.03			+
	Daily vs. rare pain	9 (1)		M 6.31 (1.21-33.01)	0.03			+
	Pain several times/week vs. monthly	34 (2)	CR 1.58 (1.15-2.17)		0.005			+
	Daily pain frequency vs. monthly Longer pain duration per 10-months increase	34 (2) 34 (2)	1.58 (1.17-2.14) CR 1.04 (1.01-1.07)		0.003			+
		34 [2]	CK 1.04 (1.01-1.07)		0.01			

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

BMJ (	Open
-------	------

2         9 to 12 M         Also abdominal pain (d) at less ta week         38 (d)         40           3         9 to 12 F         Also abdominal pain (d) at less ta week         38 (d)         40           4         9 to 12 F         Also abdominal pain (d) at less ta week         38 (d)         40           4         9 to 12 Other musculosketal symptoms: upper externities at least once a week         38 (d)         40           5         9 to 12 Other musculosketal symptoms: chest at least once a week         38 (d)         40           9 to 12 Other musculosketal symptoms: chest at least once a week         38 (d)         40           9 to 12 Other musculosketal symptoms back at less once a week         38 (d)         40           9 to 12 Other musculosketal symptoms as well: lower externities at least once a week         38 (d)         40           9 to 12 Other musculosketal symptoms as well: lower externities at least once a week         38 (d)         40           9 to 12 Other musculosketal symptoms as well: lower externities at least once a week         38 (d)         40           10 to 16 Duration of pain episodes > hours s. <3 hours         20 (11)         2.3 (1.1.4.5)           10 to 16 Lower pain threshold at least once a week         33 (2)         2.3 (1.2.3.4.37)           10 to 16 Lower pain threshold at least once a week         33 (2)         2.3 (1.2.3.4.37) <th>001    </th> <th></th>	001	
3         9         0.12 F         Also addoming pain (d) at least oweek         38 (4)           40.0           4         9         10.12 F         Also addoming pain (d) at least oweek         38 (4)           40.0           5         9         10.12 F         Also addoming pain (d) at least oweek         38 (4)           40.0           5         9         10.12 F         Other musculosketal symptoms: chect at least once a week         38 (4)           0.00           9         10.12 F         Other musculosketal symptoms: chect at least once a week         38 (4)            0.00           9         10.12 F         Other musculosketal symptoms: as well: lower extermities at least once a week         38 (4)             0.00           9         10.12 M         Other musculosketal symptoms as well: lower extermities at least once a week         38 (4)            0.00           10         10         10         10         10         10         10.10         10         10.10         10         10.10         10         10.10         10.10         10.10         10.10         10.11	001	
3       9 to 12.F       Also addominal pain (d) at least a wesk       38 (d)              0.00         4       9 to 12.M       Other musculoskied al symptoms: chest at least once a wesk       38 (d)         0.00         5       to 12.F       Other musculoskied al symptoms: chest at least once a wesk       38 (d)         0.00         9       to 12.M       Other musculoskied al symptoms as well: lower extermities at least once a week       38 (d)          0.00         9       to 12.M       Other musculoskied al symptoms as well: lower extermities at least once a week       38 (d)         0.00         8       to 12.F       Other musculoskied al symptoms as well: lower extermities at least once a week       20 (11)        2.3 (1.1.4.5)        0.00       0	001	
4         9 to 1.2         Other musculosketal symptoms: chest at least once a week         38 (4)         0.00           5         9 to 1.2 K         Other musculosketal symptoms: chest at least once a week         38 (4)         0.00           6         9 to 1.2 K         Other musculosketal symptoms: back at least once a week         38 (4)         0.00           9 to 1.2 K         Other musculosketal symptoms: back at least once a week         38 (4)         0.00           9 to 1.2 K         Other musculosketal symptoms as well: lower extermities at least once a week         38 (4)         0.00           8 to 1.2 F         Other musculosketal symptoms as well: lower extermities at least once a week         38 (4)         0.00           8 to 1.2 F         Other musculosketal symptoms as well: lower extermities at least once a week         38 (4)         0.00           9 to 10 to 16         Dute on pain episode > 3 hours vs. <3 hours	008	
5         9 to 12 M         Other musculoskeletal symptoms: chest at least once a week         38 (4)         0.00           6         9 to 12         Other musculoskeletal symptoms: back at least once a week         38 (4)         0.00           7         9 to 12 M         Other musculoskeletal symptoms: back at least once a week         38 (4)         0.00           9 to 12 M         Other musculoskeletal symptoms: back at least once a week         38 (4)         0.00           9 to 12 M         Other musculoskeletal symptoms as well: lower externities at least once a week         38 (4)         0.00           8 5.11 /14         Headneb s/= 1time/week         20 (11)         2.3 (1.1.4.5)         0.00           10 to 16         Duration of pain episodes > 3 hours so. < 3 hours	001 001 001 001 001 001 001 001 001 001	
5         9         12.F         Other musculosketal symptoms: back at least once a week         38 (4)         0.00           9         10.12         Other musculosketal symptoms: back at least once a week         38 (4)          <0.00	001 001 001 001 001 001 001 001 001 001	
6         9 to 12         Other musculoskeletal symptoms as well: lower extremities at least once a week         38 (4)	001 001 001 001 001 001 001 001 001 001	
7       9 to 12. M       Other musculoskeletal symptoms as well: lower extremities at least once a week       38 (4)         0.00         8       9 to 12. F       Other musculoskeletal symptoms as well: lower extremities at least once a week       38 (4)       0.00         9       10 to 16       Duration of pain episodes >3 hours s. <3 hours	001 003 003 000 000 000 000 000 000 000	
8         9 to 12 F         Other musculoskelard symptoms as well: lower extremities at least once a week         38 (4)         0.00           9         10 to 16         Duration of pain episodes > 3 hours so. < 3 hours	.05	
8       1.1.1.4       Headach = /= time/week       20 (11)       2.3 (1.1.4.5)         9       10 to 16       Duration of pain episodes > 3 hours vs. < 3 hours	.05	
9         10 to 16         Duration of pain episodes > 3 hours vs. < 3 hours         20 (11)         U 3.1 (1.1-8.2)           10         10 to 16         Lower pain threshold at atteior tiblal region (pressure level < 5kg/cm2)		
10       10       to 16       Lower pain threshold       40 (5)       0.0         11       10       to 16       Lower pain threshold at anterior tiplal region (pressure level < 5ke/cm 2)		
10         10<		
Pyrchological PROGNOSTIC FACTORS         m         <		_
12         General psychological 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)         10 to 16       Offen/sometimes nervous       20 (11)       M.2.1 (1.3.3.4)         16 to 18 M       Internalization (e)       24 (2)        <0.0         16 to 18 F       Higher internalization score (e)       24 (2)        <0.0         16 to 18 F       Higher internalization score (e)       24 (2)        <0.0         16 to 18 F       Higher externalization score (e)       24 (2)        <0.0         10 to 16       Self-perception of not feeling completely healthy       20 (11)       U1.7 (1.1-2.8)          20       10 to 15       EQ-5D index score 0-25 vs. 75-100% quartiles (f)       9 (1)       U0.08       <0.0         12 to 15       EQ-5D index score 0-25 vs. 75-100% quartiles (f)       9 (1)       U0.08       <0.0         21 to 15       EQ-5D index score 0-25 tw s. 75-1000 % (f)       34 (2)       CR 1.81 (1.14-2.85)       0.0         22 to 15       EQ-5D index score 0-25 tw s. 75-th 000 % (f)       34 (2)       CR 1.81 (1.14-2.85)       0.00         23 to 15		
16 M       Externalization (e)       33 (2)       2.17 (1.24-3.81)         14       16 F       Internalization (e)       33 (2)       3.70 (1.88-7.27)         16 to 16       Often/sometimes nervous       20 (11)       M 2.1 (1.3-3.4)          16 to 18 M       Internalization (e)       24 (2)        <0.0		
14       16 F       Internalization (e)       33 (2)       3.70 (1.88-7.27)         15       10 to 16       Often/sometimes nervous       20 (11)       M 2.1 (1.3-3.4)         16       16 to 18 M       Internalization (e)       24 (2)       <0.0		
15       10 to 16       Often/sometimes nervous       20 (11)       M 2.1 (1.3-3.4)         16       16 to 18 M       Internalization (e)       24 (2)       <0.0		-
16       16 <td< td=""><td></td><td>-</td></td<>		-
16 to 18 M       Externalization (e)       24 (2)        <0.0	.001	-
16       to table Higher internalization score (e)       24 (2)        <0.0		-
18       16 to 18 F       Higher extenalization score (e)       24 (2)        <0.0		
19       10 to 16       Self-perception of not feeling completely healthy       20 (11)       U 1.7 (1.1-2.8)         20       10 to 16       Unsatisfied with own appearance       20 (11)       U 1.6 (1.1-2.5)         21       12 to 15       EQ-5D index score 0-25 vs. 75-100% quartiles (f)       9 (1)       U 0.08       <0.01		
10 to 16       Unsatisfied with own appearance       20 (11)       U 1.6 (1.1-2.5)         20       12 to 15       EQ-5D index score 0.25 vs. 75-100% quartiles (f)       9 (1)       U 0.08       <0.00		
20       12 to 15       EQ-5D index score 0-25 vs. 75-100% quartiles (f)       9 (1)       U 0.08       <0.00		
21       12 to 15       EQ-5D index score 0.25 vs. 25-50% quartiles (f)       9 (1)       U 0.29       <0.00	001	
22       12 to 15       EQ-5D index score 25-50th % vs. 75th-100th % (f)       34 (2)       CR 1.81 (1.14-2.85)       0.00         23       12 to 15       EQ-5D index score 0-25th % vs. 75th-100th % (f)       34 (2)       CR 2.00 (1.28-3.12)       0.00         23       10 to 11       Self reported low self esteem       39 (2)       U<0.0		
12 to 15       EQ-5D index score 0-25th % vs. 75th-100th % (f)       34 (2)       CR 2.00 (1.28-3.12)       0.00         10 to 11       Self reported low self esteem       39 (2)       U < 0.		
23       10 to 11       Self reported low self esteem       39 (2)       U < 0.		
24       10 to 11       Parent reported adolescent low self esteem       39 (2)       U < 0.0		
Depressive factors       C       C       C       C         9 to 12 F       Depressive feelings       21 (4)       U1.21 (1.03-1.42)       U         9 to 12 F       Depressive symptoms in a frequency of at least once a week       38 (4)           27       9 to 12 M       Depressive symptoms in a frequency of at least once a week       38 (4)            28       12 to 16       Higher score of anxiety and depressive symptoms (g)       18 (4)       1.4 (1.03-1.90)       0.03         29       10 to 11       Self reported anxiety/depression       39 (2)       M <0.04		
9 to 12 F       Depressive feelings       21 (4)       U 1.21 (1.03-1.42)       0         26       9 to 12 F       Depressive symptoms in a frequency of at least once a week       38 (4)         <0.00	0.01	
26       9 to 12 F       Depressive symptoms in a frequency of at least once a week       38 (4)       <0.00	age	
27     9 to 12 M     Depressive symptoms in a frequency of at least once a week     38 (4)     <0.00		
28         12 to 16         Higher score of anxiety and depressive symptoms (g)         18 (4)         1.4 (1.03-1.90)         0.03           29         10 to 11         Self reported anxiety/depression         39 (2)         M <0.		-
29         10 to 11         Self reported anxiety/depression         39 (2)         M <0.           29         10 to 11         Parent reported adolescent anxiety/depression         39 (2)         < 0.0		
29     10 to 11     Parent reported adolescent apxiety/depression     39 (2)     < 0.0		
30 SOCIAL PROGNOSTIC FACTORS		
		+
2  to  17   lower natural educational land (median 10 vs. 14 year education) $22/(0)$	0.01	
32 2 to 17 Lower paternal educational level (median 10 vs. 14 years education) 22 (9) p<0.1		
33         2 to 17         Lotter indential code donaire (including to 5) 14 years code donaire)         22 (9)         p <0.1           33         2 to 17         More chronic family difficulties (mean 4.3 vs. 2.9) (h)         22 (9)         p <0.1		
34         10 to 16         Doing well in school         20 (11)         U1.8 (1.1-2.9)		-
	005	-
35         9 to 12         Higher disability index (i) 1-2 vs 0         28 (1)         1.72 (1.09-2.73)         0.00           9 to 12         Higher disability index (i) 3-5 vs 0         28 (1)         3.17 (1.54-6.55)         0.00		
36         9 to 12         Higher disability index (i) 3-5 vs. 0         21 (4)         U 1.23 (1.02-1.49)	age	-
37       11 to 14       High vs. low peer relationship problems       23 (4)       2.4 (1.3-4.2)	age, sex	-
20       11 to 14       Difficulty standing in line for 10 minutes       23 (4)       2.7 (1.5-4.9)		-
38         11 to 14         Difficulties carrying a schoolbag         23 (4)         2.1 (1.1-4.0)		
39       11 to 14       High limitation level HFAQ (j) 4-9 vs. 0-1 limitations       23 (4)       4.1 (1.05-16.2)		
40         8, 11, 14         Headache on non-school days         20 (11)         3.1 (1.3-7.3)		
12 M Use of a busietherman for basedeste an angly asia during the part 6 meeths 25 (2)		
	204	

