Early life illness factors as potential risk factors for back pain in adolescence and young adulthood

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BChiro, BSc (Hons)

This thesis is presented for the degree Doctor of Philosophy

Chiropractic Program

Discipline of Psychology, Exercise Science, Counselling and Chiropractic (PESCC)

College of Science, Health, Engineering and Education (SHEE)

Murdoch University

2021

Declaration

I declare that this thesis is my own account of my research and all assistance in preparing this thesis and all sources have been acknowledged. It contains as its main content work which has not previously been submitted for a degree at any tertiary education institution.

Amber Morgan Beynon

25th February 2021

Statement Regarding Ethical Approval

Ethical approval was obtained from the Murdoch University Human Research Ethics Committee for the studies contained in Chapters four through to seven. Details of these approvals are found in the respective manuscripts and within the appendix.

Supervisors and Co-Author Attribution Statements.

Chapters two through to seven contain manuscripts which have been published or are prepared for submission to scientific journals. These manuscripts represent collaborative works. However, the PhD candidate made the primary contribution to each manuscript as detailed below.

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Beynon AM, Hebert JJ, Leboeuf-Yde C, Walker BF. Potential risk factors and triggers for back pain in children and young adults. A scoping review, part II: unclear or mixed types of back pain. Chiropr Man Therap. 2019 Dec 1;27(1):61. DOI: 10.1186/s12998-019-0281-8

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Published manuscript: Beynon AM, Hebert JJ, Leboeuf-Yde C, Beales DJ, Jacques A, Walker BF. Early life chronic inflammatory conditions predict low back pain in adolescence and young adulthood. Eur J Pain (2020) DOI: 10.1002/ejp.1700

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Published manuscript: Beynon AM, Hebert JJ, Beales DJ, Jacques A, Walker BF. Multi-trajectory analysis of C-reactive protein and low back pain from adolescence to early adulthood. Eur Spine J (2020). DOI : 10.1007/s00586-020-06677-0

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Prepared manuscript: Beynon AM, Wedderkopp N, Walker BF, Leboeuf-Yde C, Hartvigsen J, Hebert JJ. Association between cardiovascular disease risk factors and future spinal pain with the potential moderating role of health-related physical activity (CHAMPS Study-DK)

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Chapter Seven

Prepared manuscript: Beynon AM, Wedderkopp N, Walker BF, Leboeuf-Yde C, Hartvigsen J, Hebert JJ. No association between sub-clinical elevation of C-reactive protein levels and spinal pain trajectories (CHAMPS Study-DK).

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Acknowledgements

Firstly, I would like to acknowledge my fantastic supervisors; Professor Bruce Walker AM, Professor Jeffrey Hebert, Professor Charlotte Leboeuf-Yde, Dr Anthony Armson, and Dr Stanley Innes. I was extremely lucky to have such a supportive, knowledgeable and diverse team. Each and every one of my supervisors provided key roles in this PhD journey. Professors Bruce Walker, Jeffrey Hebert, and Charlotte Leboeuf-Yde provided guidance and wisdom at every stage, and always ensured we had top quality output. Dr Anthony Armson and Dr Stanley Innes provided vital assistance at the final hurdle in getting this thesis over the line. Thank you.

Next, I would like to acknowledge all the co-investigators on the respective studies. I want to acknowledge Dr Darren Beales, Ms Angela Jacques, Professor Anne Smith, Professor Leon Straker, and Professor Flavia Cicuttini for all their hard work and expertise with the Raine Study projects. Also, Professor Niels Wedderkopp, Professor Jan Hartvigsen, Professor Bobby Jones, Dr Chinchin Wang, and Professor Ian Shrier for all their direction and insight with the CHAMPS Study-DK projects. I was very fortunate to have had the opportunity to learn from some exceptionally knowledgeable and experienced people.

The staff and other research students within the chiropractic and other health disciplines at Murdoch University have always been extremely supportive and created a great workplace atmosphere to complete my PhD. Through this PhD journey I received many wise words of wisdom from these fantastic individuals. Also, a special mention to Dr Margaret Sealey, as my academic chair, for her support and encouragement over the years. I would like to thank Chiropractic Australia Research Foundation for the scholarship that allowed me to focus my time on this PhD.

I would like to express my sincere appreciation to my partner Mike. He always provided an ear to listen to my ranting stories, provided constant encouragement, and continually attempted to reduce my stress levels. A big thank you to my parents, friends and family, who have always been extremely supportive. And finally, of course Ted who without protest (or choice) always patiently listened to me practicing presentations and discussing my studies.

Abstract

Low back pain is the leading cause of disability worldwide, affecting mainly adults but also children. Associations between chronic inflammatory conditions and low back pain have been found frequently in older populations. However, the nature of these relationships in younger populations is unknown.

The overall objective of this thesis was to investigate if early life illness factors such as childhood illnesses are risk factors for back pain in adolescence or young adulthood. Our plan involved three parts. Part 1: Literature reviews. Part 2: Analyses of longitudinal data from the Raine Study. Part 3: Analyses of longitudinal data from the CHAMPS Study-DK.

Through a two-part scoping review and a systematic review, we found that the most likely risk factors for incident back pain in young people are female sex, older age, psychological distress, and psychological features including emotional coping problems. Based on the findings of the Raine Study analyses we found that children with respiratory or atopic conditions such as asthma and allergic rhinitis, and those with several chronic inflammatory conditions are at increased odds of impactful low back pain in adolescence and young adulthood. Based on the findings of the CHAMPS Study-DK we found there were limited associations between cardiovascular disease risk factors and spinal pain in children and adolescents until the moderating role of health-related physical activity was considered. Furthermore, within both these young cohorts there did not appear to be any association between the inflammatory blood marker C-reactive protein and back pain.

We concluded that there is some evidence that early life illness factors are risk factors for back pain in young populations, but more evidence is needed to determine if this involves a causal relationship. There appears to be an association between cardiovascular disease risk factors and spinal pain, however this relationship is dependent on sex, age, and health-related physical activity behaviour.

Table of Contents

List of Publications and Presentations

Referred Journal Articles

- Beynon AM, Hebert JJ, Beales DJ, Jacques A, Walker BF. Multi-trajectory analysis of C-reactive protein and low back pain from adolescence to early adulthood. Eur Spine J (2021) DOI : 10.1007/s00586-020-06677-0
- Beynon AM, Hebert JJ, Leboeuf-Yde C, Beales DJ, Jacques A, Walker BF. Early life chronic inflammatory conditions predict low back pain in adolescence and young adulthood. Eur J Pain (2020) DOI: 10.1002/ejp.1700
- Beynon AM, Hebert JJ, Hodgetts CJ. Boulos LM, Walker BF. Chronic physical illnesses, mental health disorders, and psychological features as potential risk factors for back pain from childhood to young adulthood: a systematic review with meta-analysis. Eur Spine J 29, 480–496 (2020) DOI: 10.1007/s00586-019-06278-6
- Beynon AM, Hebert JJ, Leboeuf-Yde C, Walker BF. Potential risk factors and triggers for back pain in children and young adults. A scoping review, part I: incident and episodic back pain. Chiropr Man Therap. (2019) Dec 1;27(1):58. DOI: 10.1186/s12998-019-0280-9
- Beynon AM, Hebert JJ, Leboeuf-Yde C, Walker BF. Potential risk factors and triggers for back pain in children and young adults. A scoping review, part II: unclear or mixed types of back pain. Chiropr Man Therap. (2019) Dec 1;27(1):61. DOI: 10.1186/s12998-019-0281-8

Refereed Conference Publications (conference cancelled due to COVID-19)

- Beynon AM, Hebert JJ, Hodgetts CJ. Boulos LM, Walker BF. Chronic physical illnesses, mental health disorders, and psychological features as potential risk factors for back pain from childhood to young adulthood: a systematic review with meta-analysis. Research Poster Abstracts. Canadian Journal of Pain. 2020. 4:2, A101. DOI: 10.1080/24740527.2020.1765649
- Beynon A, Hebert JJ, Leboeuf-Yde C, Beales D, Jacques A, Walker B. What happens to children with low back pain at 14? A study of pain trajectories from 14 to 22 years of age. Research Poster Abstracts. Canadian Journal of Pain. 2020. 4:2, A113. DOI: 10.1080/24740527.2020.1765649

Podium Presentations

- Beynon A, Hebert J, Beales D, Jacques A, Walker B. Do early life chronic inflammatory conditions predict low back pain in adolescence and young adulthood? Raine Annual Scientific Meeting, Western Australia, October 30, 2020. Virtual Podium presentation.
- Beynon A, Beales D, Jacques A, Smith A, Circuttini F, Straker L. Trajectories of C-reactive protein and body mass index: are they related? Raine Annual Scientific Meeting, Western Australia, November 1, 2019. Podium presentation.
- Beynon A, Hebert JJ, Hodgetts C, Boulos L, Walker BF. Systematic review with meta-analysis of chronic physical illnesses, mental health disorders and psychological features as potential risk factors for back pain from childhood to young adulthood. Chiropractic Australia National conference, Gold Coast, Australia August 23, 2019. Podium presentation.

  Awarded Second Place Podium Presentation
- Beynon A, Hebert JJ, Leboeuf-Yde C, Walker B. Potential risk factors and triggers for back pain in children and young adults. A Scoping Review. Murdoch Annual Research Symposium, Western Australia, June 3, 2019. Podium presentation

Poster Presentations

- Beynon A, Hebert JJ, Leboeuf-Yde C, Beales D, Jacques A, Walker B. What happens to children who have low back pain at 14? A trajectory study until the age of 22. Chiropractic Australia National conference, Gold Coast, Australia August 23, 2019. Poster presentation.

  Awarded Best Overall Poster
- Beynon A, Hebert JJ, Leboeuf-Yde C, Walker B. Potential risk factors and triggers for back pain in children and young adults. A Scoping Review. Chiropractic Australia National conference, Gold Coast Australia August 23, 2019. Poster presentation

Abbreviations

β	Beta
BIC	Bayesian Information Criterion
BMI	Body mass index
BP	Back pain
BP	Blood pressure
CHAMPS Study-DK	Childhood Health, Activity, and Motor Performance School Study Denmark
CI	Confidence intervals
CRP	C-reactive protein
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis assessment model-estimated insulin resistance
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
IQR	Interquartile range
IRR	Incidence rate ratio
LBP	Low back pain
LDL-C	Low-density lipoprotein cholesterol
MBP	Mid back pain
MVPA	Moderate-to-vigorous intensity physical activity
N	Number of participants
NA	Not applicable
NR	Not reported
OR	Odds ratio
PR	Prevalence ratio
QUIPS	Quality In Prognostic Studies tool
RR	Relative Risk
SD	Standard deviation

Chapter One- Thesis introduction

Background

Back pain is a global problem affecting populations in both the developed and developing world [1], with the disability and financial costs associated constituting a large burden both to individuals and society [2]. For many, back pain begins in childhood [3, 4]. While most cases of paediatric back pain are self-limiting and benign [5-7], back pain can negatively impact on a child's sport participation and school activities [8-13]. The prevalence of paediatric back pain has been increasing since the 1980s [14, 15]. Although many children (49-53%) have been found to report little to no low back pain, some children have reported fluctuating low back pain (16-37%), and a small proportion (<1-10%) report persistent low back pain [16]. Adolescents with back pain continue to have lasting back pain into adulthood [17, 18]. This highlights the importance of reducing this global financial burden by identifying children who are at risk of developing back pain and the implementation of prevention programs. Recently, there was a call for action on the global problem of low back pain [19]. Therefore, it is logical to start this action when back pain can commence. Consequently, identifying clear early life risk factors for back pain is important [20].

Does back pain in children occur in isolation to other conditions?

Back pain aetiology is complex and has many possible contributors, including social, physical, and psychological factors, along with certain co-morbidities [21]. While some abnormalities have been identified as causes of back pain, many remain unknown [21]. Numerous studies have attempted to explore risk factors of back pain in young populations, including: family and genetic history of back pain, female sex, poor leg and lumbar flexibility, physical fitness, puberty, part time work, and posture [3, 8, 22-30]. The intent being to identify early life factors that predispose young people to back pain in later life, in order to inform future prevention strategies that reach into adulthood [17]. There is now growing evidence to suggest that the risk of developing back pain is not down to just a single factor but rather multifactorial, with risk factors in a spectrum of domains, including biological, lifestyle, and psychosocial factors [20, 31-37].

Musculoskeletal conditions frequently co-occur with other chronic diseases potentially as part of multimorbidity [38-41]. Multimorbidity refers to the co-occurrence of two or more diseases within an individual with the assumption that none of the diseases take precedence over the others [42-46]. Whereas, comorbidity is the co-occurrence of diseases or conditions additional to the index disease (the primary disease or disease of interest) [42, 47].

Comorbid or multimorbid conditions such as asthma, allergies, and depression are reportedly associated with low back pain from adolescence to adulthood [48, 49]. A systematic review and meta-analysis of cross-sectional twin studies found that young people and adults were more likely to report low back pain if they had chronic conditions such as asthma, diabetes, and headaches (pooled odds ratio (OR) range = 1.6 to 4.2) [50]. Respiratory and digestive disorders also show cross-sectional and longitudinal associations with back pain in adulthood [51, 52]. In a large Canadian National Population Health Survey adolescents and adults living with major depression were almost three times more likely (OR [95% confidence intervals (CI)] = 2.9 [1.2,7.0]) to report back pain two years later [53].

Similarly, a history of cardiovascular disease is associated with increased risk (men: OR [95% CI] = 2.2 [1.3,3.5]; women: OR [95% CI] = 2.3 [1.5,3.4]) of chronic low back pain in adults [54]. Cardiovascular disease does not typically manifest in childhood; therefore, it is not possible to investigate this in young people. However, it is possible to measure risk factors for cardiovascular disease which do begin to develop in children [55-57]. It has been found that cardiovascular disease risk factors contributing to metabolic syndromes are more prevalent in adults reporting high-intensity chronic pain (OR [95% CI] 1.4 [1.2,1.6]) [58].

However, there is a paucity of literature on systemic illnesses as risk factors for back pain, in particular whether early life illness factors predisposes an individual to back pain as an adolescent or as a young adult [48].

