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[Prognosis Protocol]

Overall prognosis of acute and chronic musculoskeletal, widespread, and neuropathic pain in children and adolescents

Laura RC Montgomery[1], Steven J Kamper[2], Zoe A Michaleff[3], Christopher M Williams[4], Amabile Dario[5], Paul Campbell[6], Alessandro Andreucci[7], Daniëlle AWM van der Windt[8], Kate M Dunn[9], Michael S Swain[10]

[1]Institute for Musculoskeletal Health, School of Public Health Faculty of Medicine and Health, The University of Sydney, Sydney, Australia. [2]School of Health Sciences, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia. [3]Institute for Musculoskeletal Health, School of Public Health, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia. [4]School of Medicine and Public Health, University of Newcastle, Callaghan, Australia. [5]The University of Sydney, Sydney, Australia. [6]School of Medicine, Keele University, Keele, UK. [7]Center for General Practice at Aalborg University, Aalborg, Denmark. [8]Department of Primary Care & Health Sciences, Keele University, Keele, UK. [9]School of Medicine, Keele University, Newcastle-under-Lyme, UK. [10]Department of Chiropractic, Macquarie University, Sydney, Australia

Contact: Steven J Kamper, steven.kamper@sydney.edu.au.

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (prognosis). The objectives are as follows:

We aim to describe the overall prognosis (focusing on the pain course) and the negative impact(s) of acute and chronic musculoskeletal, widespread, and neuropathic pain in children (aged six to 12 years) and adolescents (aged 13 to 18 years) by evaluating:

- incidence of pain recovery at three and 12 months after reporting acute or chronic pain;
- change in pain severity at three and 12 months after reporting acute or chronic pain; and
- negative impact(s) of pain at three and 12 months after reporting chronic pain.

BACKGROUND

Description of the health condition and context

All children and adolescents will experience pain before adulthood. Pain is an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (WHO 2021); it is a negative subjective experience influenced by biological, psychological, and social factors. Acute pain resolves within three months, whereas pain that persists or recurs intermittently beyond the expected time required for tissue healing (usually 12 weeks) is labelled chronic pain (WHO 2021). Pain related to recent trauma and tissue damage may be better understood and managed by children and parents (Eccleston 2021). However, chronic pain, seemingly unrelated to trauma and strongly associated with emotional distress and functional disability, can be hard to understand and manage appropriately (Eccleston 2021; WHO 2021).

Reported pain prevalence estimates vary considerably, owing to the wide range of measurement methods and pain definitions used. However, both acute and chronic pain are associated with older age, female sex, and lower socioeconomic status (King 2011; Shinde 2022). The estimated prevalence of acute pain in the self-care setting varies widely with age (between three-month old infants and 18-year-old adolescents) from 7% to 61.4% for dental pain, 2.1% to 56.6% for limb pain, 2.2% to 32.3% for temporomandibular pain, and 5% to 76.2% for neck, back and spinal pain (Shinde 2022). Up to 10% of six-year-olds have had musculoskeletal pain in the past three months, of whom one-third have chronic pain lasting longer (van den Heuvel 2020). One-third of older children (10 to 12 years) who experience acute musculoskeletal pain continue to have chronic pain at one and four years' follow-up (El-Metwally 2005). In addition, 40% of older adolescents (aged 15 to 19 years) with knee pain still report pain after five years (Rathleff 2019). In one study, 44.2% of adolescents (aged 11 to 15 years) reported some type of chronic weekly pain in the past six months, and 20.6% reported chronic weekly multisite pain (Gobina 2018). In older adolescents, the median prevalence of chronic back, musculoskeletal, or combination pain ranges from 11% to 38% (King 2011). Another trend in pain prevalence estimates is the increase over time (King 2011; Roy 2022; Stahl 2014). From 2001 to 2013, the prevalence of chronic back pain in 11- to 15-year-olds increased by 1% in younger males and by 7% in older females (Roy 2022). This trend highlights the significant and ongoing impact chronic pain will have on individuals and the community in the future (Woolf 2003).

Pain in youth is associated with significant individual, social, and financial burdens (Groenewald 2014; Huguet 2008; Vega 2018; Wojtowicz 2015). For example, low back and neck pain are among the three leading causes of years lived with disability worldwide in 15- to 19-year-olds (Mokdad 2016). Up to 50% of children and adolescents with chronic pain seek health care, 25% miss school and physical activity, and a minority report disrupted sleep (Huguet 2008; Kamper 2017; King 2011; Roth-Isigkeit 2005). In particular, chronic pain is associated with signs and symptoms of negative social development (poor autonomy, identity, and peer relations), anxiety, and depression (Jones 2021; King 2011; Ripamonti 2009). Children with chronic pain are likely to suffer recurrence and persistence of pain in adulthood, as well as increased impact (Brattberg 2004; Henschke 2015; Hestbaek 2006). For example, chronic pain in childhood is associated with a lower level of education, higher odds of receiving public aid, and social impairments 12 years later (Groenewald 2020; Murray 2020).

Considerable research efforts have been directed towards understanding the epidemiology, burden, and treatment of pain in adults; however, the same cannot be said for children and adolescents (Kamper 2017). There are multiple published and ongoing Cochrane Reviews on management strategies for chronic non-cancer-related pain in children and adolescents, including pharmacological interventions (Cooper 2017a; Cooper 2017b; Cooper 2017c; Cooper 2017d; Eccleston 2017) and non-pharmacological interventions (Fisher 2018; Fisher 2019; Yamato 2020). In 2020, the World Health Organization (WHO) released updated guidelines on managing chronic pain in children (WHO 2020), and in 2021, the Lancet Child & Adolescent Health Commission set future goals and priorities to improve research and management of pain in children and adolescents (Eccleston 2021). Childhood and adolescence are periods of marked physical, cognitive, social, and emotional growth and development. Therefore, childhood and adolescence are critical periods in which we need a comprehensive understanding of the prognosis of pain and the negative impact(s) it can have on education, healthcare decision-making, the evaluation and provision of therapy, and service delivery (Hemingway 2013; Riley 2013).