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 II	10 to 11 F	Parental recurrent headache	39 (2)			p<0.05			
2	10 to 11	At least one parent with a pain syndrome	40 (5)			0.047			
3 -	10 10 10	Sleep related factors	40 (5)			0.047			
4	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</td <td>33 (2)</td> <td>0 1.10 (1.01 1.57)</td> <td>1.68 (1.05-2.68)</td> <td></td> <td>uge</td> <td></td> <td></td>	33 (2)	0 1.10 (1.01 1.57)	1.68 (1.05-2.68)		uge		
5 -	9 to 12	Day tiredness, fatigue	28 (1)		1.86 (1.16-3.00)	0.010			
5 -		Insufficient sleeping time h/day (mean 8 vs. 8.5 h/day)	24 (2)		1.80 (1.10-3.00)	0.001			
7	9 to 12 M	Difficulties falling asleep	38 (4)			< 0.001			
3		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			
0	9 to 12 F	Daytime tiredness	38 (4)			<0.001			
1	9 to 12 F	Walking up during nights	38 (4)			<0.001			
		Physical activity / inactivity							
2	16 F	>/=4 vs. 2-3 hours of moderate-to-vigorous physical activity/week	33 (2)		1.63 (1.04-2.56)				
3	16 to 18 M	Longer sitting time outside school hours (mean 6.2 h/day)	24 (2)			0.004			
Δ	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)				
15		Alcohol							
16	16 to 18 F	More than occasional consumption	24 (2)			0.038			
7		Smoking							
	16 F	Smoking vs. nonsmoking	33 (2)		1.89 (1.23-2.90)				
ŏ	16 F	Smoking 5-7 days/week vs. nonsmoking	30 (2)		2.52 (1.40-4.53)		family's SES, physical activit	ty, BMI, depressive mood	
9	16 F	Smoking 1-9 cigarettes/day vs. nonsmoking	30 (2)		2.39 (1.40-4.08)		family's SES, physical activit	ty, BMI, depressive mood	
0	16 F	Smoking > 9 cigarettes/day vs. nonsmoking	30 (2)		2.57 (1.03-6.46)		family's SES, physical activit	ty, BMI, depressive mood	
21	16 M	Smoking 1-9 cigarettes/day vs. nonsmoking	30 (2)		2.68 (1.35-5.32)		family's SES, physical activit	ty, BMI, depressive mood	
1	xplanatory n	otes							
22F	= prognostic fac	ctor only applicable for female participants, <b>M</b> = Male, when nonspecified = unisex							
23 F	R>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.							
4	<b>Cl</b> = confidence i	nterval <b>M</b> = Multivariate analysis <b>U</b> = Univariate analysis CR = Crude							
 ۲	= Group 1: prep	ubertal, group 2: became pubertal during 3 years follow-up, and group 3: pubertal at baseline. The pubertal stage was assess	ed by the presence of se	condary signs of pubertal dev	elopment. For females, pub	erty was defined l	by the stage of breast develop	oment (Tanner stage >/= 3) a	and
25 r	nenarche. For n	ales, puberty was defined in presence of a testicles volume >/= 12 ml and presence of pubic and underarm hair.							
261	= Low lumbar e								
	1.4.00	xtension strenght and high ratios between lumbar mobility and lumbar extension strenght predicts future low back pain							
		lom inal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t	o be having a psychoso	matic origin in the great major	rity of cases.				
0		lom inal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t	o be having a psychoso	natic origin in the great major	ity of cases.				
8	= Classified as: c				ity of cases.	57			
e o	I = Classified as: c = Internalizing s	om inal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition	rom rule-breaking and	aggressive behaviour.		g own current self	-rated health status on VAS 0-	-100.	
9 <sub>f</sub>	I = Classified as: c = Internalizing s = EQ-5D assesse	om inal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f	rom rule-breaking and nin 3 levels of severity: n	aggressive behaviour. o problems, moderate or seve	re problems as well as sc or in	g own current self	-rated health status on VAS 0-	-100.	
9 f 0	= Classified as: c = Internalizing s = EQ-5D assesse = Anxiety symp	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f s self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with	rom rule-breaking and nin 3 levels of severity: n ptoms: felt hopeless wh	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt o	ere problems as well as scorin down or sad.		-rated health status on VAS 0-	-100.	
29 f 80 g 81 h	= Classified as: c = Internalizing s = EQ-5D assesses = Anxiety symp = Assessment of	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing s self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym	rom rule-breaking and nin 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt o ealth of the family members.	rre problems as well as scorin Jown or sad. Score range 0-6, 6=severe f	amily difficulties.		100.	
29 f 80 g 81 h	<ul> <li>Classified as: c</li> <li>Internalizing s</li> <li>EQ-5D assesses</li> <li>Anxiety symp</li> <li>Assessment of</li> <li>Subjective disa</li> </ul>	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f s self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th	rom rule-breaking and in 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt o ealth of the family members. sa walk more than 1km, pain o	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa	amily difficulties. n disturbs hobbies	5. Range 0-5.		ue for 1
9 f 80 g 1 h 2 j	I = Classified as: c = Internalizing s = EQ-5D assesses = Anxiety symp = Assessment of = Subjective disa = The modified I	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f s self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur	rom rule-breaking and nin 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb activities difficult: reach	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt o ealth of the family members. sa walk more than 1km, pain o ing up to get a book from a hig	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo	amily difficulties. n disturbs hobbies bag to school, sitt	s. Range 0-5. ing on a school chair for a 45-		ue for 1
9 f 30 g 31 h 32 j 33 r	<ul> <li>Classified as: c</li> <li>Internalizing s</li> <li>EQ-5D assesses</li> <li>Anxiety symp</li> <li>Assessment of</li> <li>Subjective disa</li> <li>The modified Inin, sitting up in b</li> </ul>	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f s self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a	rom rule-breaking and nin 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb ne tivities difficult: reach us, and sports activities a	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt t ealth of the family members. sa walk more than 1km, pain t ing up to get a book from a hig it school. Low = 0-1 limitation,	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations c	amily difficulties. In disturbs hobbies bag to school, sitt r high = 4-9 limita	i. Range 0-5. ing on a school chair for a 45-1 tions (23).	min lesson, standing in a que	ue for 1
9 f 0 g 1 h 2 j 3 r	<ul> <li>Classified as: c</li> <li>Internalizing s</li> <li>EQ-5D assesses</li> <li>Anxiety symp</li> <li>Assessment of</li> <li>Subjective disa</li> <li>The modified Inin, sitting up in b</li> </ul>	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f s self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b : pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel	rom rule-breaking and nin 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb ne tivities difficult: reach us, and sports activities a	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt t ealth of the family members. sa walk more than 1km, pain t ing up to get a book from a hig it school. Low = 0-1 limitation,	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations c	amily difficulties. In disturbs hobbies bag to school, sitt r high = 4-9 limita	i. Range 0-5. ing on a school chair for a 45-1 tions (23).	min lesson, standing in a que	ue for 1
9 f 0 g 1 h 2 j 3 r 4 k	= Classified as: c = Internalizing s = EQ-5D assesse = Anxiety symp = Assessment of = Subjective disa = The modified I nin, sitting up in b = Yunus criteria = SES: Socioeco	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f s self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b : pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel	rom rule-breaking and nin 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb ne tivities difficult: reach us, and sports activities a	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt t ealth of the family members. sa walk more than 1km, pain t ing up to get a book from a hig it school. Low = 0-1 limitation,	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations c	amily difficulties. In disturbs hobbies bag to school, sitt r high = 4-9 limita	i. Range 0-5. ing on a school chair for a 45-1 tions (23).	min lesson, standing in a que	ue for 1
9 ff 9 ff 1 h 2 j 3 r 4 k	Classified as: c     Internalizing s     EQ-5D assesse     Anxiety symp     Assessment of     Subjective disa     The modified I nin, sitting up in b     E Yunus criteria     SES: Socioeco n = CD1: Children	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed to ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f s self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b : pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel nomic status 's depression Inventory. Cut off point >/= 13 indicating depressive symptoms	rom rule-breaking and nin 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb nctivities difficult: reach us, and sports activities a ling in hands and feet, fa	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt t ealth of the family members. sa walk more than 1km, pain t ing up to get a book from a hig it school. Low = 0-1 limitation,	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations c	amily difficulties. In disturbs hobbies bag to school, sitt r high = 4-9 limita	i. Range 0-5. ing on a school chair for a 45-1 tions (23).	min lesson, standing in a que	ue for 1
e 9 f 1 0 g 1 1 1 2 j 3 r 4 k 5 r 6 1	Classified as: c     Internalizing s     EQ-5D assesse     Anxiety symp     Assessment of     Subjective disa     The modified I nin, sitting up in b     Yunus criteria     SES: Socioeco     n = CD1: Children     dentified base	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f is self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel nomic status 's depression Inventory. Cut off point >/= 13 indicating depressive symptoms <b>seline factors without association to persistent musculoskeletal pain, divided in pain type (study</b>	rom rule-breaking and in 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb inctivities difficult: reach us, and sports activities a ing in hands and feet, fa ID	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt of ealth of the family members. sa walk more than 1km, pain of ing up to get a book from a hig t school. Low = 0-1 limitation, tigue, numbness in hands and	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations of feet, feeling excited and ner	amily difficulties. n disturbs hobbies bag to school, sitt r high = 4-9 limita vous. Yes to minin	i. Range 0-5. ing on a school chair for a 45-1 tions (23).	min lesson, standing in a que	ue for 1
29 f 30 g 31 f 32 j 33 r 34 k 35 r 36 j 37 n	Classified as: c     Internalizing s     EQ-5D assesse     Anxiety symp     Assessment of     Subjective disa     The modified I nin, sitting up in b     Yunus criteria     SES: Socioeco     n = CD1: Children     dentified base	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing fa self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and the bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur 4annover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b : pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel nomic status 's depression Inventory. Cut off point >/= 13 indicating depressive symptoms seline factors without association to persistent musculoskeletal pain, divided in pain type (study Female: sitting h/day, sleep h/day, Male: physical activity MET-h/week and above occasional alcoh	rom rule-breaking and in 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb activities difficult: reach us, and sports activities a ling in hands and feet, fa ID ol consumption, u	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt o ealth of the family members. sa walk more than 1km, pain o ing up to get a book from a hig it school. Low = 0-1 limitation, tigue, numbness in hands and nisex: smoking pack year	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations of feet, feeling excited and ner feet, feeling excited and ner rs, body mass index (E	amily difficulties. n disturbs hobbies bag to school, sitt r high = 4-9 limita vous. Yes to minin MI) (24)	i. Range 0-5. ing on a school chair for a 45- tions (23). num 3 symptoms to meet the	min lesson, standing in a que Yunus criteria.	
29 f 30 a 31 f 32 j 33 r 33 r 34 k 35 r 36 f 37 n 38	Classified as: c     Internalizing s     EQ-5D assesse     Anxiety symp     Assessment of     Subjective disa     The modified I nin, sitting up in b     Yunus criteria     SES: Socioeco     n = CD1: Children     dentified base	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing f is self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel nomic status 's depression Inventory. Cut off point >/= 13 indicating depressive symptoms <b>seline factors without association to persistent musculoskeletal pain, divided in pain type (study</b>	rom rule-breaking and in 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb activities difficult: reach us, and sports activities a ling in hands and feet, fa ID ol consumption, u ay tiredness, difficu	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt o ealth of the family members. sa walk more than 1km, pain o ing up to get a book from a hig it school. Low = 0-1 limitation, tigue, numbness in hands and nisex: smoking pack year	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations of feet, feeling excited and ner feet, feeling excited and ner rs, body mass index (E	amily difficulties. n disturbs hobbies bag to school, sitt r high = 4-9 limita vous. Yes to minin MI) (24)	i. Range 0-5. ing on a school chair for a 45- tions (23). num 3 symptoms to meet the	min lesson, standing in a que Yunus criteria.	
29 f 30 g 31 f 32 j 33 r 33 r 34 k 35 r 36 f 37 n 38	Classified as: c     Internalizing s     EQ-5D assesse     Anxiety symp     Assessment of     Subjective disa     The modified I nin, sitting up in b     Yunus criteria     SES: Socioeco     n = CD1: Children     dentified base	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed to the physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing for self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and the bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur dannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b : pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel nomic status 's depression Inventory. Cut off point >/= 13 indicating depressive symptoms <b>steline factors without association to persistent musculoskeletal pain, divided in pain type (study</b> Female: sitting h/day, sleep h/day, Male: physical activity MET-h/week and above occasional alcoh Exercise frequency >3 vs. <3t/week, disability index 1-5 vs. 0 (i), waking up during nights (Male), d	rom rule-breaking and in 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb activities difficult: reach us, and sports activities a ling in hands and feet, fa <b>ID</b> of consumption, u ay tiredness, difficu ttle run test (21)	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt o ealth of the family members. sa walk more than 1km, pain o ing up to get a book from a hig it school. Low = 0-1 limitation, tigue, numbness in hands and nisex: smoking pack year lty falling asleep, depres	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations of feet, feeling excited and ner feet, feeling excited and ner irs, body mass index (E ssive feelings (Male), ho	amily difficulties. n disturbs hobbies bag to school, sitt r high = 4-9 limita vous. Yes to minin MI) (24)	i. Range 0-5. ing on a school chair for a 45- tions (23). num 3 symptoms to meet the	min lesson, standing in a que Yunus criteria.	
29 f f 30 i 31 f i 33 r i 33 r i 33 r i 33 r i 1 33 r i 1 33 f f r 1 33 f f r 1 1 5 7 7 1 5 7 7 7 8 3 8 3 8 3 8 3 7 7 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Classified as: c     Internalizing s     EQ-5D assesse     Anxiety symp     Assessment of     Subjective disa     The modified I nin, sitting up in b     Yunus criteria     SES: Socioeco     n = CD1: Children     dentified base	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed to the physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing if a self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and the bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur 4annover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b : pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel nomic status 's depression Inventory. Cut off point >/= 13 indicating depressive symptoms <b>seeline factors without association to persistent musculoskeletal pain, divided in pain type (study</b> Female: sitting h/day, sleep h/day, Male: physical activity MET-h/week and above occasional alcoh Exercise frequency >3 vs. <3t/week, disability index 1-5 vs. 0 (i), waking up during nights (Male), d being asbcent due to pain, maximum volume O2 intake (per unit increase) measured during a shu	rom rule-breaking and in 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb activities difficult: reach us, and sports activities a ling in hands and feet, fa ol consumption, u ay tiredness, difficu ttle run test (21) us criteria (k), incre	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt of ealth of the family members. sa walk more than 1km, pain of ing up to get a book from a hig it school. Low = 0-1 limitation, tigue, numbness in hands and nisex: smoking pack yea Ity falling asleep, depres	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations c feet, feeling excited and ner feet, feeling excited and ner ssive feelings (Male), ho ssive feelings (Male), ho and hypermobility (28)	amily difficulties. n disturbs hobbies bag to school, sitt r high = 4-9 limita vous. Yes to minin MI) (24)	i. Range 0-5. ing on a school chair for a 45- tions (23). num 3 symptoms to meet the	min lesson, standing in a que Yunus criteria.	
29 <sup>e</sup> 30 <u>e</u> 31 <sup>b</sup> 32 <sup>j</sup> 33 <sup>r</sup> 34 <sup>k</sup> 35 <sup>r</sup> 36 <sup>l</sup>	Classified as: c     Internalizing s     EQ-5D assesse     Anxiety symp     Assessment of     Subjective disa     The modified I nin, sitting up in b     Yunus criteria     SES: Socioeco     n = CD1: Children     dentified base	ominal pain, headache, depressive symptoms, day tiredness, difficulties in falling asleep, waking up during nghts are believed t ther physical and psychological symptoms, without further definition core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing d is self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and with toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive sym information about employment and education, economic matters, housing, marital or family discord, social networks and th bility index calculated from answers to the following proposals: difficulty in falling asleep because of pain, difficulty sitting dur 4-annover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily a ed from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a b : pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swel nomic status 's depression Inventory. Cut off point >/= 13 indicating depressive symptoms <b>seline factors without association to persistent musculoskeletal pain, divided in pain type (study</b> Female: sitting h/day, sleep h/day, Male: physical activity MET-h/week and above occasional alcoh Exercise frequency >3 vs. <3t/week, disability index 1-5 vs. 0 (i), waking up during nights (Male), d being asbcent due to pain, maximum volume O2 intake (per unit increase) measured during a shu Headache, stomachache, depressive feelings, difficulty falling asleep, waking up during nights, Yun	rom rule-breaking and in 3 levels of severity: n ptoms: felt hopeless wh e physical and mental h ing a lesson, pain disturb activities difficult: reach us, and sports activities a ling in hands and feet, fa ol consumption, u ay tiredness, difficu ttle run test (21) us criteria (k), incre	aggressive behaviour. o problems, moderate or seve en thinking of the future, felt of ealth of the family members. sa walk more than 1km, pain of ing up to get a book from a hig it school. Low = 0-1 limitation, tigue, numbness in hands and nisex: smoking pack yea Ity falling asleep, depres	re problems as well as scorin down or sad. Score range 0-6, 6=severe f disturbs physical exercise, pa gh shelf, carrying your schoo moderate = 2-3 limitations c feet, feeling excited and ner feet, feeling excited and ner ssive feelings (Male), ho ssive feelings (Male), ho and hypermobility (28)	amily difficulties. n disturbs hobbies bag to school, sitt r high = 4-9 limita vous. Yes to minin MI) (24)	i. Range 0-5. ing on a school chair for a 45- tions (23). num 3 symptoms to meet the	min lesson, standing in a que Yunus criteria.	

	Increasing age, sex, family history of related diseases, VAS score assessed by physicians,	elevated C-reactive protein (C	RP), erythrocyte sedim	entation rate (ESR), pla	telet count, lowe	r score in psychoso	cial functioning ref	lecting mental
	health and functioning at school/work, within the family, with friends and in other soc	ial activities (Children's Glob	al Assessment Scale, C	GAS) (22)				
Low back	Extension strength (minutes) and plain saggital mobility (36)							
	Akward trunk postures, physically demanding job (working hands above shoulders, aw	ward trunk posture and stan	ding or walking), work	ing regularly or irregula	rly, duration of w	ork, work with spe	cific physical load f	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 so	ocks, high conduct pro	blems, high hyperactiv	ity, high prosocia	al behavior, widesp	read pain, headach	e, stomachach
	in the past month compared to none, daytime tiredness on a scale 0-10, 5-10 vs. 0-4,	pain start < 12 months ago,	oain lasts = 7 days, p</th <th>ain today, pain severit</th> <th>y on a scale 0-10</th> <th>, 4-10 vs. 0-3, Han</th> <th>nover 2-3 vs. 0-1 (2</th> <th>23)</th>	ain today, pain severit	y on a scale 0-10	, 4-10 vs. 0-3, Han	nover 2-3 vs. 0-1 (2	23)
	Sex, increasing age, tobacco, profession: hairdresser and media/design compared to elec	ctrician, western ethnicity cor	npared to non-western	ethnicity, moderate/h	igh vs. Iow socio	-economic status (S	SES) (I), moderate/hi	igh vs. Iow
	physical activity level, BMI, moderate/high physical work demand vs. low (26)							<u> </u>
Vnoo	Increasing age compared to 15, participation in sports, BMI, EQ-5D index score 50-75th	norcontilo compared to 75		nuon cu compared to m	onthly (21)			
Knee				quericy compared to m				
Kilee	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w	eek pain frequency compared	l to rarely (9)					
	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypermodeline	eek pain frequency compared obility score >/= 6 vs. < 6. Af	l to rarely (9) er 4 years follow-up: e	xercise frequency 5-7 t	/week vs. 0-2 t, l			
Lowerlimb	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypermodeline	eek pain frequency compared obility score >/= 6 vs. < 6. Af	l to rarely (9) er 4 years follow-up: e	xercise frequency 5-7 t	/week vs. 0-2 t, l			
Lower limb	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hyperno and 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a w school abscence due to pain vs. never abscent, disability symptoms >/=3 vs. =2. volu</th <th>eek pain frequency compared obility score &gt;/= 6 vs. &lt; 6. Af eek, multisite pain, female se meO2 max average or abov</th> <th>l to rarely (9) ær 4 years follow-up: e x, headache, stomacha</th> <th>xercise frequency 5-7 t ache, depressive feeling</th> <th>/week vs. 0-2 t, lo s, difficulty fallin</th> <th></th> <th></th> <th></th>	eek pain frequency compared obility score >/= 6 vs. < 6. Af eek, multisite pain, female se meO2 max average or abov	l to rarely (9) ær 4 years follow-up: e x, headache, stomacha	xercise frequency 5-7 t ache, depressive feeling	/week vs. 0-2 t, lo s, difficulty fallin			
Lower limb	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypernor and 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a w school abscence due to pain vs. never abscent. disability symptoms >/=3 vs.,	eek pain frequency compared obility score >/= 6 vs. < 6. Af eek, multisite pain, female se meO2 max average or abov	l to rarely (9) ær 4 years follow-up: e x, headache, stomacha	xercise frequency 5-7 t ache, depressive feeling	/week vs. 0-2 t, lo s, difficulty fallin			
Lower limb Neck Growing pair	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypernor and 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a w school abscence due to pain vs. never abscent, disability symptoms >/=3 vs. =2. volu<br Joint hypermobility Beighton 6-9, physical activity at least half and hour more than 3 ti n Sex, ethnicity, increasing age (40)	eek pain frequency compared obility score >/= 6 vs. < 6. Af eek, multisite pain, female se meO2 max average or abov	l to rarely (9) ær 4 years follow-up: e x, headache, stomacha	xercise frequency 5-7 t ache, depressive feeling	/week vs. 0-2 t, lo s, difficulty fallin			
Lower limb	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypernor and 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a w school abscence due to pain vs. never abscent. disability symptoms >/=3 vs. =2. volu<br Joint hypermobility Beighton 6-9, physical activity at least half and hour more than 3 ti n Sex, ethnicity, increasing age (40) Sex (19)	eek pain frequency compared bbility score >/= 6 vs. < 6. Af eek, multisite pain, female so me02 max average or abov mes a week (38)	l to rarely (9) er 4 years follow-up: e x, headache, stomach: e. exercise frequency 3	xercise frequency 5-7 t ache, depressive feeling -4 t/week vs. 0-2 t (11	/week vs. 0-2 t, lo s, difficulty fallin	g asleep, day tiredr	iess, waking up dur	ring nights,
Lower limb Neck Growing pair	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w         After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypernor         and 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a w         school abscence due to pain vs. never abscent. disability symptoms >/=3 vs.          Joint hypermobility Beighton 6-9, physical activity at least half and hour more than 3 ti         n Sex, ethnicity, increasing age (40)         Sex (19)         Pain frequency, pain in daily activities, physiotherapy, relaxation therapy, sport activity,	eek pain frequency compared bbility score >/= 6 vs. < 6. Af eek, multisite pain, female so me02 max average or abov mes a week (38)	l to rarely (9) er 4 years follow-up: e x, headache, stomach: e. exercise frequency 3	xercise frequency 5-7 t ache, depressive feeling -4 t/week vs. 0-2 t (11	/week vs. 0-2 t, lo s, difficulty fallin	g asleep, day tiredr	iess, waking up dur	ring nights,
Lower limb Neck Growing pair	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w         After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypermonand 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a w         school abscence due to pain vs. never abscent. disability symptoms >/=3 vs.          Joint hypermobility Beighton 6-9, physical activity at least half and hour more than 3 times for the second	eek pain frequency compared bbility score >/= 6 vs. < 6. Af eek, multisite pain, female so me02 max average or abov mes a week (38)	l to rarely (9) er 4 years follow-up: e x, headache, stomach: e. exercise frequency 3	xercise frequency 5-7 t ache, depressive feeling -4 t/week vs. 0-2 t (11	/week vs. 0-2 t, lo s, difficulty fallin	g asleep, day tiredr	iess, waking up dur	ring nights,
Lower limb Neck Growing pair Headache	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w         After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypernor         and 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a w         school abscence due to pain vs. never abscent. disability symptoms >/=3 vs.          Joint hypermobility Beighton 6-9, physical activity at least half and hour more than 3 ti         n Sex, ethnicity, increasing age (40)         Sex (19)         Pain frequency, pain in daily activities, physiotherapy, relaxation therapy, sport activity, stress at school, use of computer (25)         Stress (20)	eek pain frequency compared obility score >/= 6 vs. < 6. Af eek, multisite pain, female so me02 max average or abov mes a week (38) stress at home or in hobbies	I to rarely (9) er 4 years follow-up: e ex, headache, stomacha re. exercise frequency 3 , pain on palpation, p	xercise frequency 5-7 t ache, depressive feeling -4 t/week vs. 0-2 t (11 ache threshold measure	/week vs. 0-2 t, lo s, difficulty fallin	g asleep, day tiredr	iess, waking up dur	ring nights,
Lower limb Neck Growing pair	BMI, EQ-5D 50-75th percentile compared to 0-25th, monthly, weekly, several times a w         After 1 year follow-up: traumatic limb at baseline, exercise 3-4 t/week vs. 0-2 t, hypernor         and 4 years follow-up: age 11-14 vs. 9-11, frequency of exercise 2-4 times vs. once a w         school abscence due to pain vs. never abscent. disability symptoms >/=3 vs.          Joint hypermobility Beighton 6-9, physical activity at least half and hour more than 3 ti         n Sex, ethnicity, increasing age (40)         Sex (19)         Pain frequency, pain in daily activities, physiotherapy, relaxation therapy, sport activity, stress at school, use of computer (25)         Stress (20)	eek pain frequency compared obility score >/= 6 vs. < 6. Af eek, multisite pain, female so me02 max average or abov mes a week (38) stress at home or in hobbies	I to rarely (9) er 4 years follow-up: e ex, headache, stomacha re. exercise frequency 3 , pain on palpation, p	xercise frequency 5-7 t ache, depressive feeling -4 t/week vs. 0-2 t (11 ache threshold measure	/week vs. 0-2 t, lo s, difficulty fallin	g asleep, day tiredr	iess, waking up dur	ring nights,