Hypothesised biological plausibility

Systemic inflammation associated with chronic inflammatory conditions has been hypothesised to lead to pain sensitization [59]. It is plausible that there is a biological

link between inflammatory conditions and back pain because of inflammation-associated activation of the hypothalamic-pituitary-adrenal axis [49]. The presence of inflammatory conditions, particularly in early life, may lead to changes in the hypothalamic-pituitary-adrenal axis function through explicit action or by way of epigenetics [60, 61]. Hypothalamic-pituitary-adrenal axis dysfunction may increase susceptibility to pain and chronic pain disorders [62-64]. Early life stresses have been found to influence future nociceptive processing [65]. These associations have been found previously between early-life psychological stresses and increased incidence of chronic pain in later life [66], as well as between early-life pain experiences and spinal pain in pre-adolescence [67]. However, the association between hypothalamic-pituitary-adrenal axis function and musculoskeletal pain remains uncertain particularly when considering adolescents and young adults who are mostly healthy and highly sensitive to stress [68].

Another theory postulates that back pain and its occasional multimorbidities such as respiratory and digestive disorders may have common origins [51]. The potential link being that a proportion of back pain and chronic conditions could be inflammatory in nature. The inflammatory conditions and back pain could occur at any time during the lifetime either concurrently or otherwise. It may be possible to confirm this if a common inflammatory biomarker could be identified.

Could C-reactive protein be a possible factor?

C-reactive protein (CRP) is a biomarker of inflammation [69]. It is used as a screening tool for the detection of many diseases [69]. The median concentration of CRP in healthy adults is 0.8mg/L and generally levels remain stable except for transient increases related to recent trauma or infections [69]. CRP is useful as a non-specific biochemical marker of inflammation because it is not readily impacted on by other factors (i.e. food) and production of CRP is only impaired by liver failure [69].

Sub-clinical elevations in CRP are linked with multiple factors for poor health including increased cardiovascular disease risk, obesity, and insulin resistant diabetes [69-80]. CRP is positively associated with components of metabolic syndrome including; total cholesterol, glucose levels, measures of obesity, and insulin resistance [71, 74, 81-

86]. CRP also predicts future coronary events [69, 72, 78-80, 87]. In children, CRP is associated with cardiovascular disease risk factors including: HDL-cholesterol, heart rate, fibrinogen, systolic blood pressure, and to measures of adiposity [73, 76]. Physical exercise can decrease CRP levels, which could explain the protective effect of exercise for cardiovascular disease [88].

Preliminary evidence points to a link between CRP and spinal pain in adults. Two recent systematic reviews found moderate level evidence of a positive association of CRP with the presence and severity of low back pain [89, 90]. This is supported by other studies [91, 92], that have found increased levels of CRP to be associated with higher cold-pressor sensitivity, suggesting a link between inflammation and pain sensitivity.

There is cross-sectional evidence that inflammation may modify the experience of spinal pain by modulating underlying sensitisations, this means that higher levels of inflammation can increase pain sensitivity, leading to the development of chronic pain [89, 91-93]. However, the longitudinal nature of the relationship between inflammation and spinal pain is unclear. To better understand the co-development of inflammation and pain it would be important to take a life course perspective. Trajectory modelling demonstrating the time course of pain and inflammation could be useful to further explore this complex longitudinal relationship, and the possible association between chronic increased levels of CRP and the course of spinal pain. Trajectory modelling can better demonstrate the recurrent and fluctuating nature of pain conditions compared to methods that define outcomes at single time points [94].

Definitions

In order to establish a common understanding of this thesis the following definitions are provided.

Risk factor

A risk factor is defined by Porta [95] as *"a factor that is causally related to a change in the risk of a relevant health process, outcome, or condition. The causal nature of the relationship is established based on scientific evidence and causal inference."* In order to identify a causal relationship, the risk factor should be present before the onset of the disease [96]. If a factor occurs simultaneously with a disease then it can only be

concluded there is an association and not necessarily a causal relationship [96]. However, causality cannot be inferred simply because one factor precedes another [97]. According to the Bradford Hill criteria of causation, there are many tenets required to establish a causal link, namely strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy [97].

Back pain

Back pain is a symptom but can also be conceptualised as a disease, with the start of the disease occurring when the first instance back pain is felt [96]. An episode of back pain is an event of back pain, and a part of the relapsing and remitting nature of the 'disease', characterised by periods of back pain and pain-free periods [96].

Risk factor vs. trigger of back pain

A risk factor leads to the onset of back pain compared to a trigger, which could lead to an episode. A risk for the disease of back pain could be different to a trigger that leads to an episode. For example, those with a genetic predisposition could develop the 'disease' of back pain, then a trigger for an episode could be a particular movement into an awkward position [96].

Limitations and gaps in the literature

The majority of the current studies are cross-sectional in nature, in order to establish a causal relationship there should be at least a temporal relationship, in that the risk factor should be present before the onset of the disease, this can only be accomplished with longitudinal study designs [96]. Additionally, throughout the evidence there are varying or unclear definitions of back pain; therefore, it is often unclear if they included populations with incident, episodic, or ongoing back pain. As there is a lack of standardised terminology it is challenging to compare studies [20]. It is often unclear whether studies are considering risk factors for the onset of back pain or triggers of back pain episodes [96].

There is also limited research considering early life illness factors as potential risk factors for back pain. Adults are commonly included in studies that explore risk factors and triggers of back pain, however within this population it can be challenging to locate

participants who have been completely free of back pain their whole life. Hence, studying young populations brings the benefit of a higher likelihood of engaging research participants before the onset of back pain.

Thesis aim

The overall aim of this thesis was to investigate if early life illness factors such as childhood gastrointestinal, cardiovascular and respiratory illnesses, or cardiovascular disease risk factors-as potential proxy measures of underlying systemic inflammation-are risk factors for back pain in adolescence or young adulthood.

To this end, the thesis was constructed in three parts. Part 1: Reviews of the relevant literature to inform the analyses of data from selected cohort studies. Part 2: Analyses of longitudinal data from the Raine Study. Part 3: Analyses of longitudinal data from the CHAMPS Study-DK.

Background on cohort study data sourced for this thesis

The Raine Study is a longitudinal cohort investigation on a discreet Western Australian population with mothers recruited between May 1989 and Nov 1991. There were 2868 live births recruited into the Raine Study. The children have been followed from birth, until present (28 years), with data points at years 1, 2, 3, 5, 8, 10, 13, 16, 20, 23 and 27. Information has been collected on environmental, developmental, and health information covering an extensive range of health related areas. There are 25 broad areas of research including asthma and atopy, cardiovascular and metabolic health, childhood development growth, dental health, diabetes, genetic epidemiology, gastro-enterology, infection and immunity, mental health, musculoskeletal development and pain, nutrition, physical activity, ophthalmology, pregnancy and birth, reproductive health, sleep and risk-taking behaviour [98, 99].

The Childhood Health, Activity, and Motor Performance School Study Denmark (CHAMPS Study-DK) is a quasi-experimental trial designed to estimate the effects of physical education and other variables on cardiovascular disease risk factors, musculoskeletal health, and motor performance in children from Svendborg, Denmark [100]. Ten schools took part with 1218 children initially, with students in six schools receiving an increased amount of physical activity (270 minutes per week) and four

schools receiving the usual amount of physical activity (90 minutes per week). Participating children were enrolled into the study on a rolling basis starting from October 2008 to January 2009 and comprised children from 6 years to 11 years of age at the time of enrolment, and were followed until July 2014 [101, 102]. Cardiovascular disease risk exposures were taken at baseline, 2010, and 2014 [103]. Many other variables were measured at baseline and at regular intervals (at least once a year) with questionnaires, physical examinations and physical testing. Measurements included the prevalence, incidence and tracking of indicators for life-style diseases such as type two diabetes, metabolic syndrome and cardiovascular disease. This also included the prevalence, incidence and tracking of musculoskeletal injuries and back problems [100]. Cardiovascular disease risk factors included fasting blood samples comprising serum insulin, glucose, insulin resistance, triglycerides, and cholesterol, as well as systolic blood pressure and body mass index [103]. In addition, spinal pain outcomes were measured from baseline and then on a weekly basis over a five and a half-year period via SMS (text) messaging [100, 101, 104]. Physical activity was measured objectively with accelerometry [100, 105].

The Raine Study data allowed us to investigate a broad array of co-morbidities as well as the longitudinal relationship between CRP and low back pain. The CHAMPS Study-DK data allowed us to further understand the associations of cardiometabolic health, health-related physical activity, CRP and spinal pain using objective measures of cardiometabolic risk, health-related physical activity, and intensive measures of spinal pain collected each week over the course of five and a half years.

Thesis structure

This thesis contains seven published or prepared for publication research manuscripts that are arranged into eight chapters. One additional supplementary manuscript has been submitted for publication (See Appendix One). Published papers are included as formatted PDF files incorporated into this thesis along with additional text, introductions and discussion sections at the beginning and end of each chapter, to link the manuscripts. Reference lists of all the manuscripts are contained within the respective chapters.

In Chapter One we have introduced the thesis and critically reviewed the relevant literature.

Chapter Two identifies potential risk factors and potential triggers for back pain in young people through a two-part scoping review. The scoping review part I focused on studies that investigated risk factors and triggers for incident and episodic back pain. Part II includes all eligible studies with unclear or mixed definitions of back pain.

Chapter Three is a systematic review with meta-analysis of chronic physical illnesses, mental health disorders, and psychological features as potential risk factors or triggers for back pain from childhood to young adulthood.

Chapter Four involved data from the Raine Study participants (1 to 22 years of age) to investigate potential links between early life chronic or recurrent inflammatory conditions and low back pain in adolescence and young adulthood. The specific objectives of this chapter were 1) to investigate the longitudinal associations between inflammatory conditions in childhood and impactful low back pain occurrence from adolescence to young adulthood, 2) to investigate the cross-sectional associations between inflammatory conditions from adolescence to young adulthood and impactful low back pain occurrence, 3) to investigate potential dose-response relationships between the number of chronic inflammatory conditions and the occurrence of impactful low back pain.

Chapter Five also utilized data from the Raine Study participants (14 to 22 years of age) to investigate the longitudinal associations between CRP levels and low back pain from adolescence to early adulthood. First, as a preliminary study we identified trajectories of CRP and investigated the longitudinal association between trajectories of CRP and body mass index; this information is presented in Appendix One. Second, we identified the trajectories of low back pain from early adolescence through to early adulthood and investigated the associations between trajectories of CRP and low back pain.

Chapter Six includes analyses conducted to investigate the prospective association between childhood cardiovascular disease risk factors and spinal pain occurrences in

childhood and adolescence with the potential moderating role of health-related physical activity using data from the CHAMPS Study-DK.

Chapter Seven entailed investigating the longitudinal associations between sub-clinical elevations in CRP and spinal pain from childhood to adolescence based on available CHAMPS Study-DK data. Specifically, we examined for differences in mean CRP between spinal pain trajectory subgroups.

Chapter Eight provides an overview of the thesis including directions for future research.

Chapter Two- Scoping review on potential risk factors and triggers for back pain in children and young adults. Parts I and II.

Numerous studies have attempted to investigate a range of different risk factors of back pain in young populations [3, 8, 22-28]. Within this chapter we aimed to synthesize the evidence to identify all investigated risk factors and triggers for back pain in young people. Due to the considerable number of studies on "risk factors" for back pain, we conducted a two-part scoping review to summarise the evidence. By conducting a scoping review, we could also identity the gaps and major limitations within the literature.

The purpose of this scoping review was to identify potential risk factors and potential triggers for back pain in young people. The scoping review part I includes studies that investigated risk factors (with an established temporal relationship) for incident and episodic back pain. Part II includes all other eligible studies with unclear or mixed definitions of back pain.

This work underwent peer-review and is published as:

Beynon AM, Hebert JJ, Leboeuf-Yde C, Walker BF. Potential risk factors and triggers for back pain in children and young adults. A scoping review, part I: incident and episodic back pain. Chiropr Man Therap. 2019 Dec 1;27(1):58. DOI: 10.1186/s12998-019-0280-9

As of 24/02/2021: Article accesses: 1240. Citations: 3. Altmetric: 8

Beynon AM, Hebert JJ, Leboeuf-Yde C, Walker BF. Potential risk factors and triggers for back pain in children and young adults. A scoping review, part II: unclear or mixed types of back pain. Chiropr Man Therap. 2019 Dec 1;27(1):61. DOI: 10.1186/s12998-019-0281-8

As of 24/02/2021: Article accesses: 1446. Citations: 4. Altmetric: 10

Chiropractic & Manual Therapies

SCOPING REVIEWS Open Access

Potential risk factors and triggers for back pain in children and young adults. A scoping review, part I: incident and episodic back pain

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Abstract

Background: The one-month prevalence of back pain in children and adolescents has been reported at 33, 28 and 48% at ages 9, 13 and 15 respectively. There are many suspected risk factors and triggers of back pain in young people.

Objective: The purpose of this scoping review was to identify potential risk factors and potential triggers for back pain in young people. The purpose of part I was to identify potential risk factors for incident and episodic back pain in young people. Part II included all eligible studies with unclear or mixed types of back pain.

Methods: Due to the vast number of studies on "risk factors" for back pain, a two-part scoping review of the literature was chosen as the best way to summarise the evidence. We adhered to the PRISMA-ScR guideline for scoping reviews. General potential risk factors and triggers for back pain in children and young adults (≤ 24 years) were included, incorporating physical, environmental, and/or physiological factors. A search was conducted using PubMed and Cochrane databases from inception to September 2018, limited to the English language. Within part I, and because of their importance, only the results of the studies that investigated risk factors of incident back pain and back pain episodes are presented.

Results: The search identified 7356 articles, of which 91 articles were eligible for this scoping review. The majority of the eligible articles had an unclear definition of back pain (results presented in scoping review part II). There were 7 inception cohort studies included and 1 cohort study that met the criteria for part I. The most consistent risk factors for incident and episodic back pain are female sex and older age.

Conclusion: Due to inconsistent ways of reporting on the type of back pain, no definitive risk factor for back pain has been identified. In general, females often report more symptoms, also for other diseases, and older age is not a useful risk factor as it merely indicates that the onset may not be in childhood. Clearly, the time has come to study the causes of back pain from different angles.