Health outcomes

Pain is a subjective experience, the practical and perceptional concepts of which will be understood differently by the child or adolescent and their parent or guardian. In children old enough to articulate their pain experience (approximately age four), self-report measures are preferable to proxy-report measures (Huguet 2010; Tsze 2013). In children younger than seven years or in children and adolescents who are otherwise unable to comprehend a self-report measure, proxy-report measures are preferable (Kamper 2016). Use of a body pain diagram when reporting pain location increases the validity and reliability of the reported anatomical location(s) of pain in children aged over seven years (Southerst 2013; von Baeyer 2011). Proxy-report measures may under- or overestimate a child's pain experience and impact (Kamper 2016). This is not to say that the proxy report is wrong, rather that it reflects a different perception (i.e. that of the parent or guardian rather than the child or adolescent). For this reason, the two types of report are not interchangeable (Hemmingsson 2017). Approximately half of self- and proxy-report measures are in agreement: 43% to 51% for health-related quality of life (Sattoe 2012), and 52% to 68% for the presence of pain (Kamper 2016). Almost half (46%) of disagreements between self- and proxy-reports are minor for health-related quality of life (Sattoe 2012).

Pain severity or intensity is the most commonly measured pain outcome. Reliable tools for measuring acute pain intensity in children from age six years include the numeric rating scale 0–10 (NRS-11), faces pain scale-revised (FPS-R), and colour analogue scale (CAS). Less reliable tools include the visual analogue scale (VAS), Wong-Baker FACES pain rating scale, Pieces of hurt, Oucher photographic, and Oucher numeric. There are published reports of many other pain severity measures, but their validity and reliability are less certain owing to a relative lack of research.

Compared to acute pain, fewer studies have evaluated scales for measuring chronic pain intensity; however, the VAS and NRS-11 are the preferred self-report instruments for children aged six

years and older (Birnie 2019; Michaleff 2017). Better measures of chronic pain address the negative impact(s) of chronic pain on wider aspects of the child or adolescent's health and life. These measures include how the pain interferes with daily social, physical and recreational life; the individual's perception of their overall well-being; sleep quantity and quality; ability to perform physical activities; psychological and emotional well-being; and any adverse events associated with pain treatment (Palermo 2021).

Why it is important to do this review

Knowledge of the overall prognosis (focusing on pain course) and negative impact(s) of acute and chronic musculoskeletal, widespread, or neuropathic pain in children and adolescents is limited to individual studies or findings extrapolated from adult populations. Neither of these sources are sufficiently robust to inform clinical practitioners, researchers, policymakers, or the public. A comprehensive, high-quality systematic review is needed to provide clinicians with a contemporary and synthesised estimate of the prognosis of these pain conditions. Based on the results of this review, the next step will be to identify reliable risk and prognostic factors associated with the development or persistence of chronic musculoskeletal, widespread, and neuropathic pain, to help clinicians assess their patient's risk of developing these conditions and tailor treatment approaches accordingly. For example, people at low risk of developing chronic musculoskeletal, widespread, or neuropathic pain are likely to recover with minimal care. In contrast, those at high risk will likely require more comprehensive, multidisciplinary care.

Several systematic reviews have aimed to identify factors associated with persistent pain in children and adolescents. Pate 2020 reported prognostic factors for persistent pain and functional disability. In 2019, Pourbordbari and colleagues updated an earlier review by Huguet and colleagues, which identified prognostic factors for chronic musculoskeletal pain (Huguet 2016; Pourbordbari 2019). Neither of these reviews examined the overall prognosis, persistence, or negative impact(s) of musculoskeletal, widespread, or neuropathic pain on the lives of children and adolescents. Our review will address this gap in knowledge and provide estimates of the overall prognosis and course of these conditions. This information is critical to providing evidence-based education to service providers, patients, and their families, and to accurately evaluate the effectiveness of treatment strategies.

OBJECTIVES

We aim to describe the overall prognosis (focusing on the pain course) and the negative impact(s) of acute and chronic musculoskeletal, widespread, and neuropathic pain in children (aged six to 12 years) and adolescents (aged 13 to 18 years) by evaluating:

- incidence of pain recovery at three and 12 months after reporting acute or chronic pain;
- change in pain severity at three and 12 months after reporting acute or chronic pain; and
- negative impact(s) of pain at three and 12 months after reporting chronic pain.

METHODS

Criteria for considering studies for this review

Types of studies

We will include peer-reviewed, published, retrospective and prospective longitudinal studies (e.g. observational cohorts, electronic health records, and comparative epidemiology studies). These study types can provide accurate prognostic estimates that are generalisable to a wider population (Iorio 2015). We will exclude cross-sectional studies, case reports, case-control studies, and case series, as these study designs cannot provide data of value regarding overall prognosis. We will also exclude pilot studies, feasibility studies, and randomised controlled trials. These studies tend to include small selective cohorts of people who undergo a specific intervention; as such, they do not represent typical patient populations (Iorio 2015). We will exclude studies that have a follow-up period shorter than three months.