20 Prognostic factors are divided primarily in biological, psychological, and social factors and secondary according to musculoskeletal pain type. The prognostic value were reported with RR, OR, and/or p-value. Jing to move

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

# **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 31<sup>st</sup> 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 &lt;1 to 6 years&gt; or school child &lt;7 to 12 years&gt; or adolescent &lt;13 to 17 years&gt;)</unspecified></to>	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

	(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

1	
2	
3	
4	
5	
6	
7	
8	
0	
9	0
1	0
1	1 2
1	2
1	3
1	4
1	5
1	6
	7
1	, 8
1	0
1	9 0
2	0
2	1 2
2	2
2	3
2	5
2	4
2	5
2	6
2	7
2	, ,
2	8
2	9 0
3	0
3	1
2	2
3	3
3	4
3	4 5
3	6
3	
-	8
3	9
4	0
4	
4	
4	3
4	4
4	5
4	6
4	
4	-
4	9
5	0
5	
5	
5	
5	4
	5
	6
	7
	8
5	0

60

# CINAHL Ebsco May 31<sup>st</sup> 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
\$12	(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

1	
2 3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13 14	
14 15	
16	
16 17	
18	
18 19	
20	
21	
22	
23	
24 25	
25 26	
20	
28	
29	
30	
31	
32	
33	
34 25	
35 36 37	
37	
38	
39	
40	
41	
42	
43	
44 45	
45 46	
40 47	
48	
49	
50	
51	
52	
53	
54 55	
55 56	
50 57	
58	

60

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

12 071

#### **BMJ** Open

Cochrane June 9<sup>th</sup> 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)) (backache or headache) #2 #3 #1 or #2 (juvenile or adolescen\* or preadolescence or Preadolescent or preschool or child or #4 children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild\* or teenager) #5 #3 and #4 (predict\* or long term or Follow-up or Prospective or cohort or cluster or prognosis or #6 prognostic or Mediator\* or treatment effect modifier\* or longitudinal\*) 399020 #7 #5 and #6 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 9<sup>th</sup> 2017

9         11.041         Michael Direct Control (Control (Contro) (Control (Contro) (Control (Control (Contro) (Con	Set	Results	Save History / Create Alert Open Saved History	Edit Sets	Combine Sets AND OR Combine	Delete Set: Select All X Delete
# 8       5,905,200       ts=[predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or prognosis or prognosis or mediator* or treatment effect modifier* or long ituridinal*, Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years         # 7       29,467       #6 AND #5 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI	# 9	11,624	#8 AND #7 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	Edit		
Indexes-SCI-EXPANDED, SSCI, A&ICI, CPCI-S, CPCI-SSH, ESCI Timespan=All years         # 6       2,457,687         ts=(juvenile or adolescent or preadolescent or preadoles	#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*)	Edit		
# 6       2,457,687       ts=[juvenile or adolescent or preadolescent or pre	# 7	29,467		Edit	8	8
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: Control of the second secon	¢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)	Edit		
#4       66,234       ts=(backache or headache) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years       Edit       Image: Science of the	¥5	240,860		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 back ache or headache or joint or PFP or tendinitis or cervical or jaw or limb or shoulder or amm or elbow or wrist retropatellar or lego or ankle or foot or heel or arthralgia or osteochondritis or osteocod 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	¥ 4	66,234	ts=(backache or headache)	Edit		
<ul> <li># 2 2,616,397 TS=(musculoskeletal or back pain or backache 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 ache or back pain or headache or hip or knee or patella' or patellofemoral or retropatellar or leg or ankle or foot or heel or arthraigia or osteochondritis or osgood or growing pain' or scheuermann) indexes=SCI-EXPANDED, SSCI, A&amp;HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years</li> <li>Edit</li> </ul>	#3	191,133	#2 AND #1	Edit		
1 491,777 ts=(pain or ache) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	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 anthradja or osteochondritis or osgood or growing pain* or scheuermann)	Edit		
	# 1	491,777	ts=(pain or ache)	Edit		
					O AND O OR	Select All

# SportDiscus June 9<sup>th</sup> 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

OT-seeker June 9<sup>th</sup> 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 children or prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild\* or teenager

1
2
3
-
4
5
6
7
8
9
10
11
12
13
14
15
16
17
10
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
59 60
60

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 12="" age="" to="" yrs=""> or 200 adolescence <age 13="" 17="" to="" yrs="">)</age></birth>	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

# 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

31			Page	
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60			Reporting Item	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	2
	Rationale	#3	findings; systematic review registration number 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	<b>#5</b> For	Indicate if a review protocol exists, if and where it can be peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	3

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29	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
30 31 32 33 34	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
35 36 37 38 39 40 41	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
42 43 44 45	Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	4
46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	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	<b>#16</b> For	Describe methods of additional analyses (e.g., sensitivity or peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5

Page 33 of 44

BMJ Open

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30	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	
31 32 33 34	Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	5	
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59	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	
60		For	peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		

The PRISMA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 29. June 2018 using <u>http://www.goodreports.org/</u>, a tool made by the <u>EQUATOR Network</u> in collaboration with <u>Penelope.ai</u>

Je.

## PROSPERO

International prospective register of systematic reviews

## UNIVERSITY of York Centre for Reviews and Dissemination

## 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

## PROSPERO International prospective register of systematic reviews

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.

Give the electronic mail address of the named contact.

negar@dcm.aau.dk

#### 8. Named contact address

Give the full postal address for the named contact.

#### Dr. Negar Pourbordbari

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

## PROSPERO

#### International prospective register of systematic reviews

- 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

#### PROSPERO International prospective register of systematic reviews

National Institute for Health Research

#### 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

#### PROSPERO

#### International prospective register of systematic reviews

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 followup 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).

#### PROSPERO International prospective register of systematic reviews

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 metaanalysis 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

PROSPERO

No			
Meta-analysis No			
Methodology No			
Network meta- No	analysis		
Pre-clinical No			
Prevention No			
Prognostic Yes			
Prospective me No	eta-analysis (PMA		
Qualitative syn No	nthesis		
Review of revie No	ews		
Service deliver No	ry		
Systematic rev Yes	view		
Other No			
Alcohol/substa No	of the review ance misuse/abuse	е	
Blood and imm No	nune system		
Cancer No			
Cardiovasculaı No	r		
Care of the eld No	lerly		
Child health No			
Complementar No	ry therapies		
Crime and just No	lice		
Dental No			
Digestive syste No	em		
Ear, nose and No	throat		

#### PROSPERO International prospective register of systematic reviews

No	
Endocrii No	ne and metabolic disorders
Eye diso No	orders
General No	interest
Genetic No	5
Health i No	nequalities/health equity
Infectior No	as and infestations
Internati No	onal development
Mental I No	nealth and behavioural conditions
Musculo No	skeletal
Neurolo No	gical
Nursing No	
Obstetri No	cs and gynaecology
Oral hea No	cs and gynaecology alth e care rative care herapy
Palliativ No	e care
Periope No	rative care
Physioth No	nerapy
Pregnar No	icy and childbirth
Public h No	ealth (including social determinants of health)
Rehabili No	tation
Respira No	ory disorders
Service No	delivery
Skin dis No	orders
Social c No	are
Surgery No	
Traniaal	Medicine

NHS National Institute for Health Research

## PROSPERO

## International prospective register of systematic reviews

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



#### PROSPERO International prospective register of systematic reviews

#### 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/MusculoskeletalPainFactS heets/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.

# **BMJ Open**

#### Poor prognosis of child and adolescent Musculoskeletal Pain

#### a Systematic Literature Review

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-024921.R1
Article Type:	Research
Date Submitted by the Author:	02-Apr-2019
Complete List of Authors:	Pourbordbari, Negar; Research unit for general practice in Aalborg Denmark, Clinical medicine Riis, Allan; Department of Clinical Medicine at Aalborg University, Research Unit for General Practice in Aalborg Jensen, Martin Bach; Department of Clinical Medicine at Aalborg University, Research Unit for General Practice in Aalborg Olesen, Jens; Department of Clinical Medicine at Aalborg University, Research Unit for General Practice in Aalborg Research Unit for General Practice in Aalborg Rathleff, Michael ; Department of Clinical Medicine at Aalborg University, Research Unit for General Practice in Aalborg
<b>Primary Subject Heading</b> :	General practice / Family practice
Secondary Subject Heading:	Medical management
Keywords:	musculoskeletal pain, adolescents, children, prognosis, general practice
Note: The following files were s You must view these files (e.g.	ubmitted by the author for peer review, but cannot be converted to PDF. movies) online.
Systematic-review-animation-fi	nal.mp4

## SCHOLARONE<sup>™</sup> Manuscripts

#### 

## Poor prognosis of child and adolescent Musculoskeletal Pain a Systematic Literature Review

#### **Authors**

Pourbordbari N<sup>1</sup>, Riis A<sup>1</sup>, Jensen MB<sup>1</sup>, Olesen JL<sup>1</sup>, Rathleff MS<sup>1</sup>

#### Affiliation:

- Research Unit for General Practice in Aalborg,
- Department of Clinical Medicine,
- Aalborg University,
- Denmark.

#### Authors and contact information

- Corresponding author Negar Pourbordbari MD,
- Research Unit for General Practice in Aalborg, N. C. Y. O. Y.
- Department of Clinical Medicine,
- Aalborg University,
- Denmark.
- Email: negar@dcm.aau.dk.

## Abstract

### Objectives

To identify baseline patient characteristics that are: (i) associated with a poor outcome on follow up regardless of which treatment was provided (prognosis); or (ii) associated with a successful outcome to a specific treatment (treatment effect modifiers).

#### 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- 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- to 19-year-old children and adolescents with self-reported musculoskeletal pain. Risk of bias assessment was conducted with the QUIPS 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.

#### Registration

The protocol for this review was developed using the PRISMA-P 2015 statement, inspired by the Cochrane Central Register of Controlled Trials, and registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO, ID: 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.

#### Keywords

musculoskeletal pain; adolescents; children; prognosis; general practice

#### Introduction

General practice is often the point of first contact into the health care 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 (2-6). A recent systematic review reported that 40% of an adolescent population had experienced pain during the past six 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 one year later (10, 11) and that 21% of 12-35-year-olds had persistent knee pain six 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 (i) poor outcome on follow-up (prognosis) or (ii) 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 (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- to 19-years-old, 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**

5

6 7

8

9

10

11

12

13

14 15

16 17

18

19

20

21 22

23

24

25

26 27

28

29

30

31

32

33

34

35

36 37

38

39 40

41

42

43 44

45

46

47

48

49

50 51

52

53

54

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: odds ratios (OR), relative risks (RR), (95% confidence intervals (95%CI)), and/or P-values. If possible, we extracted the adjusted associations.

Data were extracted with a pre-defined 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 sub-grouped our identified prognostic factors in accordance with the biopsychosocial model (16, 17): eziezoni

Biological prognostic factors:

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

Psychological prognostic factors

- -General psychological factors
- -Depressive factors

Social prognostic factors:

- -General social factors
- -Factors related to sleep/davtime 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 odds ratios (OR), relative risks (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% confidence interval. As for Pvalue, 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 PRISMA checklist when writing our report (18) (Appendix 2).

#### Patient 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.

Study (reference)	MSK pain type	Baseline age (years)	Recruitment setting	Study popula tion (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 93 (20)	Back, Head	8, 11, 13	School	471	2	Back 15 Head 40	Back 4 Head 20	Back 9.3 Head 30.7
Brattberg 04 (21)	General MSK	10, 13, 16	School	597	11	59	39	20
El-Metwally 04 (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 05 (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)	Headachea	13	School	311	3	54	70.5	48
Lunde (28)	Low back	15 - 19	School	420	6.5	N/A	N/A	39
Mikkelsson 97 (29)	Neck, WSP, low back	9 - 12	School	1756	1	N/A	N/A	Neck 48.3 WSP 29.7 Low back 34.
Mikkelsson 98 (30)	General MSK	9 - 12	School	1756	1	N/A	N/A	52.9
Mikkelsson 99 (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 08 (32)	Low back	16	Community	2969	2	N/A	N/A	27.1
Mikkonen 11 (33)	Low back	16	Community	728	2	53	46	50.4
Mikkonen 13 (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 16 (36)	Knee	16 - 18	School	504	2	N/A	N/A	55.9
Rathleff 16 (37)	Knee (PFP)	15 - 19	School	121	3 months	N/A	N/A	74.4
Sjolie (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 <sup>b</sup>	2	N/A	N/A	Head 29 Back 21.7
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

MSK = Musculoskeletal

N/A = not applicable

A = Headache: non migrainous WSP = Widespread pain

b = included stomachache participants

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.

**Table 2** Risk of bias in included studies. With the Quality in Prognostic Studies (QUIPS) 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.

	D	Study	Study	Prognostic factor	Outcome	Study	Statistical analysis and
Study author year Blauuw et al 2015	Design	participation	attrition	measurement Low	measurement	confounding Moderate	presentation
	Prospective cohort Prospective cohort	Moderate	Moderate Moderate	Low		Moderate	High
Brattberg et al 1993					Low		0
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
Holley et al 2017	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
	Prospective cohort and						
Rathleff et al 2013	nested case-control	Moderate	Low	Low	Low	Low	Low
Rathleff et al 2016*	Prospective cohort	Low	Low	Low	Low	Low	Low
Rathleff et al 2016	Prospective cohort	Low	Low	Low	Low	Low	Low
	Prospective cohort						
	study with a cross						
Sjolie et al 2001	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

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

Risk of bias in included studies. With the Quality in Prognostic Studies (QUIPS) 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. 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 one-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 four-year follow-up 63,5% with general musculoskeletal pain, 33,5% with neck pain, and 26% with low back pain reported pain. At nine-year follow-up 59% with general musculoskeletal pain reported pain. A complete report of all the identified prognostic factors is listed in 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 Supplemental Table 1 for explanatory notes).

Very few prognostic factors were reported on back pain, growing pain, lower limb pain, and widespread musculoskeletal pain (Supplementary Table 1); consequently, they were excluded from Figure 1. Table 3

condenses the results from 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 0-19-year-old patient with musculoskeletal pain.

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

**Table 3** What to ask in clinical practice? *4* prognostic factors belonging to *4* frequent musculoskeletal pain types in general practice: General musculoskeletal-, Low back-, Neck-, and Knee Pain.

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

The questions are proposals towards assessment of prognosis on musculoskeletal	pain.
--	-------

a = to be evaluated by clinical examination

b = this question is a suggestion for use in evaluation of quality of life

F Female patients

#### 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). 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 (e.g. 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).