Keywords: "Risk factors", "Back pain", Children, Adolescent, Young adult, Scoping review

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Background

In children, back pain was once thought to be rare. However emerging evidence suggests that this is not the case [1]. The 1 month prevalence of back pain in children and adolescents has been reported at 33, 28 and 48% at ages 9, 13 and 15 respectively [2]. A recent systematic review found that there were three common patterns of low back pain (LBP) in children and adolescence. The majority of children (49–53%) reported no or low probability of LBP, a second group reported fluctuations of LBP (16–37%), and a minority (< 1–10%) repeatedly reported LBP [3]. The consequences of back pain included the taking of medication, missing class, and seeking care [4]. Additionally, children who report back pain have been found to have difficulty with certain activities such as standing in a queue, sports activities, and carrying a school bag [5]. There are many suspected risk factors of back pain for children and young adults.

It is important to distinguish between a risk factor for back pain and a factor associated with back pain [6]. A risk factor is defined by Porta [7] as *"a factor that is causally related to a change in the risk of a relevant health process, outcome, or condition. The causal nature of the relationship is established on the basis of scientific evidence and causal inference."* Therefore, to identify a causal relationship rather than simply an association, the risk factor should be present, as a minimum, prior to the onset of the disease [6]. However, just because a factor precedes another does not automatically indicate causality [8]. According to the Bradford Hill criteria there are many tenets required to establish a causal link, namely: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy [8]. If a potential risk factor is measured concurrently with a disease, then the temporal association between the risk factor and the disease cannot be established, unless it is certain that the potential risk factor was there before the inception of the disease [6]. Therefore, generally, a prospective study design is needed to determine a risk factor [6].

If we define back pain as a 'disease', then the disease onset is probably the first instance of back pain [6]. An episode of back pain is an event of back pain, once this 'disease' has occurred, and it is a part of the relapsing and remitting nature of the 'disease', characterised by periods of back pain and pain-free periods. A risk factor is one that causes the 'disease' of back pain (marked by the first time back pain occurs) compared to a trigger, which could lead to an episode of back pain. It is possible a risk factor could also be a trigger, but not necessarily. For example, those with a genetic predisposition could be prone to develop the 'disease' of back pain, then a trigger for an episode could be a particular movement into an awkward position [6].

Thus to study the 'disease' of back pain and to identify risk factors of incident back pain, with an established temporal relationship, an inception cohort is needed [7].

Some systematic reviews have endeavoured to identify the potential risk factors of back pain in children and young adults [9–19]. Many of these located reviews focused on specific potential risk factors such as schoolbags [15], computer use [13], puberty [14], weight status [17], smoking [18], and physical activity [19]. The majority of the systematic reviews did not consider the temporal relationship between back pain and the risk factor, and combined cross-sectional studies with cohort studies and/or had unclear definitions of back pain [9, 12, 13, 15–18]. A systematic review by Ardakani et al. [6] attempted to determine if a sample of studies looking into the causes of low back pain discriminated between the back pain 'disease' and its episodes. They concluded that the majority of the included studies had an unclear definition of absence of low back pain at baseline and therefore cannot differentiate between back pain as the 'disease' and its recurring episodes [6]. Only one located systematic review by Hill and Keating [10] planned to consider the first episode of low back pain. They included only prospective studies, which they stated studied the first episode of low back pain [10]. However, half of the included articles did not actually assess the first episode of back pain and instead had unclear types of back pain, providing information on studies including first ever, episodic and ongoing back pain.

Due to the vast number of studies on risk factors for back pain, we undertook a scoping review to summarise current evidence.

The purpose of this scoping review was to identify potential risk factors and potential triggers for back pain in young people. Within this article (Part I) we included only studies that investigated risk factors (with an established temporal relationship) for incident back pain (back pain defined as the 'disease') and back pain defined as episodes. Part II includes all eligible studies with unclear or mixed definitions of back pain.

Methods

We conducted a scoping review based on established guidelines [20]. A review protocol was not included in a registry and, as this was a scoping review, we did not formally rate quality including risk of bias of each article. We began with the broad question of: *what are the potential risk factors and potential triggers for back pain in childhood and young adulthood?*

Eligibility criteria

Studies were included if they reported on any potential risk factors for pain in the thoracic and/or lumbar spine (back pain) with the majority of participants less than 25 years old at baseline. General potential risk factors and triggers for back pain in children, adolescents, and

young adults up to the age of 24 years, including physical, environmental, and/or physiological factors were considered. The age classification is based on the MeSH definition of a young adult (19–24 years). Additionally, the contemporary definitions of adolescence includes young adulthood (10–24 years) [21]. We identified original peer-reviewed studies in English from any country of origin and included cohort studies, inception cohort studies and retrospective studies. Within part I, only studies that studied risk factors of incident back pain (back pain the 'disease') and back pain episodes were included. Therefore, for incident back pain a clear definition of the back pain that included a life-time absence of back pain at baseline was required. For episodic back pain, a clear definition of back pain with pain-free periods was required, to be able to capture recurrent back pain.

Search strategies

A search was conducted using PubMed and Cochrane databases from inception to September 2018, limited to only English language peer-reviewed articles. In addition, reference lists of included papers and located systematic reviews were searched to identify other potentially suitable studies. There was no attempt to contact authors to identify additional sources. The full search strategy is listed in Additional file 1. Search results were imported into bibliographic management software and duplicates discarded. Results of the search were reported as per the PRISMA flow diagram (Fig. 1).

Study selection, data charting and synthesis of results

Titles, abstracts, and full-text articles were screened by one researcher (AB) twice, once in March 2018 and then repeated in September 2018 against the inclusion criteria. The second search identified four additional articles. Another researcher (BW) verified the study selection (titles, abstracts, and full-text screen) for accuracy. One full-text article was queried, justifications provided, and full consensus was met through discussion.

Calibration of the data charting forms was conducted by two researchers (AB and CLY). One researcher (AB)

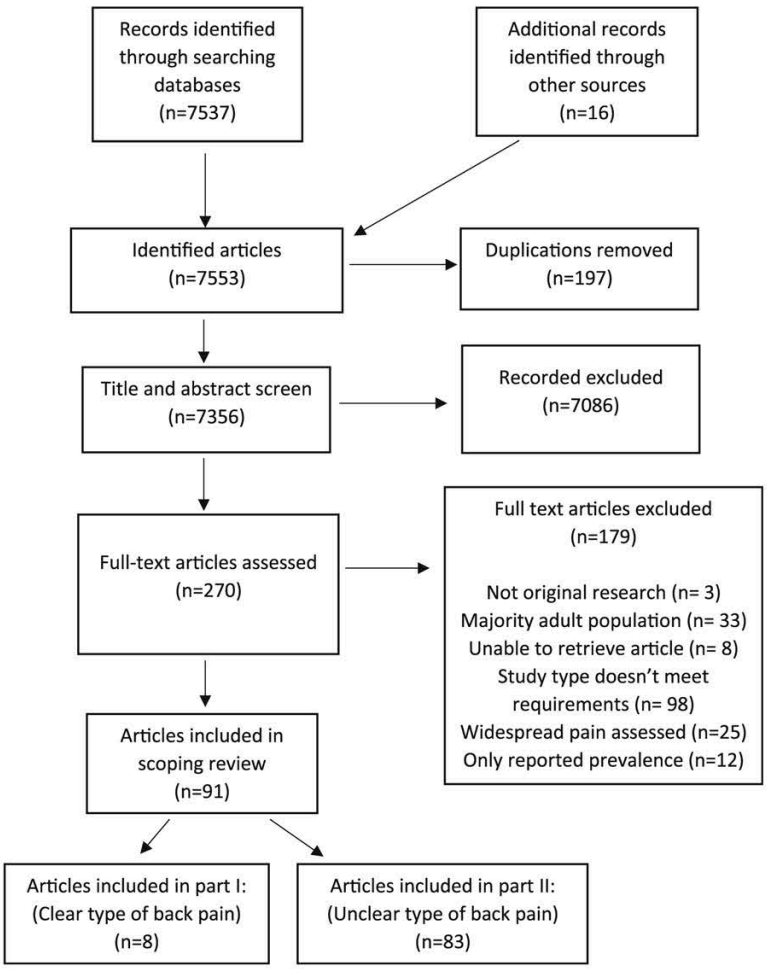

Fig. 1 Final study selection flow diagram

piloted the form on three studies and this was verified by another researcher (CLY). This was an iterative process in which there were many changes during each round. Any disagreements were resolved by a third researcher (BW).

One researcher (AB) independently charted the data (data extraction in scoping reviews [22]) using the evidence tables. Another researcher (BW) verified the data charting for accuracy. The second reviewer had ten queries which were resolved through discussion and consensus leading to five minor changes; involvement of a third reviewer was not needed. The results were summarised reporting the number of times a risk factor was investigated, the number of times it was found to be associated with back pain, and if there was an association, the strength of this association. If a study had multiple estimates for the same risk factor, the most adjusted estimate was extracted.

Clarity of definition of back pain was assessed in each study with a summative score. Individual points were given if there was a clear description of the area of back pain, a clear reporting of the recall period, a clear definition of the type of back pain, and if there was an attempt to collect valid data (maximum four points). These scores are reported in additional files.

Data were synthesised by risk factors and further, by study design. This includes inception cohort studies reporting factors that were longitudinally associated with back pain (risk factors of back pain) and cohort studies reporting factors that were longitudinally associated with back pain episodes.

Results

Study selection

The database searches identified 7537 articles and 16 additional articles were identified from searching of the relevant references lists. A total of 91 articles were eligible for inclusion in this review. In all, 83 studies were excluded for part I as they did not have a clear definition of back pain or document the absence of back pain among participants at baseline. These studies were included in part II of this review. Thus, data from 8 articles were included in the current review (Fig. 1).

Study characteristics and synthesis of results

There were 7 inception cohort studies reviewed [23–29]. These studies identified risk factors for the onset of the first episode of back pain [23–29]. Risk factors included sex, age, socioeconomic status, height, psychosocial factors, body mass index (BMI), muscle strength, physical activity, and smoking. All study populations included both males and females. The median ages of the study populations ranged from 10 to 21 years of age. Follow up periods ranged from 1 to 8 years. Charts of the summary of findings are seen in Additional file 2.

There was only one study on episodic/recurrent back pain [30]. Charts of the summary of findings are seen in Additional file 3.

Sex

Six inception cohort studies tested sex as a potential predictor of back pain [24–29], of which two reported that females had an increased incidence of back pain [24, 29], one reported a higher incidence in males [25], and three studies found no association [26–28] (Table 1). One cohort study tested sex as a potential predictor of back pain episodes and found females had an increased prevalence of back pain [30] (Table 2).

Age

Four inception cohorts tested age as a potential predictor of back pain [24–27], of which three found older age had an increased risk of back pain [24, 25, 27], and one found no association [26] (Table 1). One of these studies found age as a risk factor for back pain in males but it not in females [24], whereas another found the incidence of back pain to increase more with age in males than in females [25]. One cohort study tested age as a potential predictor of back pain episodes and found older age had an increased prevalence of back pain [30] (Table 2).

Physical activity

Three inception cohort studies tested the relationship between physical activity and back pain [23, 26, 27]. Of these, two found that increased physical activity led to a higher incidence of back pain [23, 27], whereas one found no association [26] (Table 1). One of these studies only found this relationship with a high level of vigorous physical activity [23].

Psychosocial factors

Two inception cohorts tested psychosocial factors as potential predictors of back pain [24, 26]. Both studies found that those with certain psychosocial factors had an increased incidence of back pain [24, 26]. Those factors included dysfunctional coping [24], anxiety sensitivity [24], somatosensory amplification [24], psychological distress [26], and emotional disorders or behavioural disorders [26] (Table 1).

Socioeconomic status

One inception cohort tested parental education as a potential predictor of back pain and found lower parental education led to an increased incidence of back pain [26] (Table 1).

Table 1 Inception cohorts: summary of risk factors for back pain the 'disease'

Variable	Number of studies	Number of studies: increased risk	Number of studies: decreased risk	Number of studies not significant	Strength of association (95%CI)
Female sex	6	2	1	3	*Negative association:* OR 0.4 (0.3, 0.8) [25] (c) *Positive association:* OR 1.5 (1.3, 1.7) [29] (c) OR 1.8 (1.1, 3.1) [24]
Older Age	4	3	0	1	OR 2.1 (1.2, 3.7) [25] (c) OR 1.2 (1.1, 1.3) (boys) [24] OR 3.4 [27] (graph interpretation, c)
Increased physical activity	3	2	0	1	RR 1.4 (1.1, 1.9) [23] OR 2.3 [27] (graph interpretation, c)
Psychosocial	2	2	0	0	Dysfunctional coping: OR 1.4 (1.1, 2.0) (boys) [24] Anxiety sensitivity: OR: 1.5 (1.1, 2.0) (boys) [24] Somatosensory amplification: OR 1.8 (1.0,3.1) (girls) [24] Psychological distress: OR 1.9 (1.1, 3.2) [26] Emotional or behavioural disorders: OR 1.9 (1.0, 3.4) [26]
Socioeconomic	1	1	0	0	Lower parental education: OR 1.7 (1.1, 2.8) [26]
Increased growth	1	1	0	0	Increased growth spurt one SD (4.3 cm) 11–14 yr: OR 1.3 (1.1, 1.7) [28]
Muscle strength	1	1	0	0	Increased back flexor strength OR 2.8 [27] (graph interpretation, c)
Smoking	1	1	0	0	Heavy smoking: OR 1.9 (1.1, 3.1) [26]
Increased BMI	2	0	0	2	NA
Illness	1	0	0	1	NA

OR Odds ratio, *RR* Relative risk (c): parameter measure calculated from the provided results within study i.e. percentages converted to odds ratios, *NA* Not applicable (no significant results), *BMI* Body mass index

Increased growth

One inception cohort tested increased growth as a potential predictor of back pain and found that an increased growth spurt by one standard deviation more (4.3 cm) from 11 to 14 years of age led to an increased incidence of back pain [28] (Table 1).