Targeted population

We will include studies whose participants, at enrolment, are children (aged six to 12 years) and adolescents (aged 13 to 18 years) with a pain condition. All age groups are as defined by the Medical Subject Headings (MeSH) thesaurus. At follow-up, at least 75% of participants should not have left adolescence (aged 19 years or younger), or the mean age of participants should be 19 years or younger. Studies with a mixed population of adults and children/adolescents will be eligible for inclusion if there are separate data for the children/adolescents, or if at least 75% of participants were aged 19 years or younger at follow-up, or if the average age of participants is 19 years or younger at follow-up.

We will include studies where participants, at enrolment, report a minimum pain severity of at least 3/10 on an NRS (or equivalent on other scales, e.g. face two on the FPS-R) or at least monthly pain frequency (Hirschfeld 2013; Kamper 2018). We will include the following pain categories, as defined by the International Classification of Diseases 11th Revision (ICD-11; WHO 2021).

- Acute pain (less than 12 weeks' duration; ICD-11 code MG31), including specified single- or multisite pain with actual or potential tissue damage;
- Chronic pain (more than 12 weeks' duration; ICD-11 code MG30) with a persistent or intermittent time-based pattern
  - Chronic primary pain (pain of unknown aetiology; ICD-11 code MG30.0)
    - Chronic widespread pain (including fibromyalgia and multisite pain; ICD-11 code MG30.01)
    - Chronic primary musculoskeletal pain (muscle, bone, joint, or tendon pain; ICD-11 code MG30.20)
    - Complex regional pain syndrome (ICD-11 code MG30.04)
  - Chronic secondary musculoskeletal pain (muscle, bone, joint, or tendon pain with known local or systemic aetiology; ICD-11 codes MG30.3 and MG30.31)
  - Chronic neuropathic pain (pain due to lesion of the central or peripheral nervous system with known local or systemic aetiology; ICD-11 code MG30.5)
  - Chronic post-traumatic pain (chronic pain following acute tissue damage; ICD-11 code MG30.20)

If a study reports multiple pain conditions, it will be eligible for inclusion if one or more pain conditions meet the above criteria and are reported separately.

To maintain the focus of this review on musculoskeletal, widespread, and neuropathic pain conditions, we will exclude studies that recruit participants with pain secondary to cancer (MG30.1), infection, rheumatological conditions including juvenile idiopathic arthritis (MG30.30), neurological disease including cerebral palsy (MG30.32), autoimmune disease, or metabolic disorder; abdominal or visceral pain due to mechanical, vascular and inflammatory disorder (MG30.00 and 30.4); headache including migraine (MG31.1, MG30.03, and MG30.6); and iatrogenic causes including medication side effects and procedural or postsurgical pain (MG31.2 and 30.21). The different pathogenesis of these known diseases would affect secondary pain prognosis and reduce the applicability of our findings.

Types of outcomes

We will include the following outcomes to assess the overall prognosis, focusing on the pain course and the negative impact(s) of musculoskeletal, widespread, and neuropathic pain in children and adolescents.

Primary

- Pain recovery: reported as the proportion of participants who experience recovery from pain (i.e. absolute risk) at three and 12 months or the closest reported time period. We will define recovery from acute pain as 0/10 and recovery from chronic pain as 2/10 or lower on an NRS, or the equivalent on other measures of pain intensity (Kamper 2010).
- Pain severity: reported as a change in pain intensity at three and 12 months, or the closest reported time period. We will accept the included studies' measures of pain intensity (e.g. NRS-11, VAS, FPS-R, CAS, Pieces of Hurt, Oucher, or faces scales).

Secondary

We will report the negative impacts of chronic pain at three and 12 months or the closest reported time period. We will report health outcomes as expressed in included studies. These may include, but are not limited to:

- pain-related disability (i.e. Functional Disability Inventory, Pediatric Quality of Life Inventory, Health-Related Quality of Life):
- school/work absence;
- level of participation in physical activity (i.e. objectively measured via accelerometer or pedometer, or subjectively measured via a validated survey);
- sleep duration or quality;
- chronic pain comorbidities, depression, and anxiety (i.e. Children's Depression Inventory, Revised Child Anxiety and Depression Scale, Fear of Pain Questionnaire Child);
- overall wellbeing;
- healthcare use over time; and
- adverse events from treatment.

We will accept any valid and reliable measure reported in included studies. We will place no restrictions on the method of assessment (i.e. self- or proxy-report measures). We will acknowledge the use of proxy-report measures in our risk of bias assessment and perform a sensitivity analysis to assess the effect on outcomes. If a study reports both self- and proxy-report measures, we will extract self-report data only. We will accept the moment of prognostication as the point of entry into the study or point of data provision where acute pain is less than 12 weeks duration and chronic pain is more than or equal to 12 weeks duration.

Search methods for identification of studies

Electronic searches

We will search the following databases without language or date restrictions:

- MEDLINE (via Ovid; 1946 onward);
- Embase (via Ovid; 1980 onward);
- CINAHL (via EBSCO; 1982 onward);
- PsycINFO (via EBSCO; 1806 onward); and
- LILACS (Birme; 1982 onward).

We developed the search strategy for MEDLINE with assistance from the PaPaS Review Group Information Specialist, and we will tailor the strategy to the remaining databases (see Appendix 1). Our search includes Irvin's search string for prognosis reviews (Boulos 2021). The Information Specialist will perform the searches.

Searching other resources

We will check reference lists of included studies and relevant reviews for additional studies, and perform forward citation tracking on key articles on Web of Science. We will contact experts in the field for important studies that may have been missed. We will contact study authors for additional information where necessary.