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 followup time points with a non-significant association with musculoskeletal pain at follow-up (Supplementary Table 1). Increasing age (11, 21, 23, 28, 29, 31, 36, 41) was the most frequently identified baseline factor with a nonsignificant 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

5

6

7 8

9

10

11

12

13

14

15

16 17

18

19 20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36 37

38 39

40

41

42

43

44

45

46

47

#### 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 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 PRISMA-P 2015 statement (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 i.e., female gender, older age, depression/anxiety, and long pain duration was 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.

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 e.g. 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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

 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 psycho-social 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

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. Health care practitioners should be cognisant not to assume that musculoskeletal pain during childhood or adolescence is transient or self-limiting.

#### Supplementary information

Additional information accompanies this paper in the form of Figure 1: Prognostic factors for persistent musculoskeletal pain, according to pain type, population size, sex, follow-up, and the biopsychosocial model, Figure 2: Persistent musculoskeletal pain, stratified by 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 persisted in above 50% of participants with general musculoskeletal pain after 1, 2, 3, 4, and 9 years follow-up, Figure 3: PRISMA Flow chart presenting the flow of citations reviewed in the course of the systematic review: 48,538 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, Appendix 1: Search string, Appendix 2: Completed PRISMA checklist, Appendix 3: Protocol, and Supplementary Table 1: Estimates on prognostic factors specified according to musculoskeletal pain type, baseline age, and follow-up in the included studies, and an animation showing how our findings can be used in a clinical setting, see the Supplementary file: https://youtu.be/raltzsgkTHc

#### Author contributions

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, MBJ, and JLO contributed with important reflections and revisions to both.

#### Funding

This work was supported by The Research Unit for General Practice in Aalborg, Denmark, without any further funders.

#### **Ethical approval**

Not applicable.

#### **Competing interests**

The authors have declared no competing interests.

#### Data sharing statement

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

5	
6 7	
8	
9	
10 11	
12	
11 12 13	
14 15	
15	
16 17 18	
18	
19	
20 21	
22	
21 22 23	
24	
25 26	
24 25 26 27 28 29	
28	
29 30	
31	
31 32	
33	
34 35	
36	
36 37 38	
38	
39 40 41 42	
41	
42	
43 44	
45	
46	
47	
48 49	
50	
51	
52	
53 54	
55	
56 57	
57	

## References

1. Michaleff ZA, Campbell P, Protheroe J, Rajani A, Dunn KM. Consultation patterns of children and adolescents with knee pain in UK general practice: analysis of medical records. BMC Musculoskelet Disord. 2017;18(1):239.

2. Hofel L, Draheim N, Hafner R, Haas JP. Pain syndrome of the musculoskeletal system in children and adolescents. Zeitschrift Fur Rheumatologie. 2016;75(3):292-301.

3. King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. Pain. 2011;152(12):2729-38.

4. Auvinen JP, Paananen MVJ, Tammelin TH, Taimela SP, Mutanen POA, Zitting PJ, et al. Musculoskeletal pain combinations in adolescents. Spine. 2009;34(11):1192-7.

5. De Inocencio J. Epidemiology of musculoskeletal pain in primary care. Arch Dis Child. 2004;89(5):431-4.

6. Michaleff ZA, Kamper SJ, Stinson JN, Hestbaek L, Williams CM, Campbell P, et al. Measuring Musculoskeletal Pain in Infants, Children, and Adolescents. J Orthop Sports Phys Ther. 2017;47(10):712-30.

7. Smedbraten BK, Natvig B, Rutle O, Bruusgaard D. Self-reported bodily pain in schoolchildren. Scand J Rheumatol. 1998;27(4):273-6.

8. McGrath P. Psychological guidelines for helping children cope with chronic benign intractable pain. The Clinical journal of pain. 1986.

9. Rathleff CR, Olesen JL, Roos EM, Rasmussen S, Rathleff MS. Half of 12-15-year-olds with knee pain still have pain after one year. Danish Medical Journal. 2013;60 (11) (no pagination)(A4725).

10. Kastelein M, Luijsterburg PA, Heintjes EM, van Middelkoop M, Verhaar JA, Koes BW, et al. The 6-year trajectory of non-traumatic knee symptoms (including patellofemoral pain) in adolescents and young adults in general practice: a study of clinical predictors. British journal of sports medicine. 2015;49(6):400-5.

11. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Lower limb pain in a preadolescent population: prognosis and risk factors for chronicity--a prospective 1- and 4-year follow-up study. Pediatrics. 2005;116(3):673-81.

12. Huguet A, Tougas ME, Hayden J, McGrath PJ, Stinson JN, Chambers CT. Systematic review with meta-analysis of childhood and adolescent risk and prognostic factors for musculoskeletal pain. Pain. 2016;157(12):2640-56.

13. iasp. Acute Musculoskeletal Pain [Available from: <u>https://www.iasp-</u>

pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/MusculoskeletalPainFactSheets/Ac utePain\_Final.pdf.

14. Cochrane Training. Data collection form for intervention reviews 2014 [Available from: <u>http://training.cochrane.org/resource/data-collection-forms-intervention-reviews</u>.

15. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.

16. Engel GL. The Need for a New Medical Model: A Challenge for Biomedicine Science 1977;196(No. 4286):19-136.

17. Stanford EA, Chambers CT, Biesanz JC, Chen E. The frequency, trajectories and predictors of adolescent recurrent pain: A population-based approach. Pain. 2008;138(1):11-21.

18. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

19. Blaauw BA, Dyb G, Hagen K, Holmen TL, Linde M, Wentzel-Larsen T, et al. The relationship of anxiety, depression and behavioral problems with recurrent headache in late adolescence - a Young-HUNT follow-up study. Journal of Headache and Pain. 2015;16(1):1-7.

20. Brattberg G. Back pain and headache in Swedish schoolchildren: A longitudinal study. Pain Clinic. 1993;6(3):157-62.

21. Brattberg G. Do pain problems in young school children persist into early adulthood? A 13year follow-up. European Journal of Pain. 2004;8(3):187-99.

22. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Prognosis of nonspecific musculoskeletal pain in preadolescents: A prospective 4-year follow-up study till adolescence. Pain. 2004;110(3):550-9.

23. Flato B, Aasland A, Vandvik IH, Forre O. Outcome and predictive factors in children with chronic idiopathic musculoskeletal pain. Clinical and Experimental Rheumatology. 1997;15(5):569-77.

24. Holley AL, Wilson AC, Palermo TM. Predictors of the transition from acute to persistent musculoskeletal pain in children and adolescents: a prospective study. Pain. 2017;158(5):794-801.
25. Jones GT, Macfarlane GJ. Predicting persistent low back pain in schoolchildren: A

prospective cohort study. Arthritis Care and Research. 2009;61(10):1359-66.

26. Jussila L, Paananen M, Nayha S, Taimela S, Tammelin T, Auvinen J, et al. Psychosocial and lifestyle correlates of musculoskeletal pain patterns in adolescence: A 2-year follow-up study. European Journal of Pain (United Kingdom). 2014;18(1):139-46.

27. Laimi K, Vahlberg T, Salminen JJ, Metsahonkala L, Mikkelsson M, Anttila P, et al. Does neck pain determine the outcome of adolescent headache? Cephalalgia. 2007;27(3):244-53.

28. Lunde LK, Koch M, Hanvold TN, Waersted M, Veiersted KB. Low back pain and physical activity - A 6.5 year follow-up among young adults in their transition from school to working life. Bmc Public Health. 2015;15.

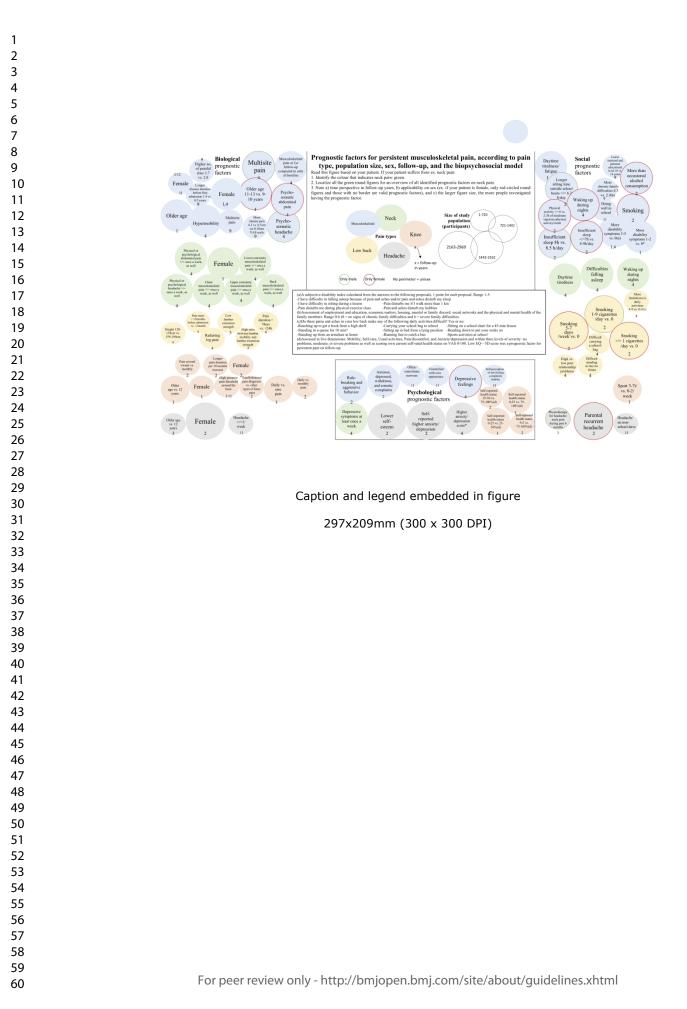
29. Mikkelsson M, Salminen JJ, Kautiainen H. Non-specific musculoskeletal pain in preadolescents. Prevalence and 1-year persistence. Pain. 1997;73(1):29-35.

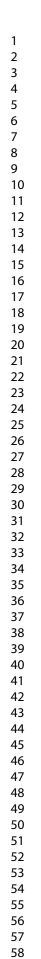
30. Mikkelsson M, Salminen JJ, Sourander A, Kautiainen H. Contributing factors to the persistence of musculoskeletal pain in preadolescents: A prospective 1-year follow-up study. Pain. 1998;77(1):67-72.

31. Mikkelsson M, Sourander A, Salminen JJ, Kautiainen H, Piha J. Widespread pain and neck pain in schoolchildren. A prospective one-year follow-up study. Acta Paediatrica, International Journal of Paediatrics. 1999;88(10):1119-24.

32. Mikkonen P, Leino-Arjas P, Remes J, Zitting P, Taimela S, Karppinen J. Is smoking a risk factor for low back pain in adolescents? A prospective cohort study. Spine. 2008;33(5):527-32.
33. Mikkonen P, Viikari-Juntura E, Remes J, Pienimaki T, Solovieva S, Taimela S, et al. Physical workload and risk of low back pain in adolescence. Occupational and Environmental Medicine. 2011.

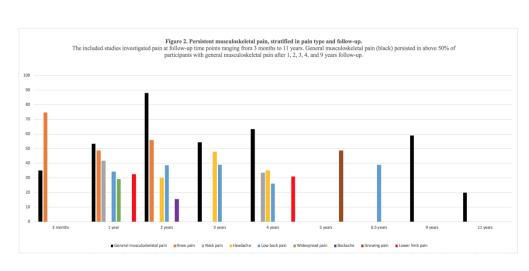
1	
2	
3	
4 5	34. Mikkonen PH, Laitinen J, Remes J, Tammelin T, Taimela S, Kaikkonen K, et al. Association
6	between overweight and low back pain: A population-based prospective cohort study of
7	adolescents. Spine. 2013;38(12):1026-33.
8	35. Paananen MV, Taimela SP, Auvinen JP, Tammelin TH, Kantomaa MT, Ebeling HE, et al. Risk
9	factors for persistence of multiple musculoskeletal pains in adolescence: A 2-year follow-up study.
10	
11	European Journal of Pain. 2010;14(10):1026-32.
12	36. Rathleff MS, Rathleff CR, Olesen JL, Rasmussen S, Roos EM. Is Knee Pain During
13	Adolescence a Self-limiting Condition? Prognosis of Patellofemoral Pain and Other Types of Knee
14	Pain. American Journal of Sports Medicine. 2016;44(5):1165-71.
15 16	37. Rathleff MS, Roos EM, Olesen JL, Rasmussen S, Arendt-Nielsen L. Self-reported recovery is
10	associated with improvement in localized hyperalgesia among adolescent females with
18	patellofemoral pain: Results from a cluster randomized trial. Clinical Journal of Pain.
19	2016;32(5):428-34.
20	38. Sjolie AN, Ljunggren AE. The significance of high lumbar mobility and low lumbar strength
21	
22	for current and future low back pain in adolescents. Spine. 2001;26(23):2629-36.
23	39. Sperotto F, Brachi S, Vittadello F, Zulian F. Musculoskeletal pain in schoolchildren across
24	puberty: A 3-year follow-up study. Pediatric Rheumatology. 2015.
25	40. Stahl M, Kautiainen H, El-Metwally A, Hakkinen A, Ylinen J, Salminen JJ, et al. Non-specific
26 27	neck pain in schoolchildren: Prognosis and risk factors for occurrence and persistence. A 4-year
27	follow-up study. Pain. 2008;137(2):316-22.
29	41. Uziel Y, Chapnick G, Jaber L, Nemet D, Hashkes PJ. Five-Year Outcome of Children With
30	"Growing Pains": Correlations With Pain Threshold. Journal of Pediatrics. 2010;156(5):838-40.
31	42. Artus M, Campbell P, Mallen CD, Dunn KM, van der Windt DA. Generic prognostic factors
32	for musculoskeletal pain in primary care: a systematic review. BMJ Open. 2017;7(1):e012901.
33	
34	43. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental
35	findings. British journal of anaesthesia. 2013;111(1):52-8.
36 37	44. Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL, 3rd. Sex, gender, and
38	pain: a review of recent clinical and experimental findings. The journal of pain : official journal of
39	the American Pain Society. 2009;10(5):447-85.
40	45. Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choiniere M. A systematic
41	literature review of 10 years of research on sex/gender and pain perception - part 2: do
42	biopsychosocial factors alter pain sensitivity differently in women and men? Pain.
43	2012;153(3):619-35.
44	
45	46. Polatin P, Bevers K, Gatchel RJ. Pharmacological treatment of depression in geriatric
46	chronic pain patients: a biopsychosocial approach integrating functional restoration. Expert Rev
47 48	Clin Pharmacol. 2017;10(9):957-63.
48 49	47. Amiri RS, Jouibari MF, Nejat F, El Khashab M. Iniencephaly: Clinical, Radiological and
50	Surgical Findings. Pediatric Neurosurgery. 2010;46(4):290-3.
51	48. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to
52	chronic pain: scientific advances and future directions. Psychol Bull. 2007;133(4):581-624.
53	49. El-Metwally A, Salminen JJ, Auvinen A, Kautiainen H, Mikkelsson M. Lower limb pain in a
54	preadolescent population: Prognosis and risk factors for chronicity - A prospective 1- and 4-year
55	follow-up study. Pediatrics. 2005;116(3):673-81.
56	10110W up study. r culatilis. 2003,110(3).075-01.
57 59	
58 59	
60	





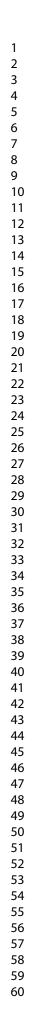
59

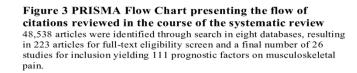
60

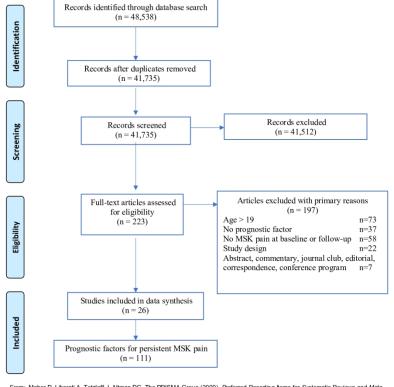


Caption : Persistent musculoskeletal pain, stratified in pain type and follow-up. The included studies investigated pain at follow-up time points ranging from 3 months to 11 years. General musculoskeletal pain (black) persisted in above 50% of participants after 1, 2, 3, 4, and 9 years follow-up.

469x212mm (300 x 300 DPI)







From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

PRISMA Flow Chart presenting the flow of citations reviewed in the course of the systematic review. 48,538 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.