Muscle strength

One inception cohort tested muscle strength as a potential predictor of back pain and found that those with an increased back flexor strength had an increased incidence of back pain. However, the study did not define what percentage of increased strength [27] (Table 1).

Smoking

One inception cohort tested smoking status as a potential predictor of back pain and found that heavy smokers in young adulthood had an increased incidence of back pain [26] (Table 1).

Anthropometric parameters (BMI)

Two inception cohorts tested increased BMI as a potential predictor of back pain and found no significant

Table 2 Cohort studies: summary of risk factors for back pain episodes

Variable	Number of studies	Number of positive	Number of negative	Number not significant	Strength of association
Female sex	1	1	0	0	OR 2.1 (1.9, 2.5) [30]
Older Age	1	1	0	0	OR: (index 9 yr boy) 2.5 (1.5, 4.1) (13 yr boy), 3.2 (1.9, 5.3) (14 yr boy), 3.1 (1.8, 8.2) (15 yr boy), 3.0 (1.8, 5.2) (16 yr boy), 3.5 (1.9, 6.3) (17 yr boy), 2.4 (1.4, 4.1) (10 yr girl), 3.4 (2.1, 5.7) (11 yr girl), 4.6 (2.8, 7.5) (12 yr girl), 5.6 (3.4, 9.2) (13 yr girl), 5.4 (3.3, 8.9) (14 yr girl), 6.7 (4.1, 11.2) (15 yr girl), 6.7 (4.0, 11.3) (16 yr girl), 7.5 (4.2, 13.2) (17 yr girl) [30]

OR Odds ratio

relationship with being in a higher BMI percentile and back pain [26, 28] (Table 1).

Systemic/illnesses

One inception cohort tested having a chronic medical condition as a potential predictor of back pain and found no significant relationship. Chronic medical conditions were collated together and were very varied, including conditions such as: asthma, heart problems, epilepsy, cancer, diabetes, missing fingers, blindness, and "muteness" [26] (Table 1).

Discussion

Overall summary of risk factors or triggers for back pain

Considering the literature included in this review within part I, the factors that were found to be the most commonly investigated potential risk factors for incident back pain are female sex and older age. Based on the one study that studied episodic back pain, the potential triggers are also female sex and older age. Other factors that were identified as potential risk factors are physical activity and psychosocial factors. Consistently there was no association or a weak association noted for body mass index, height, muscle strength, smoking, and systemic/illness factors.

Compared to previous literature

Previous systematic reviews have found similar results. Female sex [12, 16, 31] and older age [9, 12, 31] are the most frequently found risk factors for back pain during childhood and adolescence. The findings that females seem to be more at risk of back pain has been hypothesized to be due to differences in pain modulation due to oestrogen [32].

Limitations of the current literature

The major limitations of the current literature are that the majority of studies did not adequately define back pain (incident, episodic or ongoing backpain) and the absence of back pain at baseline (Additional files 4 and 5). To identify a causal relationship, the risk factor should be present prior to the onset of the disease [6]. When studying children, there is also the question of potential memory decay, particularly when asking about the prior presence of back pain.

Limitations of this review

This scoping review has some limitations. In accordance with PRISMA-ScR guidelines one researcher independently screened and conducted data charting, with a second researcher verifying the study selection and data charting for accuracy. However, while this method complies with the guidelines for scoping reviews it is not as rigorous as methods required for systematic review. Also, as complying with the guidelines for scoping reviews, there was no formal critical quality assessment of the included articles. Finally, only two key databases were searched, and articles were limited to the English language.

Recommendations for future research

Future studies should follow the population from early life and capture the proposed risk factors before the onset of back pain. They should also consider the sequence of events in the causal pathway and test their hypotheses with appropriately designed longitudinal studies and appropriate analyses. They should also have a clear and consistent definition of back pain, ideally measured through a validated questionnaire. Finally, future research should concentrate on potentially modifiable risk factors.

Conclusion

Due to inconsistent ways of reporting on the type of back pain, only a limited number of risk factors for back pain in childhood and young adulthood have been identified. Risk factors identified were predominantly biological. The most commonly investigated risk factors for back pain the 'disease' and back pain episodes are female sex and older age towards adolescence and young adulthood. In general, females often report more symptoms, also for other diseases, and older age is not a useful risk factor as it merely indicates that the onset may not be in childhood. Continued studies of similar approach seem not to be useful. Clearly, the time has come to study the causes of back pain from different angles.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12998-019-0280-9.

Additional file 1. Search strategies used for the literature search. The full search strategy for PubMed and Cochrane databases.

Additional file 2. INCEPTION COHORT STUDIES reporting factors that are longitudinally associated with back pain. Table summarising each included inception cohort study.

Additional file 3. COHORT STUDIES reporting factors that are longitudinally associated with back pain episodes. Table summarising included cohort study.

Additional file 4. Clarity of definitions of Back pain: Inception Cohort studies. Table summarising the clarity of the definitions of back pain in included inception cohort studies.

Additional file 5. Clarity of definitions of Back pain: Cohort studies. Table summarising the clarity of the definitions of back pain in included cohort study.

Abbreviations

BMI: Body mass index; CI: Confidence intervals; LBP: Low back pain; N: Number of participants; NA: Not applicable; OR: Odds ratio; RR: Relative risk

Acknowledgements
This research was carried out with funding provided by Chiropractic Australia Research Foundation.

Authors' contributions
All authors contributed to the design of the study. AB conducted the search, study selection and data charting. AB analysed and interpreted the data with the assistance of BW, JH and CLY. AB drafted the manuscript and performed revisions with substantial feedback and editing from all authors. All authors read and approved the final manuscript.

Funding
This study was funded by a scholarship from Murdoch University, Western Australia and funding provided by Chiropractic Australia Research Foundation. JH receives salary support from the Canadian Chiropractic Research Foundation and the New Brunswick Health Research Foundation. The funding sources had no involvement in study design, analysis, interpretation, or manuscript preparation.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
BW and JH are both editors and CLY is Senior Editorial Advisor of *Chiropractic & Manual Therapies* but played no part in the review of this submission and were blinded to the process. JH is an executive member of the Chiropractic Australia Research Foundation.

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Received: 9 April 2019 Accepted: 9 September 2019
Published online: 19 November 2019

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Publisher's Note

Beynon et al. Chiropractic & Manual Therapies (2019) 27:61
https://doi.org/10.1186/s12998-019-0281-8

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Potential risk factors and triggers for back pain in children and young adults. A scoping review, part II: unclear or mixed types of back pain

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Abstract

Background: Back pain is a global problem in terms of disability and financially, with a large burden both to the individual and to society. Back pain was previously believed to be uncommon in children. However, there is a growing body of evidence that this is not the case.

Objective: Part I of this scoping review studied risk factors of incident and episodic back pain. In this part II we aimed to identify all risk factors and triggers with unclear or mixed type back pain in young people and to identify any gaps in the literature.

Methods: A scoping review design was selected to summarise the evidence, as there are many studies on "risk factors" for back pain. The scoping review followed the PRISMSA-ScR guidelines. We considered all studies that tested potential risk factors and triggers for thoracic and/or lumbar spine pain, in children, adolescents, and young adults (≤ 24 years). PubMed and Cochrane databases were searched from inception to September 2018, to identify relevant English language articles. The results regarding potential risk factors were separated into temporal precursors and bidirectional risk factors and the studies were classified by study design.

Results: Our comprehensive search strategy identified 7356 articles, of which 83 articles were considered eligible for this review (part II). There were 53 cross-sectional studies and 30 cohort studies. Potential risk factors for back pain were: female sex, older age, later pubertal status, positive family history of back pain, increased growth, and a history of back pain, most of which are temporal precursor variables. There was limited research for the illness factors, spinal posture, and muscle endurance in the development of back pain.

Conclusion: Many of the included studies approached risk factors in similar ways and found factors that were associated with back pain but were not obvious risk factors as causality was uncertain. Future research should be more rigorous and innovative in the way that risk factors are considered. This could be through statistical approaches including cumulative exposures, or longitudinal approaches including multi-trajectory methods. Additionally, data on proposed risk factors should be collected before the onset of back pain.

Keywords: "Risk factors", "Back pain", Children, Adolescent, Young adult, Scoping review

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Background

Back pain is a global problem in terms of disability and financial costs, with a large burden both to the individual and to society [1]. Back pain was once believed to be uncommon in young people. However there is evidence that this is not the case [2, 3]. Back pain can start during childhood or adolescence [2, 3]. Therefore, it is important not to ignore younger populations. Numerous studies have attempted to investigate a myriad of potential risk factors of back pain in children and young adults. Identifying early life factors that predispose young people to back pain in later life may help identify at-risk populations and inform future prevention strategies. Prevention of back pain in adolescence could help the prevention of back pain into adulthood [4].

Some potential risk factors definitely occur before the inception of the disease; we define these variables as temporal precursors. Temporal precursors are variables known to have a definite preceding temporal relationship with a disease (e.g., sex, age, pubertal status, family history, family socioeconomic factors, and height). Conversely, other factors studied may not have occurred prior to the onset of the disease, and they can have a bidirectional relationship with the disease of interest. If such potential risk factor is measured concurrently with back pain, then we cannot know if the potential risk factor preceded the back pain or not. Examples include body mass index (BMI), muscle endurance and flexibility, posture, physical activity behaviour, work, screen time, inadequate sleep, smoking, illnesses, and psychosocial factors.

Due to the vast number of studies on "risk factors" for back pain a two part scoping review of the literature was chosen as the best way to summarise the evidence. Part I of this scoping review *(Potential risk factors and triggers for back pain in children and young adults. A scoping review, part I: incident and episodic back pain)* studied risk factors of incident and episodic back pain. In Part II we aimed to identify all risk factors and triggers for back pain (unclear or mixed types of back pain) in young people and to identify any gaps in the literature. Moreover, in this second part, all eligible studies (unclear or mixed types of back pain) that tested potential risk factors of back pain and triggers of its further episodes were included.

Methods

The full methods are reported elsewhere *(Potential risk factors and triggers for back pain in children and young adults. A scoping review, part I: incident and episodic back pain).* However, a summary of the methods is provided below. We undertook a scoping review in accordance with reporting guidelines (PRISMA-ScR) [5]. A review protocol was not included in a registry as PROSPERO does not currently accept registrations for scoping reviews. The broad question of interest was *what are the potential risk factors and potential triggers for back pain in childhood and young adulthood?* 'Back pain' was defined as pain within the thoracic and/or lumbar areas. A search was conducted using the PubMed and Cochrane databases from inception to September 2018. The full search strategy is listed in Additional file 1. Results of the search were reported as per the PRISMA flow diagram (Fig. 1).

Eligibility criteria

We included studies that reported on potential risk factors or triggers for pain in the thoracic and/or lumbar spine (a risk factor is the cause of 'disease' of back pain defined as the first time they have back pain compared to a trigger, which could lead to an episode of back pain when the disorder of back pain is already established). The majority of the participants were to be less than 25 years old at baseline. The age classification is based on the MeSH definition of a young adult (19–24 years). Additionally, the contemporary definitions of adolescence includes young adulthood (10–24 years) [6]. Original peer-reviewed studies in the English language from any country of origin were included and study designs comprised retrospective, cross-sectional, and prospective observational studies. Cross-sectional studies were only included if the potential risk factors met Bradford Hill's tenet of temporality for the study of risk factors or triggers (i.e., if the exposure was classified as a temporal precursor e.g. age) [7].

Study selection, data charting and synthesis of results

Titles, abstracts, and full-text articles were screened by one researcher (AB) twice (March 2018 and then September 2018) against the inclusion criteria. The second search identified four additional articles due to the passage of time. Another researcher (BW) verified the study selection for accuracy (titles, abstracts, and full-text screen) and full consensus was met through discussion.

Calibration of the data charting forms was conducted by two researchers (AB and CLY). One researcher (AB) piloted the form on three studies. This process was verified by another researcher (CLY). This was an iterative process in which there were many changes during each round. Any disagreements were resolved by a third researcher (BW).

Charting of data (data extraction in scoping reviews [8]) was completed by one researcher (AB) using the evidence tables. This information was checked for errors several times with an audit of all data entered with at least a week between each audit. Potential risk factors or triggers were separated into temporal precursors or potentially bidirectional risk factors. Results for the cross-sectional and prospective studies are reported together for potential risk factors that are inherently present before the back pain

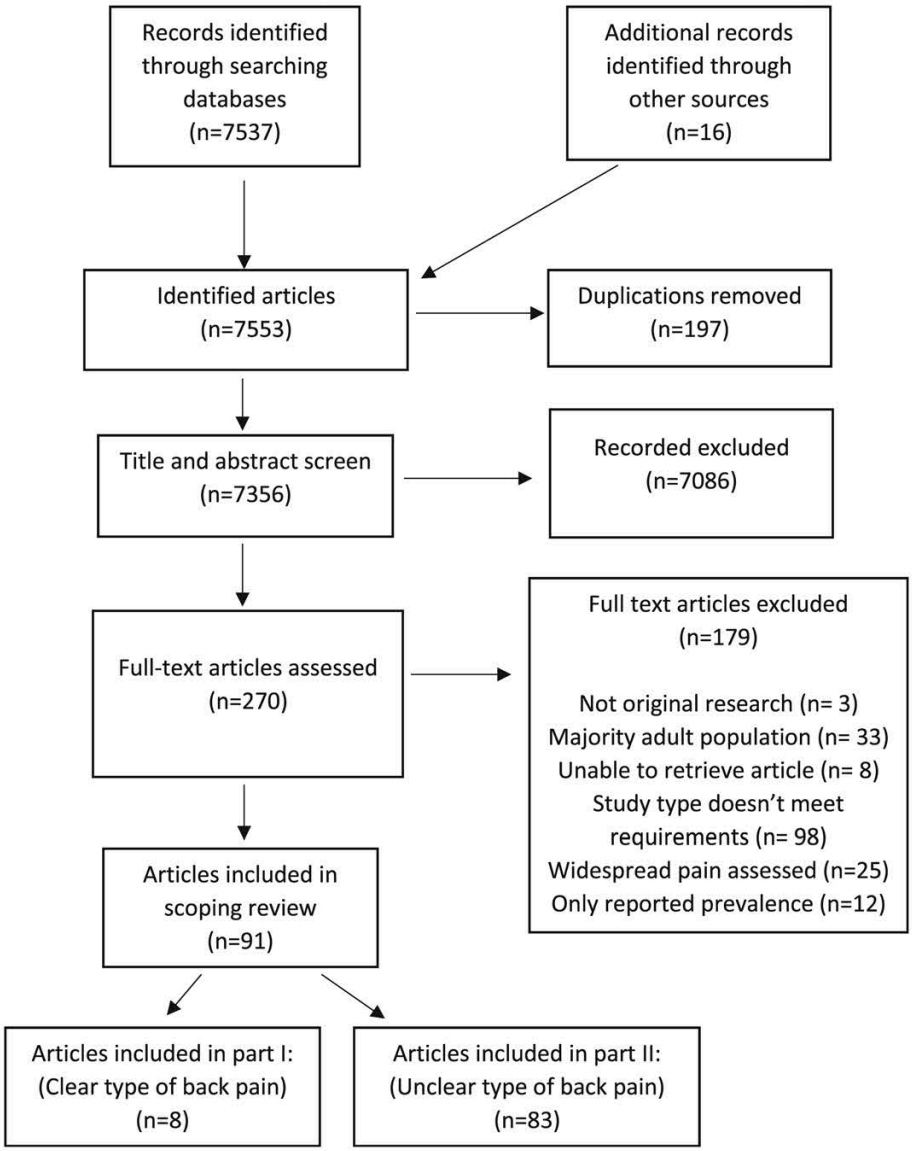

Fig. 1 Final study selection flow diagram

(temporal precursors). If a study had multiple estimates for the same risk factor the most adjusted estimate of association was extracted. Clarity of definition of back pain was assessed in each study with a summative score provided. Individual points were given if there was a clear description of the area of back pain, a clear reporting of the recall period, a clear definition of the type of back pain, and if there was an attempt to collect valid data (maximum four points).