Data collection

Selection of studies

We will enter search results into Covidence systematic review software (Covidence). Two review authors will independently screen search returns after deduplication. We will first screen titles and abstracts to eliminate obviously ineligible records, then assess the full texts of the remaining records against our inclusion and exclusion criteria. We will resolve any disagreements through discussion, or by involving a third review author if necessary. Where studies partially overlap with inclusion criteria, we will document our decision to include or exclude them. Appendix 2 contains a list of preliminary selected studies.

Data extraction and management

Two review authors will independently extract included study data into a CHARMS data extraction form, modified a priori (Moons 2014; Riley 2019; see Appendix 3). We will extract the following details.

- Source of data: study design (including prospective or retrospective), aim, funding, author conflicts of interest
- Participants: recruitment method, sample size, geographical and contextual setting, inclusion and exclusion criteria, age and sex distribution, natural or clinical course, and any intervention/treatment received
- Pain condition(s): condition, description

- Pain recovery: measurement method, proportion with the condition at baseline and follow-up, definition of recovery, proportion recovered
- Pain severity: measurement method, mean pain severity at baseline and follow-up, minimally important difference (MID)
- Negative impact: definition of each outcome of interest, measurement method, number of participants with the outcome, MID
- Analysis: missing data, method of analysis, results (including estimate and measure of variance), covariates included in the analysis

We will pilot the data extraction form and make any necessary changes before completing independent study extraction. If we identify multiple reports for the same study, we will collate them so that each study, rather than each report, is the unit of interest in the review. We will resolve any disagreements through discussion or by involving a third review author, if necessary.

Assessment of risk of bias in included studies

Two review authors will independently apply a QUIPS risk of bias assessment, modified a priori (see Appendix 4). This will include rating each study at 'high', 'unclear' or 'low' risk of bias in the domains of study participation, study attrition, health outcome measurement (overall prognosis), health outcome measurement (pain impact), and statistical analysis and reporting. Two domains usually included in the QUIPS risk of bias assessment (prognostic factor measurement and study confounding) are not applicable to overall prognosis reviews (Iorio 2015). We will apply our modified QUIPS risk of bias tool as follows.

- Study participation: we will rate studies at high risk of bias for this domain if there is poor participation in the study by eligible persons, as health outcomes are very likely to be different for study participants and eligible non-participants. We will also assign a high risk of bias to retrospective studies where high study participation may be misleading due to participant selection based on data availability. Where there is good participation and prospective study design, we will assign a low risk of bias; unless we rate one other criterion as high risk or three as unclear risk, in which case we will consider the study at unclear risk of bias related to study participation.
- Study attrition: studies that have less than 85% of included participants at final follow-up will be at high risk of bias, likewise retrospective studies where low attrition may be misleading due to participant selection based on data availability. When at least 85% of participants complete follow-up, health outcomes are unlikely to be different for completing and non-completing participants, so we will rate the study at low risk of attrition bias; unless we have rated one other criterion as high risk or three as unclear risk, in which case we will consider the study at unclear risk of attrition bias.
- Health outcome measurement (overall prognosis and pain impact): we will consider a study at high risk of bias for these domains where the method of outcome measurement has poor reliability and validity and is, therefore, likely to be different between participants, and where proxy-report measures are used in place of self-report measures in children aged six years or over who are able to comprehend pain. Where the outcome measure is both valid and reliable, we will judge the study at low risk of bias; unless we rate two other criteria at high or unclear risk, in which case we will consider the study at unclear risk for this domain.
- Statistical analysis and reporting: we will rate a study at high risk of bias related to analysis or reporting where there is insufficient data to assess analytic strategy and model-building process, and the results are selectively reported. We will assign a low risk of bias where analytic strategy and model-building process are sufficiently outlined and all results are adequately reported. Where a study meets part of each of these criteria, we will rate it at unclear risk of bias.
- We will rate the overall risk of bias as low when three of the five domains (including study attrition) score low, high when three of the five domains (including study attrition) score high, and unclear when a study does not meet the overall low or overall high risk of bias criteria. We will use the overall risk of bias in our sensitivity analyses and GRADE application.

We will resolve any disagreements through discussion or by involving a third review author, if necessary.

Measures of prognosis

Pain recovery and pain severity measures

- We will present the proportion of participants who recover from pain with a measure of variance (e.g. 95% confidence interval (CI), standard error (SE)).
- We will present the mean difference (MD) in pain severity with a measure of variance. Where measurement scales differ across studies, we will present the standardised mean difference (SMD).

Negative pain impact measures

- We will present continuous pain impact outcomes as MDs and measures of variance where measurement scales are the same across included studies. Where measurement scales are different, we will present SMDs and measures of variance.
- We will present categorical pain impact outcomes as the proportion of participants experiencing the impact with a measure of variance. We will convert measures in line with the majority of studies (e.g. we will convert risk ratios (RRs) to odds ratios (ORs) if most studies report ORs). We will present the ratio and measure of variance (e.g. 95% CI, SE).

Where studies report differences in relation to groups without pain (e.g. in comparative epidemiological studies) or between relevant subgroups, we will present absolute values for those subgroups. We will not report relative measures (e.g. based on age or sex). We will extract both unadjusted and adjusted measures, including the set of adjustment factors included in estimates of pain course and impact. Where individual studies report MIDs, we will extract these data, as the MID will vary depending on the type of reporting (self or proxy) and baseline presentation (i.e. a small change may be more significant for a child experiencing more severe pain; Ebrahim 2017).