215x279mm (200 x 200 DPI)

## 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 &lt;1 to 6 years&gt; or school child &lt;7 to 12 years&gt; or adolescent &lt;13 to 17 years&gt;)</unspecified></to>	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

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	

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

**BMJ** Open

S5S2 OR S3 OR S4Search modes - Boolean/Phrase12,235S4(MH "Referred Pain")Search modes - Boolean/Phrase284S3(MH "Breakthrough Pain")Search modes - Boolean/Phrase58S2(MH "Chronic Pain")Search modes - Boolean/Phrase11,921MH "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 "Chest Pain") OR (MH "Arthralgia") OR (MH "Neck Pain") OR (MH "Elbow Pain") OR (MH "Heel Pain") OR (MH "Chest Pain") OR (MH "Elbow Pain") OR (MH "Heel Pain") OR (MH "Chest Pain") OR (MH "Elbow Pain") OR (MH "Abdominal Pain")Search modes - Boolean/Phrase40,609	S6	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
S3(MH "Breakthrough Pain")Search modes - Boolean/Phrase58S2(MH "Chronic Pain")Search modes - Boolean/Phrase11,921(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 "Metatarsalgia") OR (MH "Muscle Pain") OR (MH "Neck Pain") OR (MH "Arthralgia") 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 "Chest Pain") OR (MH "Elbow Pain") OR (MH "Heel Pain") OR (MH "Search modes - Boolean/Phrase40,609	S5	S2 OR S3 OR S4	Search modes - Boolean/Phrase	12,235
S2(MH "Chronic Pain")Search modes - Boolean/Phrase11,921S2(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 "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 (MHSearch modes - Boolean/Phrase40,609	S4	(MH "Referred Pain")	Search modes - Boolean/Phrase	284
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 (MHSearch modes - Boolean/Phrase40,609	S3	(MH "Breakthrough Pain")	Search modes - Boolean/Phrase	58
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 (MHSearch modes - Boolean/Phrase40,609	S2	(MH "Chronic Pain")	Search modes - Boolean/Phrase	11,921
	S1	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	Search modes - Boolean/Phrase	40,609

Page 22 of 53

Cochrane June 9th 2017 Search Name: Date Run: 09/06/17 10:28:15.152 **Description:** ID Search Hits ((pain or ache) next/3 (musculoskeletal or back pain or backache or headache or joint or #1 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 (predict\* or long term or Follow-up or Prospective or cohort or cluster or prognosis or #6 prognostic or Mediator\* or treatment effect modifier\* or longitudinal\*) 399020 #7 #5 and #6 4430 Review only 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	Select All
#9	11,624	#8 AND #7	C alla		× Delete
		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=ScHzPANDED, SSCI, A&HOL (CPCI-S, CPCI-SSH, ESCI Timespan=AII 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 anthralgia or orsecochondritis or osgood or growing pain* or scheuermann) Indexes=ScHzerPANDED, SSCI, A&HCI, CPCI-S, SPH, 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		
					-
				O AND O OR Combine	
					Select Al

	BMJ Open		
portDiscus Ju	ne 9 <sup>th</sup> 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
		2	
	For peer review only - http://bmjopen.bmj.c	om/sito/about/auidali	inoc vhtml

OT-seeker June 9<sup>th</sup> 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

#### PsychInfo June 9<sup>th</sup> 2017

sychlnf	o June 9 <sup>th</sup> 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 12="" age="" to="" yrs=""> or 200 adolescence <age 13="" 17="" to="" yrs="">)</age></birth>	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

15,728

Items found

23	1	.9 not 22	1,97
1	e	exp Musculoskeletal Disorders/	15,7
		ory 01.02.2019 5.2017-01.02.2019	
listory			
	ad histoi Add to	ryClear history	
Search	builder	Query	
<u>#60</u>	Add	Search ((((((((((((((((((((((((((((((((((((	R ) OR Mesh]) tal[Text ord] OR t Word] Word] Word] Word] Word] Word] Word] Word] Word] OR Word] OR Yord] OR Yord] OR Yord] OR Yord] OR Yord] OR Yord] OR Yord] OR Yord] Cast al[Text Word] OR Cast al[Text Word] OR Yord] Text t Word] Text ttion

Search	Add to builder	Query	Items found
		"Comment" [Publication Type]) OR "Editorial" [Publication Type]) Filters: Publication date from 2017/05/31 to 2019/12/31	
<u>#59</u>	Add	Search ((((((((((((((((((((((((((((((((((((	29128
<u>#58</u>	<u>Add</u>	Search ((((("Systematic Review" [Publication Type]) OR "Meta-Analysis" [Publication Type]) OR "Case Reports" [Publication Type]) OR "Letter" [Publication Type]) OR "Historical Article" [Publication Type]) OR "Comment" [Publication Type]) OR "Editorial" [Publication Type]	<u>3926007</u>
<u>#43</u>	<u>Add</u>	Search (((((((((((((((((((("Back Pain"[Mesh:NoExp]) OR "Musculoskeletal Pain"[Mesh]) OR "Abdominal Pain"[Mesh:NoExp]) OR "Low Back Pain"[Mesh]) OR "Arthralgia"[Mesh]) OR "Chest Pain"[Mesh]) OR "Facial Pain"[Mesh:NoExp]) OR "Flank Pain"[Mesh]) OR "Metatarsalgia"[Mesh:NoExp]) OR "Neck Pain"[Mesh])) OR ((((((("Acute Pain"[Mesh]) OR "Chronic Pain"[Mesh])) OR "Breakthrough Pain"[Mesh])) OR ((((((("Acute Pain"[Mesh])) OR "Chronic Pain"[Mesh])) OR "Breakthrough Pain"[Mesh])) OR "Pain, Intractable"[Mesh]) OR "Pain, Referred"[Mesh])) AND ((musculoskeletal[Text Word] OR back pain[Text Word] OR backache[Text Word] OR headache[Text Word] OR joint[Text	<u>33553</u>

Search	Add to builder	Query	Items found
		Word] OR PFP[Text Word] OR tendinitis[Text Word] OR cervical[Text Word] OR jaw[Text Word] OR limb[Text Word] OR shoulder[Text Word] OR arm[Text Word] OR elbow[Text Word] OR wrist[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR collar[Text Word] OR vertebral[Text Word] OR lumbar[Text Word] OR back[Text Word] OR backache[Text Word] OR back pain[Text Word] OR headache[Text Word] OR hip[Text Word] OR knee[Text Word] OR patella*[Text Word] OR headache[Text Word] OR hip[Text Word] OR knee[Text Word] OR patella*[Text Word] OR ankle[Text Word] OR foot[Text Word] OR heel[Text Word] OR growing pain*[Text Word] OR osteochondritis[Text Word] OR osgood[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word] OR osgood[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word]) OR (hackache[Text Word] OR headache[Text Word] OR back[Text Word] OR joint[Text Word] OR PFP[Text Word] OR tendinitis[Text Word] OR back[Text Word] OR joint[Text Word] OR PFP[Text Word] OR tendinitis[Text Word] OR back[Text Word] OR joint[Text Word] OR limb[Text Word] OR schoulder[Text Word] OR arm[Text Word] OR finger[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR wrist[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR retropatellar[Text Word] OR vertebral[Text Word] OR patellofemoral[Text Word] OR retropatellar[Text Word] OR arthralgia[Text Word] OR scheuermann[Text Word] OR retropatellar[Text Word] OR arthralgia[Text Word] OR scheuermann[Text Word] OR nee[Text Word] OR arthralgia[Text Word] OR scheuermann[Text Word] OR child[Text Word] OR children[Text Word] OR preschool[Text Word] OR child[Text Word] OR children[Text Word] OR preschool[Text Word] OR child[Text Word] OR children[Text Word] OR preschool[Text Word] OR child[Text Word] OR children[Text Word] OR schoolchild*[Text Word] OR padeiatric[Text Word] OR pediatric[Text Word] OR preschool[Text Word] OR padeiatric[Text Word] OR pediatric[Text Word] OR prosposi[Text Word] OR childhood[Text Word] OR schoo	
<u>#42</u>	<u>Add</u>	Search (predict*[Text Word] OR long term[Text Word] OR Follow-up[Text Word] OR Prospective[Text Word] OR cohort[Text Word] OR cluster[Text Word] OR prognosis[Text Word] OR prognostic[Text Word] OR Mediator*[Text Word] OR treatment effect modifier*[Text Word] OR longitudinal*[Text Word])	<u>4564026</u>
<u>#41</u>	Add	Search ((((((((((((((("Back Pain"[Mesh:NoExp]) OR "Musculoskeletal Pain"[Mesh]) OR "Abdominal Pain"[Mesh:NoExp]) OR "Low Back Pain"[Mesh]) OR "Arthralgia"[Mesh]) OR "Chest Pain"[Mesh]) OR "Facial Pain"[Mesh:NoExp]) OR "Flank Pain"[Mesh]) OR "Metatarsalgia"[Mesh:NoExp]) OR "Neck Pain"[Mesh])) OR ((((((("Acute Pain"[Mesh]) OR "Chronic Pain"[Mesh]) OR "Breakthrough Pain"[Mesh])) OR "Pain, Intractable"[Mesh]) OR "Pain, Referred"[Mesh])) AND ((musculoskeletal[Text Word] OR back pain[Text Word] OR backache[Text Word] OR headache[Text Word] OR ipint[Text Word] OR PFP[Text Word] OR tendinitis[Text Word] OR cervical[Text Word] OR elbow[Text Word] OR wrist[Text Word] OR shoulder[Text Word] OR arm[Text Word] OR finger[Text Word] OR wrist[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR collar[Text Word] OR vertebral[Text Word] OR lumbar[Text Word] OR back[Text Word] OR backache[Text Word] OR back pain[Text Word] OR headache[Text Word] OR hip[Text Word] OR knee[Text Word] OR patella*[Text Word] OR patellofemoral[Text Word] OR retropatellar[Text Word] OR patella*[Text Word] OR scheuermann[Text Word] OR osgood[Text Word] OR growing pain*[Text Word] OR osteochondritis[Text Word] OR sogood[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word] OR ache[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word] OR ache[Text Word] OR headache[Text Word] OR back[Text Word] OR joint[Text Word] OR PFP[Text Word] OR tendinitis[Text Word] OR cervical[Text Word] OR joint[Text Word] OR limb[Text Word] OR shoulder[Text	83258

Search	Add to builder	Query	Items found
		Word] OR arm[Text Word] OR elbow[Text Word] OR wrist[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR collar[Text Word] OR vertebral[Text Word] OR lumbar[Text Word] OR hip[Text Word] OR knee[Text Word] OR patella*[Text Word] OR patellofemoral[Text Word] OR retropatellar[Text Word] OR leg[Text Word] OR ankle[Text Word] OR foot[Text Word] OR heel[Text Word] OR arthralgia[Text Word] OR osteochondritis[Text Word] OR osgood[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word] OR osgood[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word])))) AND ((((juvenile[Text Word] OR adolescen*[Text Word] OR preadolescence[Text Word] OR Preadolescent[Text Word] OR preschool[Text Word] OR child[Text Word] OR children[Text Word] OR prepubertal[Text Word] OR kids[Text Word] OR paediatric[Text Word] OR pediatric[Text Word] OR youth[Text Word] OR young[Text Word] OR childhood[Text Word] OR schoolchild*[Text Word] OR teenager[Text Word])))) OR (((("Adolescent"[Mesh]) OR "Child"[Mesh])) OR "Infant"[Mesh]))	
<u>#40</u>	<u>Add</u>	Search (((juvenile[Text Word] OR adolescen*[Text Word] OR preadolescence[Text Word] OR Preadolescent[Text Word] OR preschool[Text Word] OR child[Text Word] OR children[Text Word] OR prepubertal[Text Word] OR kids[Text Word] OR paediatric[Text Word] OR pediatric[Text Word] OR youth[Text Word] OR young[Text Word] OR childhood[Text Word] OR schoolchild*[Text Word] OR teenager[Text Word]))) OR ((("Adolescent"[Mesh]) OR "Child"[Mesh]) OR "Infant"[Mesh])	4321275
<u>#39</u>	<u>Add</u>	Search (juvenile[Text Word] OR adolescen*[Text Word] OR preadolescence[Text Word] OR Preadolescent[Text Word] OR preschool[Text Word] OR child[Text Word] OR children[Text Word] OR prepubertal[Text Word] OR kids[Text Word] OR paediatric[Text Word] OR pediatric[Text Word] OR youth[Text Word] OR young[Text Word] OR childhood[Text Word] OR schoolchild*[Text Word] OR teenager[Text Word])	<u>392041</u>
<u>#38</u>	Add	Search (("Adolescent"[Mesh]) OR "Child"[Mesh]) OR "Infant"[Mesh]	<u>336673</u>
<u>#31</u>	Add	Search (((((((("Back Pain"[Mesh:NoExp]) OR "Musculoskeletal Pain"[Mesh]) OR "Abdominal Pain"[Mesh:NoExp]) OR "Low Back Pain"[Mesh]) OR "Arthralgia"[Mesh]) OR "Chest Pain"[Mesh]) OR "Facial Pain"[Mesh:NoExp]) OR ("Flank Pain"[Mesh]) OR "Metatarsalgia"[Mesh:NoExp]) OR "Neck Pain"[Mesh]) OR ("(((((("Acute Pain"[Mesh]) OR "Chronic Pain"[Mesh]) OR "Breakthrough Pain"[Mesh]) OR ("Pain, Intractable"[Mesh]) OR "Pain, Referred"[Mesh])) AND ((musculoskeletal[Text Word] OR back pain[Text Word] OR backache[Text Word] OR headache[Text Word] OR joint[Text Word] OR PFP[Text Word] OR tendinitis[Text Word] OR cervical[Text Word] OR elbow[Text Word] OR limb[Text Word] OR shoulder[Text Word] OR arm[Text Word] OR elbow[Text Word] OR collar[Text Word] OR shoulder[Text Word] OR hand[Text Word] OR finger[Text Word] OR collar[Text Word] OR vertebral[Text Word] OR hand[Text Word] OR headache[Text Word] OR backache[Text Word] OR back pain[Text Word] OR headache[Text Word] OR collar[Text Word] OR vertebral[Text Word] OR lumbar[Text Word] OR back[Text Word] OR backache[Text Word] OR back pain[Text Word] OR headache[Text Word] OR hip[Text Word] OR knee[Text Word] OR patella*[Text Word] OR patellofemoral[Text Word] OR retropatellar[Text Word] OR patella*[Text Word] OR osteochondritis[Text Word] OR osgood[Text Word] OR headache[Text Word] OR ankle[Text Word] OR ache[Text Word] OR heel[Text Word] OR headache[Text Word] OR scheuermann[Text Word] OR ache[Text Word] OR prowing pain*[Text Word] OR cervical[Text Word] OR ache[Text Word] OR headache[Text Word] OR scheuermann[Text Word] OR ache[Text Word] OR hinb[Text Word] OR shoulder[Text Word] OR joint[Text Word] OR PFP[Text Word] OR headache[Text Word] OR cervical[Text Word] OR jaw[Text Word] OR hinb[Text Word] OR shoulder[Text Word] OR anthralgia[Text Word] OR jaw[Text Word] OR carpal[Text Word] OR hand[Text Word] OR jaw[Text Word] OR wrist[Text Word] OR extebral[Text Word] OR jaw[Text Word] OR hinb[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR knee[Text Word] OR ve	38026

1	
2	
3	
4	
5	
-	
6	
7	
8	
9	
-	0
1	1
1	2
1	3
1	4
1	5
	~
1	
	8
1	9
2	0
	1
2	
	_
2	
	4
2	5
2	6
2	
	, 8
	9
	0
3	1
3	2
3	
	4
	5
	6
3	7
3	8
	9
	0
4	
4	
4	
4	4
4	5
4	
7	7
4	~
4	
	9
5	0
5	1
5	
	2 3
	4
	5
5	6
5	7
	8
	9
5	

Search	Add to builder	Query	Items found
<u>#30</u>	Add	Search ((pain[Text Word] OR ache[Text Word])) AND (musculoskeletal[Text Word] OR back[Text Word] OR joint[Text Word] OR PFP[Text Word] OR tendinitis[Text Word] OR cervical[Text Word] OR jaw[Text Word] OR limb[Text Word] OR shoulder[Text Word] OR arm[Text Word] OR elbow[Text Word] OR wrist[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR collar[Text Word] OR vertebral[Text Word] OR lumbar[Text Word] OR hip[Text Word] OR knee[Text Word] OR patellofemoral[Text Word] OR knee[Text Word] OR leg[Text Word] OR ankle[Text Word] OR foot[Text Word] OR heel[Text Word] OR arthralgia[Text Word] OR osteochondritis[Text Word] OR osgood[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word])	<u>231899</u>
<u>#29</u>	Add	Search (backache[Text Word] OR headache[Text Word])	81147
<u>#28</u>	Add	Search (((((("Acute Pain"[Mesh]) OR "Chronic Pain"[Mesh]) OR "Breakthrough Pain"[Mesh]) OR "Pain, Intractable"[Mesh]) OR "Pain, Referred"[Mesh])) AND ((musculoskeletal[Text Word] OR back pain[Text Word] OR backache[Text Word] OR headache[Text Word] OR joint[Text Word] OR PFP[Text Word] OR tendinitis[Text Word] OR cervical[Text Word] OR jaw[Text Word] OR limb[Text Word] OR shoulder[Text Word] OR arm[Text Word] OR elbow[Text Word] OR wrist[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR wrist[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR collar[Text Word] OR vertebral[Text Word] OR lumbar[Text Word] OR back[Text Word] OR backache[Text Word] OR back pain[Text Word] OR headache[Text Word] OR hip[Text Word] OR knee[Text Word] OR patella*[Text Word] OR patellofemoral[Text Word] OR retropatellar[Text Word] OR arthralgia[Text Word] OR ankle[Text Word] OR foot[Text Word] OR heel[Text Word] OR arthralgia[Text Word] OR scheuermann[Text Word] OR osgood[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word]))	<u>5826</u>
<u>#27</u>	Add	Search (musculoskeletal[Text Word] OR back pain[Text Word] OR backache[Text Word] OR headache[Text Word] OR joint[Text Word] OR PFP[Text Word] OR tendinitis[Text Word] OR cervical[Text Word] OR jaw[Text Word] OR limb[Text Word] OR shoulder[Text Word] OR arm[Text Word] OR elbow[Text Word] OR wrist[Text Word] OR carpal[Text Word] OR hand[Text Word] OR finger[Text Word] OR collar[Text Word] OR vertebral[Text Word] OR lumbar[Text Word] OR back[Text Word] OR backache[Text Word] OR back pain[Text Word] OR headache[Text Word] OR backache[Text Word] OR patella*[Text Word] OR headache[Text Word] OR hip[Text Word] OR knee[Text Word] OR patella*[Text Word] OR patellofemoral[Text Word] OR retropatellar[Text Word] OR leg[Text Word] OR ankle[Text Word] OR foot[Text Word] OR heel[Text Word] OR arthralgia[Text Word] OR osteochondritis[Text Word] OR osgood[Text Word] OR growing pain*[Text Word] OR scheuermann[Text Word])	2077798
<u>#26</u>	Add	Search (((("Acute Pain"[Mesh]) OR "Chronic Pain"[Mesh]) OR "Breakthrough Pain"[Mesh]) OR "Pain, Intractable"[Mesh]) OR "Pain, Referred"[Mesh]	<u>19040</u>
<u>#19</u>	<u>Add</u>	Search ((((((("Back Pain"[Mesh:NoExp]) OR "Musculoskeletal Pain"[Mesh]) OR "Abdominal Pain"[Mesh:NoExp]) OR "Low Back Pain"[Mesh]) OR "Arthralgia"[Mesh]) OR "Chest Pain"[Mesh]) OR "Facial Pain"[Mesh:NoExp]) OR "Flank Pain"[Mesh]) OR "Metatarsalgia"[Mesh:NoExp]) OR "Neck Pain"[Mesh]	<u>133062</u>