Results

Study selection

Our database searches identified 7537 articles and a subsequent search of the relevant references lists resulted in an additional 16 articles. In all, 91 articles were considered eligible for this review. Eight studies appeared to have studied risk factors of incident back pain and back pain episodes (reported in part I). Within part II, 83 studies were included, as these failed to clearly identify whether they studied inception events or ongoing/episodes of back pain (Fig. 1).

Study characteristics and synthesis of results

Of the 83 articles included in this review, 30 (36%) were prospective cohort studies [4, 9–37]. The majority of cohort studies did not have a clear description of back pain or captured a mixture of back pain types. Thus, many studies appear to have dealt with either back pain episodes or the incidence of back pain. They only

considered a limited time frame and did not report details of the previous pain-free period. Therefore, these studies could reflect a mixture of first time, recurrent, and ongoing back pain episodes.

The included studies included temporal precursor variables such as sex, age, pubertal status, family history, socioeconomic status, and height. Potential bidirectional variables included BMI, muscle endurance and flexibility, posture, physical activity and work, screen time, inadequate sleep, carrying bags, smoking, illnesses, and psychosocial factors. Charts of the summary of findings are reported in Additional file 2.

There were 53 cross-sectional studies included in this review [38–90]. These studies reported factors that could potentially be associated with back pain such as sex, age, pubertal status, family history, and socioeconomic status. Charts of the summary of findings are seen in Additional file 3.

Temporal precursor variables

Sex

In the 53 studies reporting on sex and back pain, 32 studies found a positive association with female sex and back pain, three studies found a higher prevalence of back pain in males, and 18 studies found no association with sex (Table 1). There was generally a positive association between female sex and back pain.

Age

In the 34 studies reporting on age and back pain (Table 1), there was generally a higher prevalence of back pain with advancing age in children towards adolescence and young adulthood.

Family history

In the 19 studies reporting on family history and back pain (Table 1), there was by and large a higher prevalence in those with a positive family history of back pain.

Socioeconomic status

In 15 studies there were inconsistent estimates of association for the relationship between socioeconomic factors and back pain. Seven studies reported positive associations between certain socioeconomic factors and back pain, whereas eight studies reported no association (Table 1).

Increased height or increased growth spurt

In the 12 studies on height or increased growth there were inconsistent estimates of association for the relationship between these and back pain (Table 1). Overall height does not appear to be a risk factor for back pain. However, the occurrence of 'growth spurts' has been found to be positively associated with back pain.

Pubertal status

As demonstrated in Table 1, in the six studies that reported on pubertal status and back pain, there was an association with back pain typically seen in those with an advanced pubertal status.

History of back pain

Three studies reported on history of back pain and risk of further back pain (Table 1). All studies found a positive association with odds ratios ≥2.7.

Bidirectional variables

Physical activity and work

Ten studies considered physical activity and/or work as a potential risk factor of back pain. Six studies reported that with certain types of physical activity or work there was an increased prevalence of back pain, whereas four studies found no association (Table 2). It appears certain types of work such as white-collar work or manual work, and vigorous or high levels of physical activity may be associated with back pain.

Psychosocial factors

In the seven studies that tested psychosocial factors as risk factors of back pain, four studies found an increased risk of back pain, while three studies found no association (Table 2). Some psychosocial factors (depression, anxiety and 'peer problems') were associated with back pain while internalising, anxiety sensitivity, dysfunctional coping, and catastrophizing were not associated with future back pain.

Body mass index

In the eight studies that reported on BMI and back pain (Table 2), three studies reported an increased prevalence and five studies found no association (Table 2). There were inconsistent estimates of association, with insufficient evidence to conclude that there is a relationship between BMI and back pain.

Smoking

In the six studies that reported on smoking and back pain (Table 2), all found a positive association between the two. It does appear that smoking has some relationship with back pain.

Systemic factors /illnesses

Four studies tested systemic factors or illnesses as potential risk factors of back pain. Three studies found positive associations whereas one found none (Table 2). Associations with back pain were stronger with certain

Table 1 Summary of temporal precursor variables: cross-sectional and prospective studies

Variable	Number of studies	Number of studies: Increased risk	Number of studies: Decreased risk	Number of studies not significant	Strength of association (95% CI)	
Female sex	53	32	3	18	*Positive association:* OR 1.9 (1.4, 2.0) (c) [10] OR 1.9 (1.4, 2.4) (c) [16] OR 2.4 (1.9, 3.1) (LBP), OR 2.2 (1.6, 2.9)(MBP) (c) [17] OR 1.6 (1.2, 2.0) [26] OR 1.7 (1.4, 2.1) (c) [28] OR 1.6 (1.4, 2.0) (c) [29] OR 7.7 (4.7, 12.6)) [34] OR 1.7 (1.5, 2.0) [39] OR 1.3 (1.4, 3.3) [42] OR 1.5 (1.2, 1.8) [43] OR 2.2 (1.4, 3.3) [44] OR 1.5 (1.1, 1.9) [45] OR 1.5 (1.1, 1.9) [47] OR 2.4 (1.7, 3.3) [51] OR 1.5 (1.0, 2.1) [53] OR 2.1 (1.6, 2.9) [54] OR 1.4 (1.0, 2.1) (c) [58]	OR 1.1 (1.1, 1.2) [59] OR 1.9 (1.7, 2.2) [64] OR 2.1 (1.6, 2.7) [66] PR 1.1 (1.1, 1.2) [69] PR 1.2 (1.1, 1.3) [70] OR 1.6 (1.3, 2.1) [74] OR 1.8 (1.2, 2.7) (c) [76] OR 4.6 (1.8, 11.7) [78] OR 2.2 (1.6, 2.9) [77] OR 2.4 (1.9, 3.2) [79] OR 1.6 (1.3, 2.0) (c) [81] OR 1.8 (1.3, 2.4) (c) [83] OR 2.7 (1.2, 6.1) [84] Females: 28%, Males 19% [85] OR 1.9 (1.3, 3.0) [89] *Negative association:* Males: HR 3.2 (2.7, 3.7) [27] OR 0.6 (0.4, 0.8) [50] OR 0.3 (0.2, 0.5) (c) [68]
Older Age	34	19	2	13	*Positive association:* OR 2.9 (2.6, 3.3) (c) [32] OR 1.5 (1.1, 2.3) [35] OR (17 index), 21 yr 2.2 (1.2, 4.2), 23 yr 3.2 (1.7, 6.2), 24 yr 2.8 (1.5, 5.3) [42] OR (10–11 index), 12–14 yr: 1.1 (1.1, 1.3) [47] OR 1.1 (1.1, 1.2) [51] (15 index) 16/17 yr OR 1.7 (1.2, 2.3), 18/19 yr: OR 1.8 (1.2, 2.8) [53] 14 to 15 yr: 6.4% increase [54] OR 1.2 [58] *r* 0.2 [61] (17/18 index), 21+ yr: OR 1.6 (1.2, 2.1) [65] (10–12 index), 13–16 yr: OR 1.5 (1.2, 2.0) [66] (per year): OR 1.2 (1.1, 1.4) [72] OR 1.2 (1.1, 1.3) [74] Older 25.1%, younger adolescents 12.4% [75] (12 index), 14 yrs.: OR 1.3 (1.1, 1.7) [80] Younger age: OR 1.5 (males), OR 1.4 (females) [81] 11 yr 18%, 14 yr 34% (girls) 11 yr 14%, 14 yr 25% (boys) [85] OR 1.3 (1.1, 1.7) [88] OR 1.3 (1.2–1.4) [89] *Negative association:* Younger age: OR 0.2 (0.1, 0.6) [46] OR 0.5 (0.4, 0.6) [67]	
Positive family history	19	15	0	4	OR 3.6 (1.3, 10.2) [11] OR 2.1 (1.4, 3.1) [35] OR 2.0 (1.1, 4.0) [36] OR 2.6 (1.4, 5.9) [38] OR 2.1 [40] OR 3.8 (2.9, 5.9) [41] OR 1.8 (1.4, 2.4) [43] OR: 1.5 (1.1, 1.9) (c) [48]	OR 1.7 [58] OR 1.8 (1.5, 2.0) [64] PR 1.2 (1.2, 1.3) [69] PR 1.2 (1.1, 1.3) [70] OR 2.0 (1.2, 3.3) [72] OR 2.3 (1.2, 4.7) [89] OR 2.6 (1.9, 3.6) [90]
Socioeconomic factors	15	7	0	8	Higher Socioeconomic index:	

Table 1 Summary of temporal precursor variables: cross-sectional and prospective studies *(Continued)*

Variable	Number of studies	Number of studies: Increased risk	Number of studies: Decreased risk	Number of studies not significant	Strength of association (95% CI)
					OR 0.8 (0.7, 1.0) [34] Higher social class: OR: 0.9 (0.8, 0.9) [55] Parental low level of education: OR 1.8 (1.1, 2.0) [62] Ethnicity: (Index white) Asian PR: 1.2 (1.1, 1.4), indigenous PR: 1.4 (1.3, 1.5) [70] Non-white: PR 1.4 (1.0, 1.9) [71] Location (index peripheral center) Urban centre: OR 3.1 [73] Residence: 52% (city), 43% (village) [83]
Increased height or increased growth spurt	12	4	1	7	High growth spurt: OR 3.1 (1.5, 6.0) [4] linear growth: IRR 1.2 (1.2, 1.2) [18] Shorter than median height (158 cm): RR 2.1 (1.2, 3.8) [23] Height: OR 1.2 (1.0–1.5) [31] Taller: *t* test – 3.3 [58]
Later pubertal status	6	4	1	1	*Positive association* IRR 1.5 (1.2, 2.0) (Tanner stage 2), IRR 2.1 (1.5, 3.0) (Tanner stage 3) IRR 3.3 (2.1, 5.0) (Tanner stage 4/5) [18] OR 1.6 (1.3, 2.0) (USA), OR 1.3 (1.1, 1.6) (Dutch) [22] OR 2.0 (girls), OR 1.9 (boys) [63] Stage 4: OR 2.0 (1.3, 3.5), stage 5: OR 2.1 (1.1, 1.4) [86] *Negative association:* HR 0.6 (0.5, 0.8) (males) [27]
History of back pain	3	3	0	0	BP in adolescence for BP in adulthood: OR 4.3 (3.5, 5.4) [21] History of BP: OR 2.7 (1.1, 7.1) (ever), OR 9.1 (3.0, 27.2) (> 7 days) [33] History of BP: OR 7.7 (4.7–12.6) (girls) [34]

OR odds ratio, *PR* prevalence ratio, *HR* hazard ratio, *RR* relative risk, *IRR* incidence rate ratio, *LBP* low back pain, *MBP* mid back pain, *BP* back pain, (c): parameter measure calculated from the provided results within study i.e. percentages converted to odds ratios

systemic diseases such as having asthma, headaches, abdominal pain, and colds/minor illnesses. These may be co-morbidities to back pain, meaning that one could be a precursor to the other or they could have a common cause.

Spinal posture and sitting posture

Four studies reported on certain aspects of posture and back pain (Table 2). All four studies indicated that from a preliminary viewpoint abnormal spinal posture and certain sitting positions were associated with back pain.

Sleep

As seen in Table 2, in the three studies that reported on sleep and back pain, there was a positive association between back pain and insufficient sleep.

Flexibility

Three studies tested muscle flexibility as a risk factor for back pain (Table 2). Two studies found a positive association with decreased flexibility of hamstrings or quadriceps, and back pain, while one study found no association.

Screen time

Three studies reported inconsistent estimates of associations between screen time and back pain. One study reported a higher prevalence of back pain with increased television time, whereas two reported none (Table 2).

Backpack factors

In three studies, there were inconsistent estimates of association between backpack factors and back pain. One study of these three reported a higher prevalence of back pain with a heavier school satchel (Table 2).