Dealing with missing data

Where possible, we will calculate the missing data from raw data (e.g. proportion changed or MD) or contact the study authors for additional or missing information. If we cannot retrieve or calculate the necessary information, we will document this and consider the possible impact of the missing data on the risk of bias for each study and on the certainty of the evidence for the overall review.

We will also compare the characteristics of studies included and excluded from the meta-analysis based on missing data and report differences in study samples.

Assessment of heterogeneity

We will perform meta-analyses if we identify at least two studies that provide clinically and methodologically homogeneous data for the same outcome. Data permitting, we will perform subgroup analyses based on study-level characteristics. We will visually inspect forest plots for variation in point estimates and overlapping CIs and assess the I^2 and Tau^2 statistics. We will interpret the I^2 statistic as follows, in accordance with the *Cochrane Handbook for Systematic Reviews for Interventions* (Higgins 2019):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

If subgroup analyses are not possible, we will provide a narrative synthesis of clinical and methodological differences, which may explain variance in pain course and negative impact(s).

Assessment of reporting deficiencies

If we include at least 10 studies in a meta-analysis, we will create and inspect funnel plots to assess reporting bias (Riley 2016). If meta-analysis is not applicable, we will not run any tests or investigations for reporting deficiencies.

Data synthesis

Data synthesis and meta-analysis approaches

We will report our findings as a narrative synthesis. We will synthesise the outcomes pain recovery and pain severity in children and adolescents at three and 12 months (or the closest reported time frames) after reporting acute pain or chronic pain, and negative impact(s) of pain in children and adolescents at three and 12 months (or the closest reported time frames) after reporting chronic pain. We will summarise the results for our primary outcomes in a summary of findings table (Appendix 5).

We expect a high level of methodological and clinical heterogeneity, which would limit the possibility of performing meta-analyses. However, we will perform random-effects meta-analyses in STATA/IC if at least two studies provide clinically and methodologically homogeneous data for the same outcome. We will complete meta-analyses in the same manner as described in 'Assessment of heterogeneity'.

Subgroup analysis and investigation of heterogeneity

Data permitting (at least two studies), we will perform subgroup analyses to investigate heterogeneity related to:

- age;
- sex;
- socioeconomic status;
- ethnicity;
- pain diagnosis/type;
- pain severity at baseline; and
- specific populations (e.g. specialist-based, elite sporting).

Pain is associated with older age, female sex, and lower socioeconomic status (King 2011). Research suggests that ethnicity influences pain beliefs, cognition, and behaviour (Orhan 2018).

Sensitivity analysis

Data permitting (at least two studies), we will perform sensitivity analyses to assess the robustness of our results. We will assess the effect of:

- risk of bias on outcomes, by excluding studies with an overall high risk of bias from analyses;
- high study attrition in retrospective studies where participants may be recruited based on the availability of outcome data, by excluding these studies from analyses; and
- self- and proxy-reported pain measures, by excluding proxy-reported measures from analyses.

Assessment of the quality of the evidence

We will use an adapted GRADE framework for prognosis research (Hayden 2014; Iorio 2015). Two review authors will independently apply the GRADE criteria for each review outcome. We will consider the body of evidence from longitudinal cohort studies that we anticipate including in the review to be of high certainty initially (Iorio 2015). We will downgrade the certainty of the evidence by one or two levels for study limitations (risk of bias), inconsistency, imprecision, indirectness, and publication bias. We will upgrade by one level for moderate to large effect size and exposure-response trend (Appendix 6). We will rate the certainty of evidence as high, moderate, low, or very low. We will resolve any disagreements through discussion or by involving a third review author, if necessary.

Conclusions and summary of findings

We will report a qualitative narrative review and, data permitting, quantitative results of meta-analyses in a summary of findings table (Appendix 5). We will summarise our findings for our primary outcomes (incidence of pain recovery and change in pain severity in children and adolescents at three and 12 months after reporting acute or chronic pain) and for negative impact(s) in children and adolescents at three and 12 months after reporting chronic pain, although we will only include our primary outcomes in the summary of findings table.

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Editorial and peer-reviewer contributions

The Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS) supported the authors in the development of this review.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Dr Neil O'Connell, PaPaS Co-ordinating Editor, and Reader at Brunel University London

- Managing Editor (conducted editorial checks and supported editorial team): Anna Erskine (Oxford University Hospitals (OUH) NHS Foundation Trust, Oxford, UK)
- Assistant Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Kerry Harding (Oxford University Hospitals (OUH) NHS Foundation Trust, Oxford, UK)
- Copy-editing (initial copy-edit and final proofread): Julia Turner
- Peer-reviewers (provided comments and recommended an editorial decision): Jonanne Abbott, Information Specialist with Cochrane PaPaS (search review); Helmar Bornemann-Cimenti (clinical/content review); M. Dulce Estêvão, School of Health, University of Algarve, Faro, Portugal (consumer review); Nuala Livingstone, Evidence Production and Methods Directorate (methods review); Tamara Kredo, South African Medical Research Council (clinical/content review); Ewan McNicol, MCPHS University, Boston, Massachusetts, USA (clinical/content review); Dr Manasi Murthy Mittinty, PhD MD, Lecturer University of Sydney (clinical/content review); Katrina Williams, Department of Paediatrics, Monash University and Developmental Paediatrics, Monash Children's Hospital, Convenor for Cochrane Prognosis Methods Group, Director of Cochrane Child Health Field and Editor of Cochrane Developmental, Psychosocial and Learning Problems Group (methods review).

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APPENDICES

Appendix 1. MEDLINE search strategy

1. Child/

2. (child* or boy* or girl* or preadolescen* or prepube* or preteen* or pre-teen* or pre-pubube* or pre-adolescen* or schoolchild*).tw.