# Embase.com 31.05.2017-01.02.2019

No.	Query	Results
#29	#28 AND [31-5-2017]/sd	3306
#28	#24 NOT #27	25542
#27	#25 OR #26	18603
#26	#24 AND ('case report'/de OR 'systematic review'/de OR 'meta analysis'/de)	11517
#25	#24 AND ('Conference Abstract'/it OR 'Editorial'/it OR 'Letter'/it)	9403
#24		44145
#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*	6151238
#22	#19 OR #21	121885
#21	#18 AND #20	82516
#20		2498081
#19	#18 AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim)	90443
#18		710948
#17	((pain OR ache) NEAR/3 (musculoskeletal OR 'back pain' 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 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)):ti,ab,kw	150092
#16	backache:ti,ab,kw,de OR headache:ti,ab,kw,de	293040
#15		17347
#14	musculoskeletal:ti,ab,kw OR 'back pain':ti,ab,kw OR joint:ti,ab,kw OR pfp:ti,ab,kw OR tendinitis:ti,ab,kw OR cervical:ti,ab,kw OR jaw:ti,ab,kw OR limb:ti,ab,kw OR shoulder:ti,ab,kw OR arm:ti,ab,kw OR elbow:ti,ab,kw OR wrist:ti,ab,kw OR carpal:ti,ab,kw OR hand:ti,ab,kw OR finger:ti,ab,kw OR collar:ti,ab,kw OR vertebral:ti,ab,kw OR lumbar:ti,ab,kw OR back:ti,ab,kw OR backache:ti,ab,kw OR headache:ti,ab,kw OR hip:ti,ab,kw OR knee:ti,ab,kw OR patella*:ti,ab,kw OR patellofemoral:ti,ab,kw OR retropatellar:ti,ab,kw OR leg:ti,ab,kw OR ankle:ti,ab,kw OR foot:ti,ab,kw OR heel:ti,ab,kw OR arthralgia:ti,ab,kw OR osteochondritis:ti,ab,kw OR osgood:ti,ab,kw OR 'growing pain*':ti,ab,kw OR scheuermann:ti,ab,kw	2376662
#13	#9 OR #10 OR #11 OR #12	59894
#12	'referred pain'/exp	109
#11	'intractable pain'/exp	465
#10	'breakthrough pain'/exp	134
#9	'chronic pain'/exp	5361
	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	62805
#8		118
#8 #7	'metatarsalgia'/exp	118
#8 #7 #6	'metatarsalgia'/exp 'arthralgia'/exp	5470
#8 #7 #6 #5	'metatarsalgia'/exp 'arthralgia'/exp 'thorax pain'/exp	5470 7934
#8 #7 #6 #5 #4	'metatarsalgia'/exp 'arthralgia'/exp 'thorax pain'/exp 'flank pain'/exp	5470 7934 633
#8 #7 #6 #5	'metatarsalgia'/exp 'arthralgia'/exp 'thorax pain'/exp	

# CINAHL (EBSCONet) 01.06.2017-01.02.2019

Search ID#	Search Terms	Search Options	Results
S19	s16 not s17	Limiters - Published Date: 20170601- 20191231 Search modes - Boolean/Phrase	971
S18	s16 not s17	Search modes - Boolean/Phrase	7,109
S17	PT (Systematic Review or Meta Analysis)	Search modes - Boolean/Phrase	87,387
S16	S14 AND S15	Search modes - Boolean/Phrase	7,276
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	1,025,399
S14	S11 OR S13	Search modes - Boolean/Phrase	21,414
S13	S10 AND S12	Search modes - Boolean/Phrase	21,266
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	1,048,327
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		15,463
S10	S1 OR S7 OR S8 OR S9	Search modes - Boolean/Phrase	107,547
S9	STOK 37 OK 38 OK 39       Search modes - Boolean/Phrase         ((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		61,789
S8	backache or headache	Search modes - Boolean/Phrase	26,017
S7	S5 AND S6	Search modes - Boolean/Phrase	7,112
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)		542,363
S5	S2 OR S3 OR S4	Search modes - Boolean/Phrase	18,849
S4	(MH "Referred Pain")	Search modes - Boolean/Phrase	406

S3	(MH "Breakthrough Pain")	Search modes - Boolean/Phrase	128
S2	(MH "Chronic Pain")	Search modes - Boolean/Phrase	18,360
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	66,335

#### Web of Science 2017-11.02.2019

Set Re	Results	Save History / Create Alert Open Saved History	Edit Sets	Combine Sets	Delete Sets
				Combine	× Delete
# 10	2,497	#8 AND #7 Refined by: PUBLICATION YEARS: (2019 OR 2018 OR 2017 ) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years			
#9		#8 AND #7 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	Edit		
#8	6,829,939	TOPIC: (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		#6 AND #5 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	Edit		
#6		TOPIC: ((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	282,070	#4 OR #3 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	Edit		
#4	74,839	TOPIC: (backache or headache) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	Edit		
#3	214,291	#2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	Edit		
#2		TOPIC: (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) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-SS, CPCI-SSH, ESCI Timespan=All years	Edit		
#1	573,235	TOPIC: (pain OR ache) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years	Edit		
					Select All
				Combine	× Delete

# PsycInfo 2017-11.02.2019

1	exp Musculoskeletal Disorders/	16869
2	headache/ or muscle contraction headache/	7319
3	myofascial pain/	329
4	back pain/	3655
5	1 or 2 or 3 or 4	27350
6	chronic pain/	12511
7	pain/	23687
8	6 or 7	35477
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	238846

	patellofemoral or retropatellar or leg or ankle or foot or heel or arthralgia or osteochondritis	
	or osgood or growing pain* or scheuermann).mp.	
10	8 and 9	9902
11	(backache or headache).mp.	19554
12	((pain or ache) adj3 (musculoskeletal or back or joint or PFP or tendinitis or cervical or jaw or	10225
	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.	
13	5 or 10 or 11 or 12	46619
14	limit 13 to (100 childhood <birth 12="" age="" to="" yrs=""> or 200 adolescence <age 13="" 17="" to="" yrs="">)</age></birth>	5926
15	(juvenile or adolescen* or preadolescence or Preadolescent or preschool or child or children or	961911
	prepubertal or kids or paediatric or pediatric or youth or young or childhood or schoolchild* or	
	teenager).mp.	
16	13 and 15	5867
17	14 or 16	8172
18	(predict* or long term or Follow-up or Prospective or cohort or cluster or prognosis or	798327
	prognostic or Mediator* or treatment effect modifier* or longitudinal*).mp.	
19	17 and 18	2298
20	(((systematic or method*) adj3 (review* or overview* or study or studies or search* or	166163
	approach*)) or meta analy* or meta-analy* or metaanaly*).ti,ab,id.	
21	limit 19 to ("0830 systematic review" or 1200 meta analysis)	45
22	20 or 21	166166
23	19 not 22	2130
24	limit 23 to yr="2017 -Current"	180

#### Cochrane Library juni 2017-11.02.2019

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))	42928
#2	(backache or headache)	27829
#3	#1 OR #2	63886
#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)	270643
#5	#3 AND #4	17122
#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*)	453684
#7	#5 AND #6 with Cochrane Library publication date Between Jun 2017 and Feb 2019	1186

# 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

31 32						
33 34			Reporting Item	Number		
35 36 37 38		#1	Identify the report as a systematic review, meta-analysis, or both.	1		
39 40	Structured	#2	Provide a structured summary including, as applicable:	2		
40 41 42 43 44 45 46 47	summary		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			
48 49 50 51	Rationale	#3	Describe the rationale for the review in the context of what is already known.	3		
52 53 54 55 56	Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3		
57 58 59 60	Protocol and	<b>#5</b> For	Indicate if a review protocol exists, if and where it can be peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	3		

Page 37 of 53

BMJ Open

1 2 3	registration		accessed (e.g., Web address) and, if available, provide registration information including the registration number.				
4 5 6 7 8 9 10 11 12 13 14	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			
15 16 17 18	Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3			
19 20 21 22 23	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			
24 25	Data collection	#10	Describe the method of data extraction from reports (e.g., piloted	4			
26 27 28 29	process		forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.				
<ol> <li>29</li> <li>30</li> <li>31</li> <li>32</li> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> </ol>	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			
52 53	Risk of bias	#15	Specify any assessment of risk of bias that may affect the	5			
54 55 56	across studies		cumulative evidence (e.g., publication bias, selective reporting within studies).				
57 58	Additional	#16	Describe methods of additional analyses (e.g., sensitivity or	5			
59 60		For	peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml				

BMJ Open

1 2 3	analyses		subgroup analyses, meta-regression), if done, indicating which were pre-specified.				
4 5 6 7 8 9 10 11 12 13 14	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			
15 16 17	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			
$\begin{array}{c} 18\\ 19\\ 20\\ 21\\ 22\\ 23\\ 24\\ 25\\ 26\\ 27\\ 28\\ 29\\ 30\\ 31\\ 32\\ 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 45\\ 46\\ 47\\ 48\\ 49\\ 50\\ 51\\ 52\\ 53\\ 54\\ 55\\ 56\\ 57\\ 58\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 80\\ 8$	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			
59 60		For	peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml				

The PRISMA checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 29. June 2018 using <u>http://www.goodreports.org/</u>, a tool made by the EQUATOR Network in collaboration with Penelope.ai

tor preserve wiew only

# PROSPERO International prospective register of systematic reviews

National Institute for Health Research

# UNIVERSITY of York Centre for Reviews and Dissemination

# 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

PROSPERO International prospective register of sy	stematic reviews		NHS al Institute for ealth Research
Review stage		Started	Completed
Preliminary searches		Yes	Yes

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.

Give the electronic mail address of the named contact.

negar@dcm.aau.dk

#### 8. Named contact address

Give the full postal address for the named contact.

#### Dr. Negar Pourbordbari

Research Unit of General Practice in Aalborg and Department of Clinical Medicine, Aalborg University Fyrkildevej 7, 9220 Aalborg

Denmark

#### 9. Named contact phone number.

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

#### 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.

# PROSPERO International prospective register of systematic reviews

# National Institute for Health Research

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

# PROSPERO

# International prospective register of systematic reviews

#### 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

#### PROSPERO International prospective register of systematic reviews

National Institute for Health Research

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 followup 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).

#### PROSPERO International prospective register of systematic reviews

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 metaanalysis 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

NHS National Institute for Health Research

#### **PROSPERO** International prospective register of systematic reviews

1

2	International prospective register of systematic reviews
3	Νο
4 5	Meta-analysis
6	No
7 8	Methodology No
9 10	Network meta-analysis
11	No
12 13	Pre-clinical No
14 15	Prevention No
16 17	Prognostic Yes
18 19	Prospective meta-analysis (PMA)
20 21 22	Qualitative synthesis No
23 24	Review of reviews No
25 26	Service delivery No
27 28	Systematic review Yes
29 30 31 32	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
33 34 35 36	Health area of the review Alcohol/substance misuse/abuse No
37 38 39	Blood and immune system Z
40 41	Cancer No Cardiovascular No Care of the elderly
42 43	Cardiovascular No
44 45	Care of the elderly No
46 47 48	Child health No
49 50	Complementary therapies No
51 52	Crime and justice No
53 54	Dental No
55 56 57	Digestive system No
57 58 59	Ear, nose and throat No
60	Education

5	· · · · · · · · · · · · · · · · · · ·
1	PROSPERO
2	International prospective register of systematic reviews
3	
4	No
5	Endocrine and metabolic disorders
6	No
7	
8	Eye disorders No
9	
9 10	General interest
11	No
12	Genetics
13	No
14	Health inequalities/health equity
15	No
16	
10	Infections and infestations
18	No
19	International development
20	No
20	Mental health and behavioural conditions
22	No
22	Musculoskeletal
23	No
25	
26	Neurological No
20	NU
28	Nursing
29	No
30	No Musculoskeletal No Neurological No Nursing No Obstetrics and gynaecology No Oral health No Palliative care No Perioperative care
31	No
32	Oral health
33	No
34	Dellistics sees
35	Palliative care No
36	
37	Perioperative care
38	No
39	Physiotherapy
40	No
41	Pallative care No Perioperative care No Physiotherapy No Pregnancy and childbirth No Public health (including social determinants of health) No Rehabilitation
42	No
43	Public health (including social determinants of health)
44	No
45	
46	Rehabilitation
47	No
48	Respiratory disorders
49	No
50	Service delivery
51	No
52	Skin disorders
53	No
54	
55	Social care No
56	
57	Surgery
58	No
59	Tropical Medicine
60	No

National Institute for

Health Research

# PROSPERO International prospective register of systematic reviews

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

2 3

4

#### PROSPERO

#### International prospective register of systematic reviews

#### 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/MusculoskeletalPainFactS heets/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.

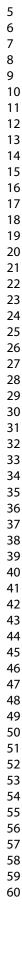
http://training.cochrane.org/resource/data-collection-forms-intervention-reviews 2014.

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.



Supple	ementary table 1. Estimates on prognostic factors specified	Musculoskeletal pain	Neck pain					Τ
accordi	ng to musculoskeletal pain type, baseline age, and follow-up	Low back pain	Low limb pain	Headache				╈
	in the included studies	Knee pain	Back pain	Growing pain				╈
	Prognostic factors subgrouped according to the biopsychosocial model	Study ID (Follow- up, yrs)	RR (95% CI)	OR (95% CI)	p-value	Adjusted for		T
	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			_
10 to 17		50 (3mo)			0.003			╋
9 to 12		27 (1)	CP 1 20 (1 02 1 62)		0.001			+
12 to 15 12 to 15		34 (2) 9 (1)	CR 1.29 (1.02-1.63)	2 (( (1 00 12 22)	0.08			+
12 to 15 10 to 11		39 (2)		3.66 (1.09-12.33)	0.04			+
10 to 11 10 to 11		39 (2)			M < 0.001 M < 0.001			+
8, 11, 14		20 (11)		2.24 (1.24-4.20)	WI \ 0.001			+
	Older age	20 (11)		2.24 (1.24 4.20)				+
9 to 12	Older age	28 (1)		1.24 (1.02-1.50)	0.031			+
9 to 12 F	11 to 13 years vs. 9-10 years	21 (4)	M 1.40 (1.17-1.67)	1.24 (1.02 1.30)				+
12 to 15	Older age, increase per year, 12 years as referent	9 (1)	W 1.40 (1.17 1.07)	M 1.45 (1.07-1.95)	0.01			
13	Older age	25 (3)		· · · ·	0.04			T
	Body measurement factors							
8 to 13	Higher pubertal group (a) group 2 and 3 vs. group 1	37 (3)			0.022			T
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		Т
9 to 12	Hypermobility score >/=6 vs. <6	11 (4)		M 2.93 (1.13-7.70)		-		
5 (0 12	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	activity	
14 to 16	Ratio extension mobility cm/extension strength (min) (b)	36 (3)		3.2 (1.3-8.3)	0.02	gender		T
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	activity	
	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			$\square$
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 (c))	21 (4)	M 1.43 (1.12-1.83)		0.010	age		+
10 to 17	Conditioned pain modulation CPM (d)	50(3mo)			0.046			+
9 to 12 F	Abdominal pain (psychosomatic symptom (c))	21 (4) 23 (4)	U 1.20 (1.03-1.40)			age		+
11 to 14 11 to 14	Radiating leg pain vs. no radiating pain Low back pain start > 12 month prior to admission	23 (4)	2.2 (1.4-3.6) 2.4 (1.3-4.4)			age, sex 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)	1.24 (1.04-1.49)		0.01	age, sex, Divil		+
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			