Table 2 Summary of bidirectional variables

Variable	Number of studies	Number of studies: Increased risk	Number of studies: Decreased risk	Number of studies not significant	Strength of association (95% CI)
Physical activity/work	10	6	0	4	Playing sport OR 9.5 (1.9, 48.2) [11] White collar work OR 4.9 (1.7, 14.2) [13] Vigorous intensity physical activity: OR 1.2 (1.0–1.4) (diagnostic spinal pain) OR 1.3 (1.0–1.5) (traumatic) [15] High level sports activity RR 1.6 (1.1, 2.3) [24], Part-time work RR 1.5 (1.1, 2.1) [24] Provoked by manual work: OR 9.2 (2.9, 28.8) [33] Increased physical activity OR 1.9 (1.2, 2.8) [34]
Psychological factors	7	4	0	3	High level of peer problems: RR 2.3 (1.3, 4.2) [23] High level of psychological factors: RR 1.6 (1.1, 2.3) [24] Externalising behaviour: RR 1.5 (1.3, 1.7) (boys), RR 1.4 (1.3, 1.5) (girls), RR 3.6 (1.5, 8.5) (girls 18) [28] High levels of aggressive behaviour OR 1.4 (1.2, 1.6) [34] High level of somatic complaints OR 1.3 (1.1, 1.5) [34]
Higher BMI	8	3	0	5	OR 1.3 (1.0, 1.5) [11] RR 1.1 (1.0, 1.2) (girls), RR 1.1 (1.0, 1.3) (boys) [29] OR 2.9 (1.7, 5.1) (9 yr), 2.2 (1.4, 3.5) (10 yr), 1.6 (1.2, 2.1) (13 yr) [32]
Smoking	6	6	0	0	OR 2.2 (1.4, 3.5) [4] OR 2.4 (1.3, 6.0) [14] OR 3.1 (1.1, 9.2) (MB), 1.8 (1.2, 2.8) (BP) [17] OR 1.7 (1.4, 2.1) [19] HR 1.6 (1.4, 1.9) [27] OR 2.5 (1.4, 4.5) (females) [30]
Illness	4	3	0	1	Asthma OR 1.4 (1.1, 1.7) (female) [20] Headache OR 1.6 (1.1, 2.1) (female), OR 2.4 (1.2, 4.7) (male) [20] Abdominal pain RR 1.8 (1.1, 3.0) [24] Headache OR 2.4 (1.8, 3.1) [26]
Posture/ sitting position	4	4	0	0	No LB support: OR 1.7 (1.2, 2.6), OR 2.9 (1.1, 3.5) (persistent LBP) [25] Provoked by sitting OR 3.8 (1.3, 11.3) [33] Non-neutral standing posture OR 2.2 (1.3, 3.6) [34] Uncomfortable school desk OR 6.0 (3.7, 9.7) [35]
Insufficient sleep	3	3	0	0	OR 2.9 (1.7, 5.2) (girls), OR 2.4 (1.3, 4.5)(boys) [10] OR 2.2 (1.7, 3.8) [35] OR 1.2 (1.1, 1.4) [36]
Flexibility	3	2	0	1	Decreased flexibility: hamstrings OR 1.1 (1.0, 1.1) [4] Decreased flexibility: quad muscles: OR 1.7 (1.1, 2.8) [25]
Screen time	3	1	0	2	Increased TV time OR 2.0 (1.4, 2.9) [35]
Backpack factors	3	1	0	2	Heavy school satchel OR 2.2 (1.0, 4.8) [36]
Muscle endurance	1	1	0	0	Poor back muscle endurance OR 1.9 (1.2, 3.0) [34]

OR odds ratio, *RR* relative risk, *HR* hazard ratio, (c) parameter measure calculated from the provided results within study i.e. percentages converted to odds ratios

Muscle endurance

In the one study that tested muscle endurance as a risk factor of back pain, it was found that those with poor back muscle endurance had a positive association with back pain (Table 2).

Discussion

Overall summary of potential risk factors from all studies

Considering the existing literature, the factors found to be likely risk factors or triggers for back pain are female sex, older age, advanced pubertal status, high growth rate, positive family history of back pain, a history of back pain, smoking, and insufficient sleep. Most of these factors are temporal precursor. Further, they are mostly biological and non-modifiable, making them ineligible targets for preventative interventions. No association or weak associations were noted with increased screen time and work. There were mixed results for muscle flexibility, socioeconomic status, backpack-related factors, anthropometric measures including height and weight, and physical activity. There was limited research for systemic/illness

factors, muscle endurance, spinal posture, and sitting position (Table 3).

Implications of results

Previous systematic reviews found the most likely risk factors for back pain in young people to be female sex [91–93], older age [91, 92, 94], advanced pubertal status [95], positive family history of back pain [96], and a previous history of back pain [93, 97]. We advanced this knowledge by further considering the temporal relationship between the risk factors and back pain and we concluded that the most likely risk factors or triggers for back pain are predominantly biological. For example, the genetic component of back pain is potentially large [98]. A systematic review found that estimates of heritability effects ranged from 21 to 67% [99]. However, environmental exposures also have an effect, so the question arises; how large is this effect? This question could be addressed through further twin control studies. Twin studies have an advantage of reducing confounding due to genetics and can be utilised to explore the potential causal pathway between environmental factors, co-morbidities and back pain [99].

Considering the strength of associations, some factors were statistically linked to back pain, but the next question arises, are they important on a clinical or individual level?

Another issue to consider is that individual associations may well be relatively weak, but it is possible that combination of factors or the addition of factors could increase the risk of back pain rather than individual factors. This idea has been proposed previously through a dynamic multifactorial and recursive model of aetiology [100]. This model emphasizes the importance of investigating intrinsic predisposing factors along with the extrinsic factors that interact together to make an individual vulnerable to injury [100]. Certain predictive risk factors could predispose individuals to back pain, and then in combination with other potentially causal risk factors, the individual could develop back pain. For example, girls (factor 1) with advanced pubertal status (factor 2) could be susceptible to back pain that is subsequently caused by vigorous physical activity (factor 3). Therefore, from a clinical perspective, it might be important to consider the person as a whole.

Limitations of the current literature

The foremost limitations of the current literature are that the majority of studies are cross-sectional, or if longitudinal, most do not start data collection before the onset of back pain. To investigate temporality, one criterion to establish causal relationships, risk factors should be captured before the inception of the disease [101]. Therefore, the conclusions of this scoping review

Table 3 Summary of Potential Risk factors

Potential risk factor	Likely	Weak/no significance	Mixed results/ inconsistent	Limited research
Female sex	X			
Older age/ advanced pubertal status	X			
Positive family history of back pain	X			
Increased growth spurt	X			
History of back pain	X			
Smoking	X			
Insufficient sleep	X			
Increased screen time		X		
Work		X		
Psychosocial factors			X	
Muscle flexibility			X	
Socioeconomic status			X	
Backpack related factors			X	
Height and weight			X	
Physical activity			X	
Spinal posture				X
Sitting position				X
Systemic/illness factors				X
Muscle endurance				X

are limited to demonstrating association and not causation. Additionally, the definitions of 'back pain' vary from study to study (Additional files 4 and 5), this means it is not clear whether authors are considering back pain as a disease or an episode [101], or whether they are asking about back pain currently, for the past week, for the past month, or for the past year. Although the purpose of this review was to include risk factors or triggers for pain the thoracic and/or lumbar spine, some of the included studies included spinal pain in general [9, 15, 16, 18, 35, 39, 86–89]. While other studies included back pain without a clear definition of location [22, 26, 49, 50, 56, 61, 63, 69, 70, 74, 81], and therefore it is unclear what they were looking at. As the definitions on back pain are not always clear or inconsistent it is difficult to make clear definitive statements.

Limitations of this review

A potential limitation of the validity of data collected in this scoping review is that only one researcher screened and conducted data charting. Nevertheless, articles were screened twice, by the same reviewer, and a second researcher verified the process, which is consistent with the PRISMA-ScR guidelines. Only two key databases were searched, and articles were limited to English language. Consequently, we may have missed some articles. Nevertheless, this type of literature is quite stereotyped, for which reason it is unlikely that any missing articles would be of significance.

There were some contradictory findings in our result tables. Contradictory findings often result from differences in study populations, definitions of the outcome or independent variables, and differences in data quality. However, due to the nature of scoping reviews, which lack the critical approach of systematic reviews, such contradictions cannot be interpreted. Due to the nature of conflicting data the summary of potential risk factors is indicative but not unequivocal.

Recommendations for future research

Future studies should collect data from the inception of back pain by following the population from earlier life, if searching for causes of the 'disease' back pain. They should additionally collect data on proposed risk factors before the onset of back pain. If studies are attempting to identify triggers of future events, back pain episodes must be separated by non-episodes.

As highlighted within this scoping review (Additional files 4 and 5), future research should ensure that data are collected with a clear definition of back pain and ideally measured through a validated questionnaire. Additionally, future research should be more innovative in the way that risk factors are considered. This could be through statistical approaches including cumulative exposures, or longitudinal approaches such as multi-trajectory methods and through the use of twin studies.

Conclusion

Many of the included studies approached identifying risk factors in similar ways and found factors that were associated with back pain but were not obvious risk factors as causality was uncertain. Obviously, the time has come to approach this problem in other ways. It is our opinion that future research should be more rigorous and innovative in the way that risk factors for back pain are considered.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12998-019-0281-8.

Additional file 1. Search strategies used for the literature search. The full search strategy for PubMed and Cochrane databases.

Additional file 2. PROSPECTIVE STUDIES reporting factors that are longitudinally associated with back pain. Table summarising each included prospective study.

Additional file 3. CROSS-SECTIONAL STUDIES reporting factors that are associated with back pain. Table summarising included cross-sectional study.

Additional file 4. Clarity of definitions of Back pain: Prospective studies. Table summarising the clarity of the definitions of back pain in included prospective studies.

Additional file 5. Clarity of definitions of Back pain: Cross-sectional studies. Table summarising the clarity of the definitions of back pain in included cross-sectional studies.

Abbreviations

BMI: Body mass index; BP: Back pain; CI: Confidence intervals; HR: Hazard ratio; IRR: Incidence rate ratio; LBP: Low back pain; MBP: Mid back pain; N: Number of participants; NA: Not applicable; OR: Odds ratio; PR: Prevalence ratio; RR: Relative risk

Acknowledgements

This research was carried out with funding provided by Chiropractic Australia Research Foundation.

Authors' contributions

All authors contributed to the design of the study. AB conducted the search, study selection and data charting. AB analysed and interpreted the data with the assistance of BW, JH and CLY. AB drafted the manuscript and performed revisions with substantial feedback and editing from all authors. All authors read and approved the final manuscript.

Funding

This study was funded by a scholarship from Murdoch University, Western Australia and funding provided by Chiropractic Australia Research Foundation. JH receives salary support from the Canadian Chiropractic Research Foundation and the New Brunswick Health Research Foundation. The funding sources had no involvement in study design, analysis, interpretation, or manuscript preparation.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
BW and JH are both editors and CLY is Senior Editorial Advisor of *Chiropractic & Manual Therapies* but played no part in the review of this submission and were blinded to the process. JH is an executive member of the Chiropractic Australia Research Foundation.

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Received: 10 April 2019 Accepted: 9 September 2019
Published online: 19 November 2019

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Publisher's Note

Summary of Chapter Two (Parts I and II) and link to next chapter

Based on the evidence contained within part I of this scoping review, the risk factors most consistently reported as being associated with incident back pain in the reviewed studies were female sex and older age. When we consider all the literature (including studies that have unclear or mixed definitions of back pain- part II) the most likely risk factors or triggers are female sex, older age, later pubertal status, high growth rate, positive family history of back pain, and a prior history of back pain. Limited research was identified for systemic/illness factors, muscle endurance, spinal posture, and sitting position.

Most of the included studies were found not to provide an adequate definition of back pain; therefore, it was unclear if they included populations with incident, episodic, or ongoing back pain. This lack of clarity with respect to definitions for back pain resulted in an inability to directly compare studies and reach more definitive conclusions. Many studies were cross-sectional, or if longitudinal, were not inception cohorts. Therefore, the results are mainly restricted to associations and we were unable to determine the existence of causal relationships.

Notably, based on the results from this scoping review, we saw the importance of considering sex and age as covariates in our future analyses. Further, we determined that it was important to consider physical illnesses and psychological factors as potential risk factors for back pain. This was accomplished using a systematic review.

Chapter Three- Systematic review: Chronic physical illnesses, mental health disorders, and psychological features as potential risk factors for back pain from childhood to young adulthood

After taking a broad look at the literature within the scoping review, we focussed on chronic physical illnesses, mental health disorders, and psychological features as potential risk factors for back pain from childhood to young adulthood using systematic review methodology.

This work underwent peer-review and is published as:

Beynon AM, Hebert JJ, Hodgetts CJ. Boulos LM, Walker BF. Chronic physical illnesses, mental health disorders, and psychological features as potential risk factors for back pain from childhood to young adulthood: a systematic review with meta-analysis. Eur Spine J 29, 480–496 (2020). DOI: 10.1007/s00586-019-06278-6

As of 24/02/2021: Article accesses: 591. Citations: 3. Altmetric: 18

European Spine Journal (2020) 29:480–496
https://doi.org/10.1007/s00586-019-06278-6

REVIEW ARTICLE

Chronic physical illnesses, mental health disorders, and psychological features as potential risk factors for back pain from childhood to young adulthood: a systematic review with meta-analysis

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Received: 27 August 2019 / Revised: 27 August 2019 / Accepted: 29 December 2019 / Published online: 6 January 2020

Abstract

Purpose To report evidence of chronic physical illnesses, mental health disorders, and psychological features as potential risk factors for back pain in children, adolescents, and young adults.

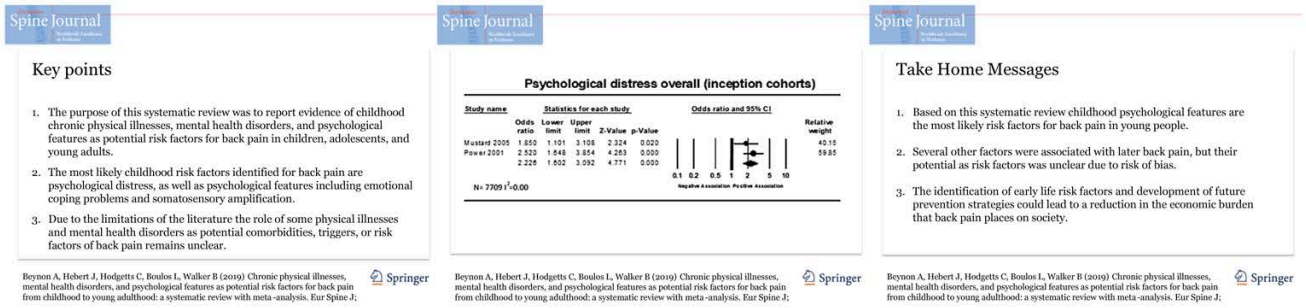
Methods This systematic review and meta-analysis included cohort and inception cohort studies that investigated potential risk factors for back pain in young people. Potential risk factors of interest were chronic physical illnesses, mental health disorders (e.g. depression, anxiety), and other psychological features (e.g. coping, resistance). Searches were conducted in MEDLINE, Embase, CINAHL, and Scopus from inception to July 2019.