3. Adolescent/

4. (adolescen* or juvenile* or teen* or youth* or young adult*).tw.

5. 1 or 2 or 3 or 4

6. Pain/

7. Acute Pain/

8. chronic pain/

9. (pain* adj3 (acute or chronic or persistent or episodic or intermittent or recurrent or widespread or multisite or multi-site or multiple site or regional or neuropathic)).tw.

10. Back Pain/

11. Low Back Pain/

12. Neck Pain/

13. backache*.tw.

14. ((back or spin* or thoracic or midback or lumbar or neck or cervical) adj3 (pain* or ache* or complaint* or symptom* or discomfort)).tw.

15. Musculoskeletal Pain/

16. Arthralgia/

17. Fibromyalgia/

18. Complex Regional Pain Syndromes/

19. (pain* adj3 (hand* or wrist* or elbow* or shoulder* or upper limb* or upper extremit* or foot or feet or ankle* or knee* or hip* or lower limb* or lower extremit* or peripheral or muscle* or ligament* or bone* or tendon* or joint*)).tw.

20. chest pain/

21. Flank pain/

22. Pelvic pain/

23. (pain* adj3 (pelvis or pelvic or flank or waist or chest or rib*)).tw.

24. or/6-23

25. Cancer Pain/

26. Pain, Postoperative/

27. Pain, Procedural/

28. Breakthrough Pain/

29. Pain, Intractable/

30. 25 or 26 or 27 or 28 or 29

31. 24 not 30

32. Prognosis/

33. (prognos* or predict*).tw.

34. Cohort Studies/

35. incidence.tw.

36. Mortality/

37. Follow-Up Studies/

38. Survival Analysis/

39. Prospective Studies/

40. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39

41. 5 and 31 and 40

42. exp animals/ not humans.sh.

43. 41 not 42

Appendix 2. Preliminary study selection

1. 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.
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6. 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.
7. 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 1999;88(10):1119-24
8. Mikkelsson M, El-Metwally A, Kautiainen H, Auvinen A, Macfarlane GJ, Salminen JJ. Onset, prognosis and risk factors for widespread pain in schoolchildren: a prospective 4-year follow-up study. Pain 2008;138(3):681-7.
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Appendix 3. Included study data extraction items

STUDY	First author

(Continued)

	Year (follow publication year with a, b, etc., if multiple in same year)
	Title
	Funding sources
	Conflict(s) of interest
Modified CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies)	
Source of data	Study design (prospective, e.g. cohort, case-control; or retrospective, e.g. registry data)
	Study aim
	Study cohort same as another study (Y/N, if yes which study?)
Participants	Recruitment method (e.g. consecutive selection, location, number of centres, setting (e.g. clinical, social media, phone, public))
	Year baseline study data were collected
	Duration of study, timing of follow-up(s)
	Setting – geographical location (city, state, country)
	Setting – social context (e.g. community, clinical, school, sporting, religious)
	Inclusion criteria
	Exclusion criteria
	Natural or clinical course? (i.e. report any treatment or intervention received, if provided, otherwise 'not reported')
Sample size	Sample size calculation performed? (Y (include how)/N/Unclear)
	Total number of included participants at baseline
	Age at baseline (mean, SD, range)
	Sex (% female)
	Total number of included participants at follow-up
	Age at follow-up (mean, SD, range)
	Sex (% female)
Pain condition and overall prognosis	Pain condition studied (add row per pain condition, i.e. multiple rows if multiple included pain conditions)
	Description of each pain condition studied (e.g. location, duration, pain criteria if provided, otherwise 'not reported')
	Chronic pain at baseline (Y/N/Unclear)

(Continued)

	Description of recovery or not for each pain condition (otherwise 'not reported')
	Measurement method including scale/tool
	Is the outcome tool validated? (Y/N/Unclear)
	Total number of participants with pain outcome at baseline
	Time of outcome occurrence or summary of duration of follow-up
	Total number of participants with pain outcome at follow-up
	Proportion (and measure of variance, e.g. 95% CI, SE) of participants recovered at follow-up (has to meet the definition of recovered or persistence in manuscript, i.e. not just absence of pain)
	Proportion (and measure of variance, e.g. 95% CI, SE) of participants who experience persistence of pain at follow-up (has to meet the definition of unrecovered or persistence of outcome in manuscript i.e. not just presence of pain)
Pain course outcome(s)	Definition of pain severity
	Measurement method including scale/tool
	Is the outcome tool validated? (Y/N/Unclear)
	Minimally important difference reported in the study
	Mean measure at baseline (and measure of variance, e.g. 95% CI, SE)
	Time of outcome occurrence or summary of duration of follow-up
	Mean measure at follow-up (and measure of variance, e.g. 95% CI, SE)
Pain impact outcome(s)	Definition of each pain impact outcome of interest including unit of measure (i.e. pain-related disability, self-rated health (e.g. short form questionnaire, QoL), school/work absence, level of participation in physical activity, sleep duration or quality, health care use (e.g. consultation, medication))
	Measurement method including scale/tool
	Is the outcome tool validated? (Y/N/Unclear)
	Time of outcome occurrence or summary of follow-up duration
	Total number of participants with pain outcome at follow-up
Missing data	Number of participants with any missing value (pain prognosis, pain course and pain impact outcomes)
	Number of participants with missing data for each outcome of interest (pain prognosis, pain course or pain impact outcomes)
	Details of attrition (loss to follow-up) and, for time-to-event outcomes, number of censored observations (ideally in each category for categorical prognostic factors of interest)
	Handling of missing data (e.g. complete case analysis, imputation, other methods)