Page 51 of 53	
---------------	--

1								
	16 to 18	Longer pain duration per 10-months increase	34 (2)	CR 1.04 (1.01-1.07)		0.01		
2	9 to 12 M	Also headache (e) at least once a week	38 (4)			<0.001		
3	9 to 12 M	Also abdominal pain (e) at least a week	38 (4)			<0.001		
4	9 to 12 F	Also headache (e) at least once a week	38 (4)			<0.001		
5	9 to 12 F	Also abdominal pain (e) at least a week	38 (4)			<0.001		
З	9 to 12	Other musculoskeletal symptoms: upper extremities at least once a week	38 (4)			<0.001		
6	9 to 12 M	Other musculoskeletal symptoms: chest at least once a week	38 (4)			0.008		
7	9 to 12 F	Other musculoskeletal symptoms: chest at least once a week	38 (4)			0.001		
8	9 to 12	Other musculoskeletal symptoms: back at least once a week	38 (4)			<0.001		
Ũ	9 to 12 M	Other musculoskeletal symptoms as well: lower extremities at least once a week	38 (4)			<0.001		
9	9 to 12 F	Other musculoskeletal symptoms as well: lower extremities at least once a week	38 (4)			0.003		
10	8, 11, 14	Headache >/= 1time/week	20 (11)		2.3 (1.1-4.5)			
11	10 to 16	Duration of pain episodes > 3 hours vs. < 3 hours	20 (11)		U 3.1 (1.1-8.2)			
11	10 to 16	Lower pain threshhold	40 (5)			<0.05		
12	10 to 16	Lower pain threshold at anterior tibial region (pressure level < 5kg/cm2)	40 (5)			<0.01		
13		PSYCHOLOGICAL PROGNOSTIC FACTORS						
11		General psychological factors						
14	16 M	Internalization (f)	33 (2)		2.32 (1.23-4.37)			
15	16 M	Externalization (f)	33 (2)		2.17 (1.24-3.81)			
16	16 F	Internalization (f)	33 (2)		3.70 (1.88-7.27)			
17	10 to 16	Often/sometimes nervous	20 (11)		M 2.1 (1.3-3.4)			
17	16 to 18 M	Internalization (f)	24 (2)			< 0.001		
18	16 to 18 M	Externalization (f)	24 (2)			< 0.001		
19	16 to 18 F	Higher internalization score (f)	24 (2)			< 0.001		
20	16 to 18 F	Higher externalization score (f)	24 (2)			< 0.001		
20	10 to 16	Self-perception of not feeling completely healthy	20 (11)		U 1.7 (1.1-2.8)			
21	10 to 16	Unsatisfied with own appearance	20 (11)		U 1.6 (1.1-2.5)			
22	12 to 15	EQ-5D index score 0-25 vs. 75-100% quartiles (g)	9 (1)		U 0.08	<0.001		
22	12 to 15	EQ-5D index score 0-25 vs. 25-50% quartiles (g)	9 (1)		U 0.29	<0.001		
25	12 to 15	EQ-5D index score 25-50th % vs. 75th-100th % (g)	34 (2)	CR 1.81 (1.14-2.85)		0.01		
24	12 to 15	EQ-5D index score 0-25th % vs. 75th-100th % (g)	34 (2)	CR 2.00 (1.28-3.12)		0.002		
25	10 to 11	Self reported low self esteem	39 (2)			U<0.01		
26	10 to 11	Parent reported adolescent low self esteem	39 (2)			U<0.01		
		Depressive factors						
27	9 to 12 F	Depressive feelings	21 (4)	U 1.21 (1.03-1.42)			age	
28		Depressive symptoms in a frequency of at least once a week	38 (4)			<0.001		
20	9 to 12 M	Depressive symptoms in a frequency of at least once a week	38 (4)			<0.001		
29	12 to 16	Higher score of anxiety and depressive symptoms (h)	18 (4)		1.4 (1.03-1.90)	0.032		
30		Self reported anxiety/depression	39 (2)			M <0.01		
31	10 to 11	Parent reported adolescent anxiety/depression	39 (2)			< 0.05		
32		SOCIAL PROGNOSTIC FACTORS						
-		General social factors						
33		Lower paternal educational level (median 10 vs. 14 years education)	22 (9)			p<0.01		
34	2 to 17	Lower maternal educational level (median 10 vs. 14 years education)	22 (9)			p<0.01		
35	2 to 17	More chronic family difficulties (mean 4.3 vs. 2.9) (i)	22 (9)			p<0.01		
36	10 to 16	Doing well in school	20 (11)		U 1.8 (1.1-2.9)			
36		Higher disability index (j) 1-2 vs 0	28 (1)	1.72 (1.09-2.73)		0.005		
37	9 to 12	Higher disability index (j) 3-5 vs 0	28 (1)	3.17 (1.54-6.55		0.005		
38	9 to 12	Higher disability index (j) 3-5 vs. 0	21 (4)	U 1.23 (1.02-1.49)			age	
20		High vs. low peer relationship problems	23 (4)	2.4 (1.3-4.2)			age, sex	
39	11 to 14	Difficulty standing in line for 10 minutes	23 (4)	2.7 (1.5-4.9)				
40	11 to 14	Difficulties carrying a schoolbag	23 (4)	2.1 (1.1-4.0)				
41	11 to 14	High limitation level HFAQ (k) 4-9 vs. 0-1 limitations	23 (4)	4.1 (1.05-16.2)				

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

44 45

Page 52	of 53
---------	-------

F = prognostic factor only applicable for female participants, M = Male, when nonspecified = unkex Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain.   Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain.   Image: Construct a second and the prognostic factor is associated with a ligher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a higher risk of persistent MSK pain.   Image: Construct a second and the prognostic factor is associated with a ligher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a ligher risk of persistent MSK pain.   Image: Construct a second and the prognostic factor is associated with a ligher risk of persistent MSK pain. Image: Construct a second and the prognostic factor is associated with a ligher risk of persistent MSK pain.   Image: Construct a second and the prognostic and prognostic and the prognostic and prognostic and the										
10         010         115         Partial recurrent headship         33         (2)         000         00000           Factor related to lesp defadem is relations         400         00000         00000         00000           Factor related to lesp defadem is relations         00000         00000         00000         00000           1000000000000000000000000000000000000	8, 11, 14	Headache on non-school days	20 (11)		3.1 (1.3-7.3)					
10 10 10         All actions gain systems         00.07         00.07           Febtor Maddo & Marcel Andrea Marcel and Marcel Andrea Marcel and Marcel Andrea Marce	13 M	Use of physiotherapy for headache or neck pain during the past 6 months	25 (3)			0.004				
Febru Prete de leg/daprie tentes         11         Image: 100 million         12,10         12,10         Image: 100 million         12,10         12,1	10 to 11 F	Parental recurrent headache	39 (2)			p<0.05				
Factor related to step/dayline torques         CI         No         No         No         No           18 10 12         Winking up dayling relations         33 (2)         1.6 (1.0.5.05)         No         Applications	10 to 16	At least one parent with a pain syndrome	40 (5)			0.047				
10         10         121         Walking up during rings         98           15         158			- (-7							
16 1         Step 4/- 78, v. 8 0 h/dy         31 (2)         1.6 8 (1.052.68)	9 to 12 F		21 (4)	U 1.18 (1.01-1.37)			age			
9         9         10         1.66 (1.16.2.00)         0.010           9         0.110         1.66 (1.16.2.00)         0.010           10         10.110         0.010         0.001           10         10.110         0.010         0.001           10         10.110         0.010         0.001           10         0.010         0.001         0.001           10         0.010         0.001         0.001           10         0.010         0.001         0.001           10         0.001         0.001         0.001           10         0.001         0.001         0.001           10         0.010         0.001         0.001         0.001           10         11.10         0.004         0.001         0.001           11.10         0.004         0.001         0.001         0.001           11.10         0.004         0.001         0.001         0.001           11.10         0.004         0.004         0.008         0.001           11.10         M4.2.01         0.008         0.008         0.008         0.008         0.008         0.008         0.008         0.008         0.008 <td></td> <td></td> <td>. ,</td> <td></td> <td>1.68 (1.05-2.68)</td> <td></td> <td>- 0-</td> <td></td> <td></td>			. ,		1.68 (1.05-2.68)		- 0-			
16       16 <td< td=""><td>-</td><td></td><td>. ,</td><td></td><td></td><td>0.010</td><td></td><td></td><td></td></td<>	-		. ,			0.010				
9 to 12 M         Difficulties failing select         38 (4)  <					1.00 (1.10 5.00)					
10         10         0.001         0.001           10         10.12         Wilding up during nights         38 (d)         0.001           10         10.12         Wilding up during nights         38 (d)         0.001           10         10.12         Minister telefones         38 (d)         0.001           10         10.12         Disting up during nights         38 (d)         0.003           10         10.12         Disting up during nights         38 (d)         0.004           10         10.12         Disting up during nights         0.004         0.004           10         10.12         Disting up during nights         0.004         0.004           10         10.12         Disting up during nights         0.004         0.004           12         10.12         Sonty participation 3-7 (twick to 24 (twick to 10.10)         0.038         0.004           12         10.12         Sonty participation 3-7 (twick to 24 (twick to 10.10)         0.038         0.004         0.038         0.004         0.038         0.004         0.038         0.004         0.038         0.004         0.038         0.004         0.038         0.021         0.038         0.021         0.038         0.021         0.038										
9 10 12 M         Walking up during nights         38 (4)         0.001           9 10 12 F         Brüches falling up during nights         38 (4)         0.001           9 10 12 F         Brüches falling up during nights         38 (4)         0.001           9 10 12 F         Brüches falling up during nights         38 (4)         0.001           9 10 12 F         Walking up during nights         38 (4)         0.001         0.001           10 12 F         Walking up during nights         38 (4)         0.001         0.001           11 fb         Max 2-3 hours of moderates vigous physical activity/week         31 (2)         1.63 (1.04-2.56)         0.008         0.008           12 fb 15 Sonding particitype on 2-10x physical activity/week         31 (1)         M 2.01 (1.20-3.36)         0.008         0.008           13 fb 17 G         Maxing particitype on 2-10x physical activity/week         32 (1)         1.63 (1.04-2.56)         0.008         0.008           14 fb 15 Sonding vigous physical activity/week         32 (1)         M 2.01 (1.20-3.36)         0.008         0.008         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001         0.001		•	· · · /							
10         10         17         0 Minute Selence         38 (4)         0.001         0.012           10         17         0 Minute Selence         38 (4)         0.001         0.012           10         17         Minute Selence         38 (4)         0.001         0.012           10         17         Minute Selence         38 (4)         0.001         0.001           11         15         50 Test Minute Selence         37 (2)         1.63 (1.04-2.6)         0.004           12         10 12         Sonte participation 3-7 (Ww.k. 0.2 (Ww.k.         9 (1)         M 2.03 (1.20-3.6)         0.004           12         10 13         Minute Selence         0.038         0.004         0.004           12         10 13         Minute Selence         0.038         0.004         0.004           14         11         M 2.43 (1.20-3.5)         0.004 <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>										
9 to 127       Dysime Endonesis       38 (4)			· · · /							
9       9.2 F. Walking up during rights       38 (i)										
Physical activity / Inactivity         Physical activity / Inactivity         Physical activity / Inactivity         Physical activity										
16 F $ -4 $ vs. 2.3 hours of moderate-vigorous physical activity week33 (2)1.03 (1.04-2.56)mmm </td <td>5 60 12 1</td> <td></td> <td>00(1)</td> <td></td> <td></td> <td>.01001</td> <td></td> <td></td> <td></td>	5 60 12 1		00(1)			.01001				
16 to 18 M       Longer stitug turne outside school hours (main 6.2 h/day)       24 (2)       0.004       0.004         9 to 12       Jacobia       M.2.01 (1.6:5.05)       0.08       0.004         9 to 12       Jacobia       M.2.01 (1.6:5.05)       0.08       0.004         16 to 18 f       Marchina norzakinał ensumation       24 (2)       0.038       0.038         16 to 18 f       Marchina norzakinał ensumation       24 (2)       0.038       0.038         16 to 18 f       Marchina norzakinał ensumation       24 (2)       0.038       0.038         16 to 18 f       Smoking S-J data/mick ski, nonsmoking       30 (2)       2.52 (1.404-0.33)       Enshytists, physkalachbia, M.A.A.A.A.A.A.A.A.A.A.A.A.A.A.A.A.A.A.A	16 F		33 (2)		1.63 (1.04-2.56)			<del>   </del>		
12 10.35       Sports participation 3-7 Uwk yo, 0.2 Uwk       9 (1)       M.2.01 (1.20-3.36)       0.0.08         9 10 12       Sports participation 3-7 Uwk yo, 0.2 Uwk       11 (1)       M.2.43 (1.16-5.05)           16 to 18.15       Monethan accountion       24 (2)       0.0.38           16 to 18.15       Monethan accountion       24 (2)       0.0.38           16 for Smoking vs. nonsmoking       33 (2)       2.55 (1.404.63)       fmmly352, phycalacturky, MM, depresent encod         16 for Smoking 2-7 days/welk vs. nonsmoking       30 (2)       2.55 (1.404.63)       fmmly352, phycalacturky, MM, depresent encod         16 for Smoking 2-9 daystrick (day vs. nonsmoking       30 (2)       2.55 (1.404.63)       fmmly352, phycalacturky, MM, depresent encod         16 for Smoking 2-9 daystrick (day vs. nonsmoking       30 (2)       2.55 (1.305.64)       fmmly352, phycalacturky, MM, depresent encod         16 for Smoking 2-9 daystrick (day vs. nonsmoking       30 (2)       2.66 (1.355.52)       fml/y352, phycalacturky, MM, depresent encod         10 for Ming 2-9 daystrick (day vs. nonsmoking       30 (2)       2.66 (1.355.62)       fml/y352, phycalacturky, MM, depresent encod         10 for Ming 2-9 daystrick (day vs. nonsmoking       00 (2)       2.66 (1.355.62)       fml/y352, phycalacturky, MM, depresent encod         <			. ,			0.004		<u>├</u>		
9 10 22       Services forwards (5,71 xs. 0.2 Aveek       11 (1)       M 2.43 (116-5:05)       International consumption         16 16 18 67       Serving       0.038       0.038       International consumption         16 16 18 67       Smoking 2: 100 aveek vs. nonsmoking       33 (2)       1.89 (1.23-2.90)       International consumption         16 16 7       Smoking 2: 2 day/week vs. nonsmoking       30 (2)       2.39 (1.404-4.5)       Immin visits, phyckalactivity, UM, depreseve mode         16 16 7       Smoking 2: 4 day vs. nonsmoking       30 (2)       2.39 (1.404-4.5)       Immi visits, phyckalactivity, UM, depreseve mode         16 16 7       Smoking 2: 4 day vs. nonsmoking       30 (2)       2.57 (1.03-6.46)       fmmi visits, phyckalactivity, UM, depreseve mode         16 16 7       Smoking 1 2: dayzet(day vs. nonsmoking       30 (2)       2.68 (1.35-3.2)       fmmi visits, phyckalactivity, UM, depreseve mode         16 16 13 5 (1.65 1 - 1.67 (1.65 1 - 1.67 (1.65 - 1.67 (					M 2.01 (1.20-3.36)			<u>├</u>		
Alcohol         Control         Control <t< td=""><td></td><td></td><td></td><td></td><td></td><td>2.300</td><td></td><td><u>├</u></td><td></td></t<>						2.300		<u>├</u>		
16 to 18 f       More than creational consumption       24 (2)       0.038         16 f       Smoking son normoking       33 (2)       1.88 (123-2.00)       male son			(-)		10. 2. <del>4</del> 3 (1.10-3.03)			<u>├</u>		
Smoking         Image: Control of the second se	16 to 18 F		24 (2)			0.038				
10 F       Smoking 5-7 day/week vs. nonsmoking       30 (2)       2.5 (1.404.53)       family SES, physicalactivhy, BML, degressive mood         16 F       Smoking 1-9 cigareties/day vs. nonsmoking       30 (2)       2.3 9 (1.404.08)       family SES, physicalactivhy, BML, degressive mood         16 F       Smoking 1-9 cigareties/day vs. nonsmoking       30 (2)       2.5 7 (1.034.64)       family SES, physicalactivhy, BML, degressive mood         25 plandory notes       80 (2)       2.6 (1.355.32)       family SES, physicalactivhy, BML, degressive mood         16 r       Smoking 2-0 cigareties/day vs. nonsmoking       30 (2)       2.6 (1.355.32)       family SES, physicalactivhy, BML, degressive mood         16 r       Smoking 2-0 cigareties/day vs. nonsmoking       30 (2)       2.6 (1.355.32)       family SES, physicalactivhy, BML, degressive mood         16 r       Smoking 2-0 cigareties/day       N= nonsmoking       10 (1.101.101.101.101.101.101.101.101.101.1	10 10 10 1		_ · (_)			0.058				
10 F       Smoking 5-7 day/week s. nonsmoking       30 (2)       2.5 2 (1.404.53)       family SES, physicalactivity, BMI, degressive mood         16 F       Smoking 2-9 digaettes/day s. nonsmoking       30 (2)       2.3 9 (1.404.08)       family SES, physicalactivity, BMI, degressive mood         16 F       Smoking 2-9 digaettes/day s. nonsmoking       30 (2)       2.3 9 (1.404.08)       family SES, physicalactivity, BMI, degressive mood         16 F       Smoking 1-9 digaettes/day s. nonsmoking       30 (2)       2.6 7 (1.034.64)       family SES, physicalactivity, BMI, degressive mood         16 F       Smoking 2-9 digaettes/day s. nonsmoking       30 (2)       2.6 8 (1.355.32)       family SES, physicalactivity, BMI, degressive mood         17 Smoking 2-0 traits pol 50 finder bartter baroscittation the physical tactivity accurate that the genometry family set fami	16 F	Smoking vs. nonsmoking	33 (2)		1.89 (1.23-2.90)					
10 F       Smoking 1-9 cigarettes/day vs. nonsmoking       30 (2)       2.39 (1.40-4.08)       fmM/v355 physicalactivhy.9M. depresave model         16 F       Smoking 3-9 cigarettes/day vs. nonsmoking       30 (2)       2.57 (1.03-6.46)       fam/v355 physicalactivky.9M. depresave model         16 M       Smoking 3-9 cigarettes/day vs. nonsmoking       30 (2)       2.56 (1.35-5.32)       fam/v355 physicalactivky.9M. depresave model         Explanatory notes       F			. ,				family's SES physical activ	ity BML depressive mood		
16 F       Smoking > 9 cigarettes/day vs. nonsmoking       30 (2)       2.57 (1.0.3-6.46)       family SSES, physicalactivity, BMI, depressive mood         L6 M       Smoking 1-9 cigarettes/day vs. nonsmoking       30 (2)       2.68 (1.3.5-5.32)       family SSES, physicalactivity, BMI, depressive mood         Explanatory motes       Image: SSES, physicalactivity, BMI, depressive mood       Image: SSES, physicalactivity, BMI, depressive mood         Conditione interval       M-Mutarities analysis       U-Univarities analysis       Image: SSES, physicalactivity, BMI, depressive mood         Second protect       Conditione interval       M-Mutarities analysis       U-Univarities analysis       Image: SSES         Second protect       Conditione interval       M-Mutarities analysis       U-Univarities analysis       Image: SSES         Second protect       Second protect factor in sacce textees on human mutarity and undira extension strength protects future is backet souther physical and underarm hair.       Image: SSES       Image: SSE					, ,					
16 M         Smoking 1-9 cigarettes/day vs. nonsmoking         30 (2)         2.68 (1.35-5.32)         family StES, physicalactivity, BMI, depressive mood           Explanatory notes   <			. ,							
Explanatory notes       Image: Second S										
F = proposite factor only applicable for females participants, M = Male, When nonspecified = unies:   R> 1 or < 1, 0 > 1 or < 1, 0 > 0.05 indicate that the prognosite factor is associated with a higherrisk of persisten MSK pain.   B = confidence interval M = Multivariate analysis   G = confidence dapin modulator CPM calculated using a ratio of conditioned heat pain threshold with a conditione stimula(cold pressol(150).   G = confidence dapin modulator CPM calculated using a ratio of conditioned heat pain threshold with a conditione stimula(cold pressol(150).   G = confidence dapin modulator CPM calculated using a ratio of conditioned heat pain threshold with a conditione stamula(cold pressol(150).   G = confidence dapin modulator CPM calculated using a ratio of conditioned pain modulator CPM calculated using a ratio of conditioned pain modulator CPM calculated using a ratio of conditioned pain modulator CPM calculated using a ratio of conditioned pain modulator CPM calculated using a ratio of conditioned pain modulator CPM calculated using a ratio of conditioned pain modulator CPM calculated using a ratio of co			()				. ,,,,,,	,, ,,		
BR3 1 or < 1, 0R3 1 or < 1, 0 < 0.05 indicate that the prognostic factor is associated with a higher risk of persistent MSK pain.										
I = confidence interval       M = Multivariate analysis       U = Univariate analysis       CR = Crude       Image: Confidence interval       M = Multivariate analysis       U = Univariate analysis       CR = Crude       Image: Confidence interval       M = Multivariate analysis       U = Univariate analysis       CR = Crude       Image: Confidence interval       M = Multivariate analysis       U = Univariate analysis       CR = Crude       Image: Confidence interval       M = Multivariate analysis       U = Univariate analysis       CR = Crude       Image: Confidence interval       Image: Confidence										
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 (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche. For males, puberty was defined by the stage of breast development (Tamer stage >/= a menarche stage) = a menarche stage and by chological symptoms, without further definition = a menarche stage and psychological symptoms, without further definition = a menarche stage and psychological symptoms, without further definition = a menarche stage and psychological symptoms, without further definition = a menarche stage and psychological symptoms, without further definition = a menarche stage and psychological symptoms, without further definition = a menarche stage and upace and psychological symptoms, without further definition = a menarche stage and psychological symptoms, without further definition = a mand and be not a mand the stage of normality and development and education, economic matters, housing, martial or farmity discord social networks and the physical and menatalheakth of the farmity members. Score range 0.6, Essever farmity difficulties = a mearche symptoms and ed										
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 humbar mobility and lumbar extension strenght predicts future low back pain c = childhood addominal pain, headache, depresseve symptoms, add truthes in alling askeep, waking up during pits are believed to be having a psychosomatic origin in the great majority of cases. d = Conditioned pain modulation CPM calculated using a ratio of conditioned heat pain threshold with a conditiones stimulus (cold pressor) (50). d = Conditioned pain modulation CPM calculated using a ratio of conditioned heat pain threshold with a conditiones stimulus (cold pressor) (50). d = Conditioned pain modulation CPM calculated from subcales: anklow/depressed, sthdrawn/depressed symptoms, and somatic complaints. Externalizing from rule-breaking and aggressive behaviour. g = Co-SD 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 coring own current self-rated health status on VAS O-100. h = Anxiety symptoms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive symptoms: felt hopeles when thinking of the future, felt down or sad. is Subjective disability index calculated from answers to the following proposals: difficulty in failing asleep because of pain, difficulty stifing during a lesson, pain disturbs awak more than 1km, pain disturbs physical accercise, pain disturbs physical accercise, pain disturbs physical accercise, pain disturbs physical accercise, pain disturbs and steres, poor sign, pain and ache in low back make any of the following al sexon, pain disturbs and feet, freally ensitters or high a -9 limitations (20). I = Subjective disability index calculated from a symptoms stere ther pain and ache in low back make any of										
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 tredness, difficulties in falling askep, waking up during nghts are believed to be having a psychosomatic origin in the great majority of cases. d = Conditioned pain modulation CPM calculated using a ratio of conditioned heat pain threshold with a conditiones stimulus (cold pressor) (50). d = Conditioned pain modulation CPM calculated using a ratio of conditioned heat pain threshold with a conditiones stimulus (cold pressor) (50). f = Internalizing score calculated from subscales: anxious/depressed symptoms, and somatic complaints. Externalizing from rule-breaking and aggressive behaviour. f = Internalizing score calculated from subscales: anxious/depressed symptoms, and somatic complaints. Externalizing from rule-breaking and aggressive behaviour. g = EQ-5D assessesself-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. h = 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. i = Subscitte disability index calculated from answers to the following proposis: difficulty in falling asleep because of pain, difficulty stitting during a lesson, pain disturbs a walk more than 1km, pain disturbs hybical exercise, pain disturbs hobbles. Range 0-5. k = The modified Hannover functionalability Questionnaite HFAQ assesses whether pain and ache in low back make any of the following daily activities affiredut: reaching up to get a book from a high sheft, carrying your school bag to school, string on a school chair for a 45- min lesson, standing up from an armchair at home			the presence of se	condary signs of pubertal dev	relopment. For females, pub	erty was defined t	by the stage of breast develo	pment (Tanner stage >/= 3) ar	na	
c = childhood abdominal pain, headache, depressive symptoms, day tiredness, difficulties in falling adeep, waking up during nghts are believed to be having a psychosomatic origin in the great majority of cases.   d = Conditioned pain modulation CPM calculated using a ratio of conditioned heat pain threshold with a conditiones stimulus (cold pressor) (50).   e = Cassfied as: other physical and psychological symptoms, without further definition   f = Internalizing x ore calculated from subcales: anxious/depressed, sthdrawn/depressed symptoms, and somatic complaints. Externalizing from rule-breaking and aggressive behaviour.   g = E0-5D assesses self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and within 3 levels of seventy: no problems, moderate or severe problems as well as scoring own current self-rated health status on VAS 0-100.   h = Arxiety symptoms: been constantly scared and uneasy, felt there and restess, worried too much about different matters. Depressive symptoms: felt hopeless when thinking of the future, felt down or sad.   i = 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 = The modified Hannover func tionalability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following proposals: difficulty in falling askeep, because of pain, difficulty sitting during a lesson, pain disturbs a walk more than km, pain disturbs hobbies. Range 0-5.   k = The modified Hannover func tionalability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following ports asses divertion a high shelf, carrying your schoolog to to hoolog to be form a high shelf,				1			1	I		
d = Conditioned pain modulation CPM calculated using a ratio of conditioned heat pain threshold with a conditiones stimulus (cold pressor) (50). e = Cassified as: other physical and psychological symptoms, without further definition f = Internalizing score calculated from subscales: anxious/depressed, sthdrawn/depressed symptoms, and somatic complaints. Externalizing from rule-breaking and aggressive behaviour. g = EQ-5D assesses self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/disc omfort, anxiety/depression and within 3 levels of severity: no problems, moderate or severe problems as well as scoring own current self-rated health status ov ND 0-100. h = 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. j = Subjective disability index calculated from answers to the following proposals: difficulty in failing asleep because of pain, difficulty sting during a lesson, pain disturbs a walk more than 1km, pain disturbs physical actercise, pain disturbs hobbles. Range 0-5. k = The modified Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following day activities difficult: reaching up tog bet a book from a high sheff, carrying your school bag to school, stuting on a school chair for a 5-min lesson, 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 li										
e = Classified as: other physical and psychological symptoms, without further definition f = Internalizing score calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing from rule-breaking and aggressive behaviour. g = 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. h = 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. i = 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 infalling asleep because of pain, dificulty sitting during a lesson, pain disturbs awalk more than 1km, pain disturbs physical-activites housing on a school chair for a 45-min lesson, standing 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 limitations or high = 4-9 limitations (23). I = 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, faeling excited and nervous. Yes to minimum 3 symptoms to meet the Yunus criteria. m = SES: Sociee commic status n = CD: Children <sup>1</sup> / <sub>2</sub> feeling excited and nervous. Yes to minimum 3 symptoms to meet the Yunus criteria. m = SES: Children <sup>1</sup> / <sub>2</sub> feeling excited and nervous. Yes to minimum 3 symptoms to meet the Yunus criteria. m = SES: Children <sup>1</sup> / <sub>2</sub> feeling ex			aving a psychoson	natic origin in the great major	ity of Cases.			<b>├</b> ────┤		
f = Internalizing score calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing from rule-breaking and aggressive behaviour.       g = EQ-5D assesses self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/disc omfort, 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.         h = 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.       in Assessment of information about temployment and education, economic matters, housing, marital or family disc ord, social networks and the physical and mental health of the family members. Scorer ange 0-6, 6.5.       is Assesser frequence in the following proposals: difficulty in falling askeep because of pain, difficulty sitting during a lesson, pain disturbs a walk more than 1km, pain disturbs hysical exercise, pain disturbs hobbies. Range 0-5.       is Assesser frequence in the physical and mental health of the family members. Scorer family difficulties and no a school chair for a 45-min lesson, standing in a que nix, 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).         I 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.         m SES: Socioec								<b>├</b> ────		
g = EQ-5D assesses elf-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.   h = 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.   i = 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.   j = 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.   k = The modified Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following dialy 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 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).   I = Yunus criteria: pain modulation by physical activity, by weather, by anxiet 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.   m = SES: Socioeconomic status   n = CDI: Children's depression Inventory. Cut off point >/= 13 indicating depressive symptoms   <			L				r	<b>├</b> ────		
h = 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. i = 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. j = 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. k = 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 q 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). I = Yunus criteria: pain modulation by physical activity, by weather, by anxiety and stress, poor skeep, 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. m = SES: Socie conomic status m = SES: Socie conomic status m = CD1: Children's depression Inventory. Cut off point >/= 13 indicating depressive symptoms leantified base line 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 f	f = Internalizing so	core calculated from subscales: anxious/depressed, sithdrawn/depressed symptoms, and somatic complaints. Externalizing from re	ule-breaking and a	ggressive behaviour.						
i = 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.       Image: Content of the family members is content of the family members. Score range 0-6, 6=severe family difficulties.         i = 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.       Image: Content of the family members. Score range 0-6, 6=severe family difficulties.         j = 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.       Image: Content of the family members. Score range 0-6, 6=severe family difficulties.         k = The modified Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily activities at school. Low = 0-1 limitation, moderate = 2-3 limitations or high = 4-9 limitations (23).         I = 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.         m = SES: Socioeconomic status       n = CO1: Children's depression Inventory. Cut off point >/= 13 indicating depressive symptoms       Image: Coll Children's depression Inventory. Cut off point >/= 13 indicating depr	g = EQ-5D assess	es self-reported health status in 5 dimensions: mobility, self-care, usual activitied, pain/discomfort, anxiety/depression and within 3 l	evels of severity: n	o problems, moderate or seve	ere problems as well as scorin	g own current sel	-rated health status on VAS (	0-100.		
j = 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 hobbles. Range 0-5.   k = 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 quint, 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).   I = 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.   m = SES: Socioeconomic status   n = CD1: Children's depression Inventory. Cut off point >/= 13 indicating depressive symptoms   Identified base line factors without association to persistent musculoskeletal pain, divided in pain type (study ID)   Musculoskeletal   Remale: sitting h/day, sleep h/day, Male: physical activity MET-h/week and above occasional alcohol consumption, unisex: smoking paste, wars, body mass index (BMI) (24)   Musculoskeletal   Renge 0:>	h = Anxiety symp	toms: been constantly scared and uneasy, felt tense and restless, worried too much about different matters. Depressive symptom	s: felt hopeless whe	en thinking of the future, felt o	down or sad.					
k = 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 q 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). I = 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. m = SES: Socioeconomic status n = CD1: 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 variations or per from school variations or persistent from school variations or persistent from school or prove from school or prove from school or prove from school or prove from school variations or persistent or prove from school variations or persistent or persistent or persistent prove from school variations	i = Assessment of	information about employment and education, economic matters, housing, marital or family discord, social networks and the phys	sical and mental he	alth of the family members.	Score range 0-6, 6=severe fa	mily difficulties.				
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). I = 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. m = SES: Socioeconomic status n = CD1: Children's depression Inventory. Cut off point >/= 13 indicating depressive symptoms Identified base line factors without association to persistent musculoskeletal pain, divided in pain type (study ID) Musculoskeletal 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 variables.	j = Subjective disa	ability 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, pa	in disturbs hobbie:	s. Range 0-5.			
I = 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.         m = SES: Socioeconomic status	<b>k</b> = The modified	Hannover functional ability Questionnaire HFAQ assesses whether pain and ache in low back make any of the following daily activity	ties difficult: reach	ing up to get a book from a hi	gh shelf, carrying your schoo	I bag to school, sit	ing on a school chair for a 45	-min lesson, standing in a queu	e for 10	
m = SES: Socioeconomic status       Image: Second status	min, sitting up in b	ped from a lying position, bending down to put your socks on, standing up from an armchair at home, running fast to catch a bus, an	d sports activities a	t school. Low = 0-1 limitation,	moderate = 2-3 limitations o	r high = 4-9 limitat	tions (23).			
m = SES: Socioeconomic status       Image: Second status	I = Yunus criteria:	pain modulation by physical activity, by weather, by anxiety and stress, poor sleep, headache, irritable bowel, soft tissue swelling in h	nands and feet, fati	gue, numbness in hands and f	eet, feeling excited and nerv	ous. Yes to minim	um 3 symptoms to meet the	e Yunus criteria.		
Identified baseline factors without association to persistent musculoskeletal pain, divided in pain type (study ID)       Image: study ID       Image: study ID <th image:="" study<="" td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></th>	<td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>									
Musculosketal 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 v	n = CDI: Children	's depression Inventory. Cut off point >/= 13 indicating depressive symptoms								
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 v	Identified ba	seline factors without association to persistent musculoskeletal pain, divided in pain type (study ID)								
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 v			onsumption. u	nisex: smoking pack ver	ars, body mass index (B	MI) (24)				
							e), abscence one day o	or more from school vs.	never	
peing aspeent due to pain, maximum volume O2 intake (per unit increase) measured during a snuttle run test (21)							,			
2										
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml		<b>–</b> – – – – – – – – – – – – – – – – – –								