Results Nineteen of 2167 screened articles were included in the qualitative synthesis, and data from 12 articles were included in the meta-analysis. Evidence from inception cohort studies demonstrated psychological distress, emotional coping problems, and somatosensory amplification to be likely risk factors for back pain. Evidence from non-inception cohort studies cannot distinguish between risk factors or back pain triggers. However, we identified several additional factors that were associated with back pain. Specifically, asthma, headaches, abdominal pain, depression, anxiety, conduct problems, somatization, and 'feeling tense' are potential risk factors or triggers for back pain. Results from the meta-analyses demonstrated the most likely risk factors for back pain in young people are psychological distress and emotional coping problems.

Conclusion Psychological features are the most likely risk factors for back pain in young people. Several other factors were associated with back pain, but their potential as risk factors was unclear due to risk of bias. Additional high-quality research is needed to better elucidate these relationships.

Graphic abstract

These slides can be retrieved under Electronic Supplementary Material.



Keywords Back pain · Systematic review · Meta-analysis · Risk factors · Children · Young adult

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-019-06278-6) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Abbreviations

QUIPS	Quality In Prognostic Studies tool
OR	Odds ratio
RR	Risk ratio

CI	Confidence intervals
N	Number of participants
SD	Standard deviation
NR	Not reported
NA	Not applicable
BP	Back pain
LBP	Low back pain
MBP	Mid-back pain
β	Beta
BMI	Body mass index

Introduction

Low back pain is the leading cause of years lived with disability worldwide [1] and affects people of all ages, including children [2, 3]. Low back pain etiology is complex and has many contributors, including social factors, physical factors, psychological factors, and certain comorbidities [4].

Asthma, allergies, and depression are reportedly associated with low back pain from adolescence to adulthood [5, 6]. A systematic review and meta-analysis of cross-sectional twin studies found that young people and adults with chronic conditions such as asthma, diabetes, and headaches were more likely to report low back pain (pooled OR range 1.6–4.2) [7]. Respiratory and digestive disorders also demonstrate cross-sectional and longitudinal associations with back pain in adults [8, 9]. Similarly, a history of cardiovascular disease is associated with increased risk of chronic low back pain in adults [10]. A large Canadian National Population Health Survey reported that adolescents and adults living with major depression were almost three times more likely to report back pain 2 years later [11].

Some etiological studies report risk factors for back pain, while others report factors that are associated with back pain. Risk factors are variables that are causally related to a change in the risk of a health process, outcome, or condition [12]. In back pain research, it is important to distinguish between potential risk factors that cause the initial onset of pain and triggers that may precipitate an episode of pain [13]. Studies investigating potential risk factors and triggers of back pain have often included adult populations in which it is difficult to identify disease-free (i.e. no history of back pain) cohorts. It would, therefore, be of value to consider young populations, ideally before the onset of back pain, to determine whether chronic illnesses and mental health conditions are in fact risk factors for back pain rather than comorbidities.

The purpose of this systematic review was to investigate whether chronic physical illnesses, mental health disorders, and psychological features are potential triggers or risk factors for back pain in children, adolescents, and young adults.

Methods

The study protocol was prospectively registered with Prospero (CRD42019119226). This systematic review and meta-analysis adhere to the Preferred Reporting Items for Systematic Review and Meta-Analysis [14] and to the Meta-analyses Of Observational Studies in Epidemiology guidelines [15].

Eligibility criteria

We included original peer-reviewed cohort or inception cohort studies that investigated potential risk factors for pain in the thoracic and/or lumbar spine (i.e. back pain) in children, adolescents, and young adults. Potential risk factors of interest were chronic physical illnesses such as cardiovascular disease, respiratory tract disease, digestive system disease, endocrine disease, or immune system disease, as well as mental health disorders (e.g. depression, anxiety), or other psychological features (e.g. coping, resistance). Back pain outcomes were either self-reported or clinically evaluated. We excluded studies when the mean baseline age was greater than 24 years of age. We did not exclude studies based on the language of publication.

Search strategies

Systematic searches were conducted in MEDLINE (Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions), Embase, CINAHL with Full Text, and Scopus from inception to 30 July 2019. Reference lists of included papers were searched to identify other potentially suitable studies.

The search was conducted by a health librarian (LB), using a back pain filter developed for the Cochrane Back and Neck Group. Due to the large recall of the search, scope was limited to risk factors by employing the causation (etiology) best balance filter developed by the McMaster Hedges Team [16]. We applied a modified age filter to identify paediatric studies [17]. A study-type filter was adapted from the SIGN Observational Studies filter; cross-sectional study queries were removed [18]. The full search strategies for each database are listed in Online Resource 1.

Search results were imported into bibliographic management software (EndNote X9.2) and duplicates discarded.

Study selection, data extraction, and risk of bias

Titles and abstracts were screened by two researchers (AB and CD or CH) against the eligibility criteria. The full text of possibly relevant papers was obtained and again assessed against the same criteria (AB and CH). Disagreements were

resolved through consensus between the reviewers and consultation with a third review author when necessary.

Data from included studies were extracted by two review authors (AB and CH) using a data collection form based on the Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) guideline [19]. Data collection forms were piloted on four studies prior to full data extraction. The piloting process did not result in changes to the form. Disagreements were resolved through consensus or consultation with a third review author.

Included articles were assessed for risk of bias by two review authors (AB and CH) with the Quality In Prognostic Studies (QUIPS) tool [20, 21] (Online Resource 2). We made minor modifications to the QUIPS tool by adopting risk factor language, rather than prognostic factor language, by changing the word prognostic to risk. Six domains were assessed for risk of bias including study participation, study attrition, risk factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. A study with a low overall risk of bias required the majority of the six domains to be scored as a low risk. A study with moderate risk of bias overall would have some items rated as moderate risk of bias within the study. A study with overall high risk of bias would have significant flaws with an associated risk of bias in relation to some of the six domains [20].

Summary of findings and synthesis of results

The characteristics of included studies were tabulated for comparison. Potential risk factors were assessed by the number of times investigated, number of times the factor was found to be associated with the outcome of interest, and the strength of the associations.

Meta-analysis of reported odds ratios (OR) and risk ratios (RR) with 95% confidence intervals [95% CI] were performed using Comprehensive Meta-Analysis v3 software (Biostat, Inc., USA). Data from studies reporting multiple potential risk factors within the same domain (e.g. 'emotional coping problems' and 'feeling tense or stressed') were first combined with fixed effect models to account for the lack of independence between study outcomes [22]. We then applied random effects models to pool data between studies [22]. Where possible, odds ratios were converted to risk ratios as $RR = OR/(1 - P_0 + (P_0 \times OR)$, where P_0 is the baseline risk or the incidence of the outcome of interest in the non-exposed group [23, 24]. Studies were assessed for statistical heterogeneity using I^2 [22, 25]. Although there is no agreement on I^2 interpretation, we applied the following criteria: 0–40% represented low heterogeneity, 30–60% represented moderate heterogeneity, 50–90% represented substantial heterogeneity, and 75–100% represented considerable heterogeneity [25]. Meta-analysis was not considered unsuitable purely due to high I^2 values, given that the individual study estimates were within a reasonable range [26, 27].

Potential risk factors were included in the meta-analysis when data were available from two or more studies. Physical illness and mental health risk factors were considered individually. However, when studies reported on many different psychological features, we further categorized these factors into seven domains: peer problems, emotional coping problems, conduct problems, hyperactivity, somatosensory amplification, feeling tense or stressed, and fatigue/tiredness.

Results

Study selection

We identified 3097 articles through searching databases and one additional record through searching the relevant references lists. After duplications were removed and records screened, 19 articles ($N = 34{,}279$ participants) met the selection criteria and were included in the qualitative synthesis. From these, 12 articles ($N = 25{,}372$ participants) were included in the meta-analysis (Fig. 1). Seven studies were excluded from the meta-analysis owing to methodological or clinical heterogeneity.

Study characteristics

Of the 19 included studies, 16 were prospective cohort studies [5, 28–42] and three were inception cohort studies [43–45]. Study populations were from Australia [30, 33, 41], Canada [32, 42, 44], England [35, 36], Finland [34, 39], UK [40, 45], China [29], Denmark [5], Germany [43], Norway [38], Sweden [28], Thailand [37], and USA [31]. The characteristics of all included studies are reported in Table 1.

Risk of bias assessment

Risk of bias results are presented in Table 2. Two studies were rated as low risk of bias, 12 studies were at moderate risk of bias, and five studies were at high risk of bias. Common sources of bias included study attrition, study participation, and outcome measurement. Study attrition concerns comprised either a high attrition rate or when reasons for drop out were not reported. Regarding study participation, the source population and/or the inclusion and exclusion criteria were often poorly described. The back pain measures were often unclear; many studies did not use validated questions and/or did not clearly specify the type of back pain (e.g. ongoing, episodic or first time). Many studies did not

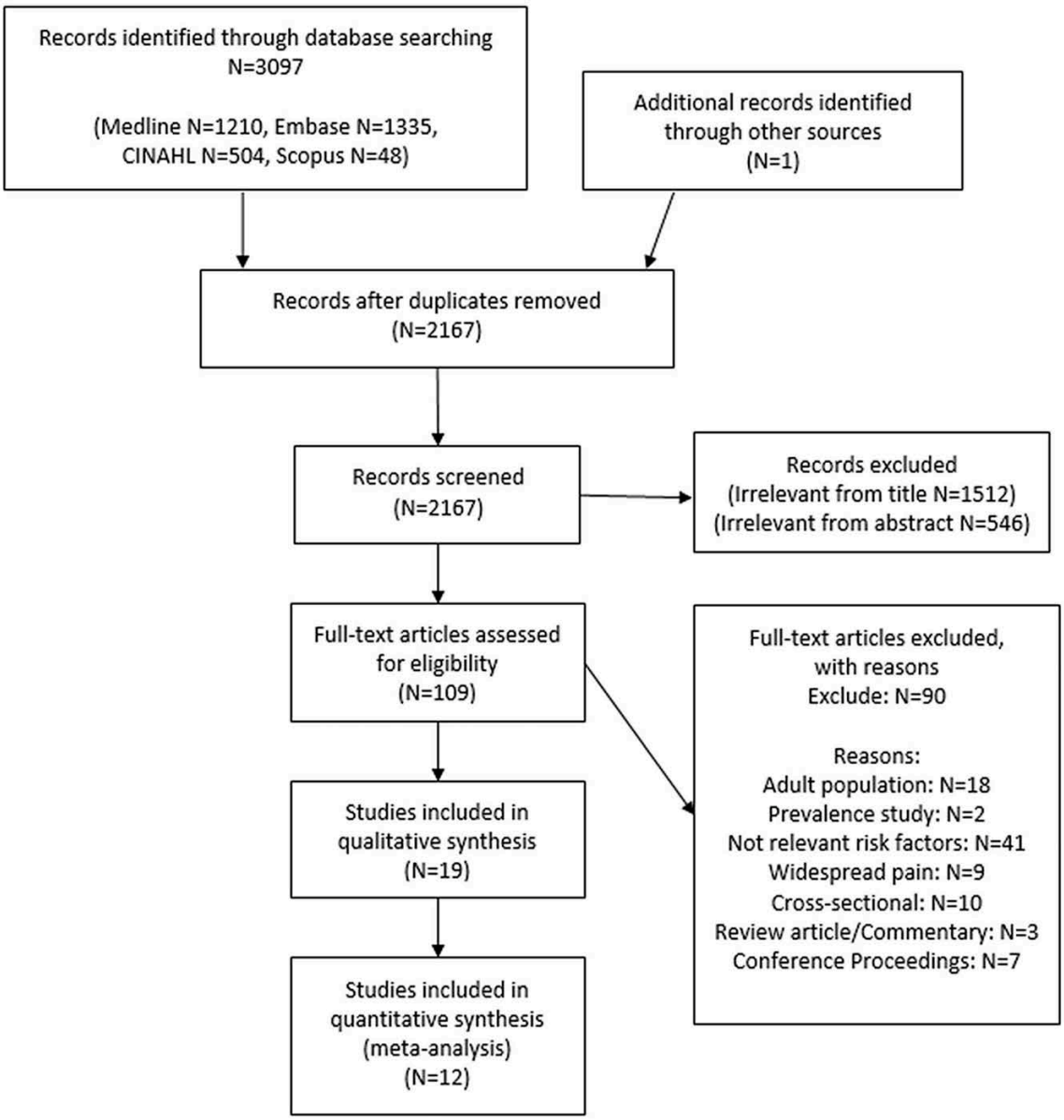


Fig. 1 Study selection flow diagram

report a clear delineation of the area of the back under study, such as with pain diagrams.

Summary of findings

Five prospective cohort studies [5, 29, 35, 36, 40] and one inception cohort study [44] investigated physical illnesses, eight prospective cohort studies investigated mental health disorders [29–33, 38, 41, 42], and 15 studies considered different psychological features as potential risk factors for back pain [28, 29, 31, 33–37, 39–45], of which three were inception cohort studies [43–45]. An overview of the results from all included studies is reported in Table 3.