(Continued)

	Missing data calculated (include method of calculation)
	Attempt to contact study authors for missing data (Y/N/No response)
Analysis	Modelling method (e.g. linear, logistic, Cox, parametric survival, competing risks regression)
	Modelling assumptions checked? (Y (include how)/N/Unclear)
	Reason for selection of covariates included in multivariable modelling (e.g. all candidate covariates considered, preselection of established covariates, retain only those significant from univariable analysis)
	Method for selection or exclusion of covariates during multivariable modelling (e.g. backward or forward selection, full model approach including all factors regardless), and criteria used for any selection or exclusion (e.g. P-value, Akaike information criterion)
	Method of handling each covariate (e.g. dichotomisation, categorisation, linear, non-linear), including values of any cutoff points used and their justification; for non-linear trends, the method of identifying non-linear relationships (e.g. splines, fractional polynomials)
Results	Unadjusted or adjusted effect estimates
	Estimate type i.e. RR/OR/HR/mean change for each outcome of interest
	Estimate
	Lower 95% confidence
	Upper 95% confidence
	SE
	Details of any non-linear relationships and whether modelling assumptions hold; in particular, for time-to-event outcomes, any evidence of non-proportional hazards (non-constant HRs) for each outcome of interest
	Set of covariates used in the adjusted analysis
Interpretation and discussion	Interpretation of the presented results
	Comparison with other studies, discussion of generalisability, strengths and limitations

CI: confidence interval; HR: hazard ratio; OR: odds ratio; QoL: quality of life; RR: risk ratio; SD: standard deviation; SE: standard error.

Appendix 4. Modified QUIPS risk of bias form

STUDY	First author
	Year (follow publication year with a, b, etc. if multiple in the same year)
	Title
Modified QUIPS (QUality In Prognostic Studies) domains	

(Continued)

1. Study participation (study sample adequately represents the population of interest)	a. Adequate participation in the study by eligible persons	*Notes*
		Yes/No/Unclear
	b. Description of the source population or population of interest	*Notes*
		Yes/No/Unclear
	c. Description of the baseline study sample	*Notes*
		Yes/No/Unclear
	d. Adequate description of the sampling frame and recruitment	*Notes*
		Yes/No/Unclear
	e. Adequate description of the period and place of recruitment	*Notes*
		Yes/No/Unclear
	f. Adequate description of inclusion and exclusion criteria	*Notes*
		Yes/No/Unclear
Domain rating	**High** (health outcomes are very likely to be different for participants and eligible non-participants)	
	Unclear (health outcomes may be different for participants and eligible non-participants)	
	Low (health outcomes are unlikely to be different for participants and eligible non-participants)	
2. Study attrition (available study data (i.e. participants not lost to follow-up) adequately represent the study sample)	a. Adequate response rate for study participants	*Notes*
		Yes/No/Unclear
	b. Description of attempts to collect information on participants who dropped out	*Notes*
		Yes/No/Unclear
	c. Reasons for loss to follow-up are provided	*Notes*
		Yes/No/Unclear
	d. Adequate description of participants lost to follow-up	*Notes*
		Yes/No/Unclear
	e. There are no important differences between participants who completed the study and those who did not	*Notes*
		Yes/No/Unclear
	f. Is follow-up sufficiently long?	*Notes*
		Yes/No/Unclear
Domain rating	**High** (health outcomes are very likely to be different for completing and non-completing participants)	

(Continued)

	Unclear (health outcomes may be different for completing and non-completing participants)	
	Low (health outcomes are unlikely to be different for completing and non-completing participants)	
3. Prognostic factor measurement (the prognostic factor is measured in a similar way for all participants)	*Not applicable for reviews of overall prognosis*	
4a. Health outcome measurement – overall prognosis and pain course (the outcome of interest is measured in a similar way for all participants)	a. A clear definition of overall prognosis outcome is provided	*Notes*
		Yes/No/Unclear
	b. Method of overall prognosis outcome measurement used has adequate validity and reliability	*Notes*
		Yes/No/Unclear
	c. Method and setting of overall prognosis outcome measurement are the same for all study participants	*Notes*
		Yes/No/Unclear
Domain rating	**High** (measurement of overall prognosis is very likely to be different for participants)	
	Unclear (measurement of overall prognosis may be different for participants)	
	Low (measurement of overall prognosis is unlikely to be different for participants)	
4b. Health outcome measurement – pain impact (outcome of interest is measured in a similar way for all participants)	a. A clear definition of pain impact outcome is provided	*Notes*
		Yes/No/Unclear
	b. Method of pain impact outcome measurement used is adequately valid and reliable	*Notes*
		Yes/No/Unclear
	c. The method and setting of pain impact outcome measurement is the same for all study participants	*Notes*
		Yes/No/Unclear
Domain rating	**High** (measurement of pain impact is very likely to be different for participants)	
	Unclear (measurement of pain impact may be different for participants)	
	Low (measurement of pain impact is unlikely to be different for participants)	
5. Study confounding (important potential confounding factors are appropriately accounted for)	*Not applicable for reviews of overall prognosis*	
6. Statistical analysis and reporting (statistical analysis is appropriate, and all primary outcomes are reported)	a. Sufficient presentation of data to assess the adequacy of the analytic strategy	*Notes*
		Yes/No/Unclear