#### BMJ Open

	Headache, stomachache, depressive feelings, difficulty			*		obility (28)			
	Male: physical activity level, sitting >4 h/day, sleep </td <td>= 7 h/day, smoking and overweight.</td> <td>Female: externalization</td> <td>on, sitting &gt; 4h/da</td> <td>y, overweight (33)</td> <td></td> <td></td> <td></td> <td></td>	= 7 h/day, smoking and overweight.	Female: externalization	on, sitting > 4h/da	y, overweight (33)				
	Increasing age (20, 27)								
	Increasing age, sex, family history of related diseases,	VAS score assessed by physicians, el	evated C-reactive prot	ein (CRP), erythroo	cyte sedimentation rate	ESR), platelet coun	, lower score in p	sychosocial function	oning reflecting m
	health and functioning at school/work, within the far	nily, with friends and in other social	l activities (Children's	Global Assessme	nt Scale, CGAS) (22)				
w back	Extension strength (minutes) and plain saggital mobil								
	Akward trunk postures, physically demanding job (wo		ard trunk posture and	standing or walki	ing) working regularly o	r irregularly duratio	n of work work w	ith specific physic	al load factors (3
	BMI (32)		and durine postare and	i standing of wark	ing,, working regularly c	rinegulary, duluar		nui speenie priyste	
	Male: smoking 5-7 d/week vs. no smoking, smoking	c) aigarattas (day (20)							
	High emotional vs. low emotional problems, reaching		onding down to put	on cocks high co	nduct problems high l	whoractivity high n	rececial hohavior	widespread pain	hoodacha, stama
	in the past month compared to none, daytime tiredne								
	Sex, increasing age, tobacco, profession: hairdresser and		ician, western ethnici	ty compared to no	on-western ethnicity, mo	derate/righ vs. lov	/ socio-economic	status (SES) (m), m	oderate/nign vs. i
	physical activity level, BMI, moderate/high physical w								<u>_</u>
nee	Increasing age compared to 15, participation in sports			,	<u>,                                     </u>	ared to monthly (34	+)		
	BMI, EQ-5D 50-75th percentile compared to 0-25th, r								
	After 1 year follow-up: traumatic limb at baseline, exe	rcise 3-4 t/week vs. 0-2 t, hypermob	ility score >/= 6 vs. <	<ol><li>After 4 years fol</li></ol>	llow-up: exercise freque	ncy 5-7 t/week vs. (	)-2 t, lower limb t	rauma at baseline.	Common after bo
werlimb	and 4 years follow-up: age 11-14 vs. 9-11, frequency	of exercise 2-4 times vs. once a week	k, multisite pain, fem	ale sex, headache,	stomachache, depressi	ve feelings, difficul	y falling asleep, da	ay tiredness, wakin	g up during night
	school abscence due to pain vs. never abscent, disabi	lity symptoms >/-3 vs -2 volum</td <td></td> <td>, ahove evercise fr</td> <td>equency 3-1 t/week vs</td> <td>0_2 + (11)</td> <td>, 0 ,,</td> <td></td> <td></td>		, ahove evercise fr	equency 3-1 t/week vs	0_2 + (11)	, 0 ,,		
eck	Joint hypermobility Beighton 6-9, physical activity at			above. exercise in	equence 3-4 0 week vs.				
	Sex, ethnicity, increasing age (39)								
adache	Sex (19)								
auacrie	Pain frequency, pain in daily activities, physiotherapy	relavation therapy sport activity st	ress at home or in ho	hhier nain on na	Instion pain threshold	measured by dolor	imeter depressive	symptoms temps	romandihular di
		, leiaxauon uleiapy, spolt activity, su	less at nome of mino	ubles, paili uli pa	ipauon, pain unesnoiu	ineasured by utili	inielei, uepiessive	symptoms, tempt	
									r
	stress at school, use of computer (25)								
	Stress (20)	· · · · · · · · · · · · · · · · · · ·							
idespread	Stress (20)	13 (n), Yunus criteria >/=3, sleep sco	re, disability index (f)	, psychosomatic s	symptoms (29)				
ick	Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p-	value.
ick	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ck	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ick	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ick	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.
Videspread ack	Stress (20) Female sex, increasing age, tender point count, CDI > 3 Stress (20)			101		nostic value wer	e reported with	RR, OR, and/or p	value.