(Continued)

	b. Strategy for model building is appropriate and is based on a conceptual framework or model	*Notes*
		Yes/No/Unclear
	c. The selected statistical model is adequate for the design of the study	*Notes*
		Yes/No/Unclear
	d. There is no selective reporting of results	*Notes*
		Yes/No/Unclear
Domain rating	**High** (reported results are very likely to be spurious or biased related to analysis or reporting)	
	Unclear (reported results may be spurious or biased related to analysis or reporting)	
	Low (reported results are unlikely to be spurious or biased related to analysis or reporting)	

Appendix 5. Draft summary of findings table

Outcomes	**No of participants** (studies)	**Estimate** Pain recovery: incidence % (95% CI) Pain intensity: mean pain intensity (95% CI)	**Certainty of the evidence** (GRADE)	**Comments**
Recovering from acute pain or developing chronic pain within 3 and 12 months (or nearest time point) of reporting *acute* pain				
Pain recovery				
3 months				
12 months				
Pain intensity				
3 months				
12 months				
Recovering from chronic pain or persistence of chronic pain within 3 and 12 months (or nearest time point) of reporting *chronic* pain				
Pain recovery				
3 months				

(Continued)

12 months
Pain intensity
3 months
12 months
CI: confidence interval.

Appendix 6. Modified GRADE assessment for judging overall certainty of evidence for prognosis[a]

Domain	Explanation
Downgrading certainty of the evidence	
Study limitations	There are serious study limitations where most evidence is rated as overall high risk of bias (downgrade one level). There are very serious study limitations where the majority of evidence is rated as overall high risk of bias (downgrade two levels). • *Unless sensitivity analysis explains methodological heterogeneity, i.e. there is a difference in point estimates between studies of overall low risk of bias and overall high risk of bias.*
Inconsistency	There is variability in point estimates across studies with little overlap of CIs. I^2 statistic > 50% representing heterogeneity of substantial or considerable importance (downgrade one level). • *Unless subgroup analysis explains clinical heterogeneity that exists in results.*
Imprecision	There are too few studies to perform a meta-analysis, AND The effect on the participant or clinical action would differ depending on the upper and lower bounds of the CI, OR There are excessively wide CIs about the pooled point estimate, especially if they span the value with no effect (downgrade one level)
Indirectness	A minority of study samples correspond to the population of interest, or a minority of study outcomes capture what is believed to be important (which reduces the generalisability or applicability of results; downgrade one level).
Publication bias	There is evidence of reporting deficiencies and publication bias, or the overall prognosis has not been repeatedly investigated (downgrade one level).
Upgrading certainty of the evidence	
Effect size	There is a moderate to large effect size reported by most studies or the pooled effect estimate (upgrade one level).

(Continued)

Effect trend	There is evidence of a well-defined pattern (linear or otherwise) suggesting an exposure-response gradient (upgrade one level).

Interpretation of GRADE ratings

Level	Explanation
High	We are very confident that the true prognosis lies close to that of the estimate.
Moderate	The true prognosis is likely to be close to the estimate, but there is a possibility that it is substantially different.
Low	We have low confidence in the estimate: the true prognosis may differ substantially from the estimate.
Very low	We have very little confidence in the estimate: the true prognosis will likely differ substantially from the estimate.

[a] GRADE application and levels of confidence were adopted from Iorio 2015 and Hayden 2014.
CI: confidence interval

CONTRIBUTIONS OF AUTHORS

Conception of review: LM, SK, ZAM, CW, ABD, PC, AA, DvdW, KD, MS
Drafting of review protocol: LM, SK, ZAM, CW, ABD, PC, AA, DvdW, KD, MS
Co-ordination of review protocol: LM

DECLARATIONS OF INTEREST

LM: LM works as a PhD candidate and receives personal funding from the Chiropractic Australia Research Foundation and travel funding from the University of Sydney. LM also works as a casual academic at Macquarie University and as a Chiropractor in private practice.
SK: SK is employed by the University of Sydney as a Professor of Allied Health. He receives fellowship funding from the National Health and Medical Research Council of Australia, paid to his employer to support his salary.
ZAM: ZAM is a Research Operations Manager, Northern New South Wales Local Health District. ZAM is an author of the following study: Michaleff et al. Child and adolescent musculoskeletal pain (CAM-Pain) feasibility study: testing a method of identifying, recruiting and collecting data from children and adolescents who consult about a musculoskeletal condition in UK general practice. BMJ Open. 2018;8:6.
CW: CW is an Associate Professor at the University of Sydney and works as a health professional for Hunter New England Health District. CW has no known financial or non-financial interests to declare in connection to this review.
ABD: ABD is an Academic Fellow at The University of Sydney and has no known financial or non-financial interests to declare in connection to this review.
PC: PC is an Honorary Reader at Keele University and Senior Research Associate at Midlands Partnership NHS Foundation Trust and has no known financial or non-financial interests to declare in connection to this review.
AA: AA is a post-doc researcher at the Center for General Practice at Aalborg University and has no known financial or non-financial interests to declare in connection to this review.
DvdW: DvdW is a Professor of Primary Care Epidemiology at Keele University and has no known financial or non-financial interests to declare in connection to this review.
KMD: KMD is a Professor of Epidemiology at Keele University with no known financial or non-financial interests in connection to the topic of the review. KMD is an author of a study that may be included: Shraim et al. Repeated primary care consultations for non-specific physical symptoms in children in the UK: a cohort study. BMC Fam Pract. 2014;15:195.
MS: MS works as a Senior Lecturer in Chiropractic at Macquarie University and has received investigator-initiated industry-supported research grants from the Macquarie Chiropractic Alumni Research Fund and Canadian Chiropractic Research Foundation. MS works as a non-executive director of Chiropractic Australia and has received financial reimbursement for work travel.

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