Physical illnesses

Four cohort studies reported on headaches as a potential risk factor for back pain [5, 29, 35, 36], with two studies reporting no association [35, 36], and two studies reporting increased odds of back pain (OR [95% CI] = 2.5 [1.6, 4.1] (n = 6554) [5], OR [95% CI) = 4.5 [1.8, 11.5] (n = 212) [29]). Abdominal pain was evaluated in three cohort studies [35, 36, 40]; two studies reported an increased risk of back pain (RR [95% CI] = 1.8 [1.1, 3.0] (n = 933) [36], RR [95% CI] = 1.8 [1.3, 2.4] (n = 3271) [40]) among participants with previous abdominal pain, and one study reported no association [35]. One inception cohort study [44] and one

Table 1 Study characteristics of the included studies

Reference, (year), country	Study design, setting/sample	Baseline: sex, age mean (SD)[a]	Sample size: baseline and completed	Follow-up: no. of times, length of time	Back pain definition	Risk factors measures	Confounders	Analysis approach
[43] Barke, (2014), Germany	Inception cohort, representative community sample	46% female, 11.25 (2.28)	Baseline: 3524 Completed: 2040	1, 12 months	Self-reported, first-time BP	Dysfunctional stress coping, pain catastrophizing, anxiety sensitivity, and somatosensory amplification	Age and sex	Logistic regression
[28] Brattberg, (1994), Sweden	Prospective cohort, school	Both % female NR, 8–13	Baseline: 591 Completed: 471	1, 2 years	Self-reported BP 'often'	Fear of schoolmates, loneliness, difficulties making friends, feelings of being outsider, been bullied, passive reactive to bullying, nervousness, difficulties verbalizing feelings, diffuse feelings of anger	Age and gender	NR
[29] Cheung, (2010), China	Prospective cohort, university	78% female, 19.4 (1.12)	Baseline: 265 Completed: 212	3, 2, 12 and 26 months	Self-reported LBP: past week, month and year	Constant tiredness, low mood, feeling tense, under stress, headaches, fatigue and anxiety	Age, gender and height	Multivariate logistic regression
[30] Coenen, (2016),Australia	Prospective cohort, birth cohort	53% female, 17 (NR)	Baseline: 2868 Completed: 1249	2, 3 years, 2 years	LBP, past month	Mental HRQOL (health-related quality of life)	Sex, waist circumference, comorbid pain	Linear and logistic regression, latent class analysis
[31] Dunn, (2011) USA	Prospective cohort, representative community sample	53% female, 11 (NR)	Baseline: 1996 Completed: 1333	11, 3 months	Presence of BP, pain persistence	Depression and somatization	NR	Latent growth curve analysis, ANOVA
[32] Feldman, (2001), Canada	Prospective cohort, high school	47% female, 13.8 (1.2)	Baseline: 810 Completed: 502	2, 6 months	Substantial LBP in last 6 months	Mental health status	Age, gender, smoking	Logistic regression, generalized estimating equations
[33] Gill, (2014), Australia	Prospective cohort, birth cohort	49% female, 14 (NR)	Baseline: 1596 Completed: 1291	1, 3 years	LBP, MBP. No BP last month at 14 years (first time or episodic)	Internalizing and externalizing behaviour, depression	Sex	Logistic regression
[34] Gustafsson, (2018), Finland	Prospective cohort, elementary school	54% female, 10 (NR)	Baseline: 1097 Completed: 568	2, 2 years, 3 years	BP preceding 6 months	Daytime sleepiness, psychological symptoms	Age and sex	Ordinal logistic regression

Table 1 (continued)

Reference, (year), country	Study design, setting/sample	Baseline: sex, age mean (SD)[a]	Sample size: baseline and completed	Follow-up: no. of times, length of time	Back pain definition	Risk factors measures	Confounders	Analysis approach
[5] Hestbaek, (2006), Denmark	Prospective cohort, twin register	52% female, 17.27 (NR)	Baseline: 9600 Completed: 6554	1, 8 years later	LBP, persistent or recurrent BP, past year	Asthma, atopic disease, headaches	Gender and age	Multivariate logistic regression
[35] Jones, (2009), England	Prospective cohort, secondary school	Both % female NR, 11–14	Baseline: 1496 Completed: 178 (54% with LBP at baseline)	2, 1 year, 3 years	LBP, persistent or recurrent past month	Headache, abdominal pain, daytime tiredness, behavioural and emotional characteristics	Age and sex	Poisson regression
[36] Jones, (2003), England	Prospective cohort, secondary school	Both % female NR, 11–14	Baseline: 1446 Completed: 933	1, 1 year	LBP, past month	Psychosocial factors, somatic complaints: headaches, abdominal pain, sore throats	Age and gender	Poisson regression model
[37] Kanchanomai, (2015), Thailand	Prospective cohort, university	74% female, 19.4 (1.1)	Baseline: 2511 Completed: 524	4, 3 months	LBP during previous 3 months	Psychosocial factors	NR	Univariate and multivariate regression models
[38] Lien, (2011), Norway	Prospective cohort, tenth-grade primary school	57% female, 15–16	Baseline: 5750 Completed: 3316	1, 3 years	Self-reported BP last 12 months	Mental distress	Ethnicity, family structure, self-perceived socioeconomic status, stratified by gender.	Multivariate logistic regressions
[39] Mikkonen, (2016), Finland	Prospective cohort, birth cohort	56% female 16 (NR)	Baseline: 7344 Completed: 1625 (55% eligible cohort)	1, 2 years	LBP during the past 6 months	Emotional and behavioural problems	Socioeconomic status, stratified by gender	Latent class analysis, log-binomial regression
[44] Mustard, (2005), Canada	Inception cohort, representative community sample	Both % female NR, 4–16	Baseline: 2867 Completed: 1928	2, 4 years, 14 years	First episode of BP	Psychological status, emotional and behavioural disorders, chronic medical conditions	Age, sex, childhood conditions, health status, behaviour, socioeconomic status, work environment	Logistic regression
[40] Muthuri (2018), England, Wales, and Scotland	Prospective cohort, birth cohort	50% female, From birth	Baseline: 5362 Completed: 3271	24, 2 yrs during childhood, 5–10 years in adulthood	BP previous 12 months	Illnesses and injury early life, abdominal pain, classroom behaviour (conduct and emotional problems)	BMI, psychiatric disorders, education level, occupation, smoking, parental BP, sex	Longitudinal latent class analysis, logistic regression models

Table 1 (continued)

Reference, (year), country	Study design, setting/sample	Baseline: sex, age mean (SD)[a]	Sample size: baseline and completed	Follow-up: no. of times, length of time	Back pain definition	Risk factors measures	Confounders	Analysis approach
[45] Power, (2001), England, Wales, and Scotland	Inception cohort, birth cohort	51% female, 23 (NR)	Baseline: 11,407 Completed: 5781	1, 10 years	Incident LBP (between 32 and 33 years)	Psychological distress	Sex, ergonomic stress, psychosocial work characteristics.	Logistic regression
[41] Smith (2017), Australia,	Prospective cohort, birth cohort	52% female, 14 (NR)	Baseline: 1608 Completed: 1088	1, 3 years	LBP, last month	Self-efficacy, depression, behavioural and emotional problems	Sex and back pain at 14 years	Multinomial logistic regression
[42] Stanford, (2008), Canada	Prospective cohort, representative community sample	49% female, 10.50 (0.50)	Baseline: 2488 Completed: 1415	5, 2 years	Backache, past 6 months	Anxiety and/or depression, self-esteem	Sex	Latent variable structural equation modelling

SD standard deviation, *NR* not reported, *NA* not applicable, *BP* back pain, *LBP* low back pain, *MBP* mid-back pain

[a]Age range reported when mean (SD) not reported

cohort study [40] reported no association between any illness or medical condition and back pain [40, 44]. In one of these studies, all chronic medical conditions were combined including: arthritis, asthma, missing fingers, blindness, and speech problems [44]. The other study included any 'serious illnesses' from 0 to 15 years of age [40]. One cohort study reported no association between atopic disease and subsequent back pain [5]; however, children and young adults with asthma demonstrated increased odds of back pain (OR [95% CI] = 1.3 [1.1, 1.6] (n = 6554) [5]).

Mental health disorders

Five cohort studies considered overall mental health status as a potential risk factor for back pain [30, 32, 38, 41, 42], three of these studies found positive associations [30, 38, 42] with increased odds in one study (OR [95% CI] = 1.6 [1.1, 2.4] (boys), OR [95% CI] = 1.5 [1.1, 1.9] (girls) (n = 3316) [38]). Two studies reported no association between overall mental health status and back pain [32, 41]. Regarding depression, two cohort studies found positive associations [31, 33] with increased odds of back pain in one study (OR [95% CI] = 1.05 [1.02, 1.08] (n = 1291) [33]); however, this study only reported an association between depression and mid-back pain, but not with low back pain [33]. Only one cohort study considered anxiety as a potential risk factor and found increased odds of back pain (OR [95% CI] = 4.6 [1.9, 11.1] (n = 212) [29]).

Psychological features

Many different psychological features have been considered as potential risk factors for back pain. Six studies considered overall psychological state [34–37, 44, 45], of which three found no association [34, 35, 37], two inception cohorts reported increased odds of back pain (OR [95% CI] = 1.8 [1.1, 3.2] (n = 1928) [44], OR [95% CI] = 2.5 [1.6, 3.9] (n = 5781) [45]), and one cohort study found an increased risk of back pain (RR [95% CI] = 1.6 [1.1, 2.3] (n = 933) [36]). Individual psychological features reported to be associated with back pain from cohort studies include conduct problems (RR [95% CI] = 2.5 [1.7, 3.7] (n = 933) [36], RR [95% CI] = 2.1 [1.3, 3.4] (n = 3271) [40]), somatization (OR [95% CI] = 1.3 [1.1, 1.5] (n = 1088) [41]), and peer problems (RR [95% CI] 2.3 [1.2, 4.2] (n = 178) [35]). Individual psychological features reported as risk factors with back pain from inception cohort studies include emotional or behavioural disorders (OR [95% CI] = 1.87 [1.02, 3.41] (n = 1928) [44]), dysfunctional coping (OR [95% CI] = 1.4 [1.1, 2.0] (boys) (n = 2040) [43]), anxiety sensitivity (OR [95% CI] = 1.5 [1.1, 2.0] (boys) (n = 2040) [43],

Table 2 Risk of bias assessment: modified QUIPS

Study	Study participation	Study attrition	Risk factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting	Overall rating
Barke (2014)	High	High	High	High	Moderate	Low	High
Brattberg (1994)	Moderate	High	High	Moderate	High	High	High
Cheung (2010)	Low	High	Moderate	Low	Low	Low	Moderate
Coenen (2016)	Moderate	High	Low	Low	Low	Low	Moderate
Dunn (2011)	Low	Moderate	Low	High	High	Moderate	High
Feldman (2001)	Low	Low	Low	Moderate	Low	Low	Low
Gill (2014)	Moderate	Moderate	Low	Moderate	Moderate	Low	Moderate
Gustafsson (2018)	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate
Hestbaek (2006)	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Jones (2009)	Moderate	High	Moderate	Moderate	Low	Low	Moderate
Jones (2003)	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate
Kanchanomai (2015)	Low	High	Low	Moderate	High	Moderate	High
Lien (2011)	Low	High	Low	High	Low	Low	High
Mikkonen (2016)	Moderate	High	Low	Moderate	Low	Low	Moderate
Mustard (2005)	Moderate	High	Low	Low	Low	Low	Moderate
Muthuri (2018)	Low	Moderate	Low	Moderate	Low	Low	Moderate
Power (2001)	Moderate	High	Low	Moderate	Low	Low	Moderate
Smith (2017)	Low	High	Low	Low	Low	Low	Low
Stanford (2008)	Low	Low	Low	Moderate	Low	Low	Moderate

and somatosensory amplification (OR [95% CI] = 1.8 [1.0, 3.1] (girls) (n = 2040) [43]).

Meta-analysis

Physical illnesses

Only one study reported on asthma and atopic disease [5]; therefore, these factors were not included in a meta-analysis. Two studies considered any illness or medical condition as a potential risk factor for back pain [40, 44]; however, the conditions were too varied to combine in a meaningful way. We synthesized data from four studies investigating two types of physical illness [5, 35, 36, 40]. Overall, there was a positive association between headaches at 11–22 years of age and experiencing back pain 1–8 years later (pooled RR [95% CI] = 1.9 [1.4, 2.6]; n = 7665; I^2 = 0.00) (Fig. 2) [5, 35, 36]. Similarly, data combined from three studies [35, 36, 40] demonstrated a positive association between abdominal pain at ages 11–14 years and back pain 1–3 years later (pooled RR [95% CI] = 1.7 [1.3, 2.2]; n = 4382; I^2 = 0.00) (Fig. 2).

Mental health disorders

Mental health disorders including depression, and mental health status overall could not be included in a meta-analysis due to the large methodological and statistical heterogeneity between the studies. Anxiety was investigated as a potential risk factor for back pain in only one study.

Psychological features

Eleven studies considering psychological features as potential risk factors for back pain were included in the meta-analysis [28, 29, 33, 35, 36, 39–41, 43–45]. Of the included studies, four studies reported risk ratios [35, 36, 39, 40], and seven studies reported odds ratios [28, 29, 33, 41, 43–45], odds ratios could not be converted to risk ratios from the information provided within these studies. Two inception cohort studies evaluated the role of psychological distress overall [44, 45]. Participants with psychological distress had increased odds of back pain (pooled OR [95% CI] = 2.2 [1.6, 3.1]; n = 7709; I^2 = 0.00) (Fig. 3). Based on two cohort studies, psychosocial difficulties were not associated with increased risk of back pain (pooled RR [95% CI] = 1.4 [0.96, 1.97]; n = 1111; I^2 = 28.56) (Fig. 3) [35, 36].

Emotional coping problems were associated with increased odds of back pain (pooled OR [95% CI] = 1.4 [1.1, 1.8]; 3968; I^2 = 0.00) based on two inception cohorts [43, 44]

Table 3 Results from included studies

Study	Potential risk factor for back pain	Results (95% CI)	Overall findings/alternative presentation of results
Barke (2014)	Dysfunctional coping	OR 1.44 (1.06, 1.97) (boys) (adjusted for age) *OR 1.36 (0.68, 2.72) (girls) (adjusted for age)*	Positive association Boys: dysfunctional coping, anxiety sensitivity Girls: somatosensory amplification Protective association Girls: pain catastrophizing No association Boys: pain catastrophizing, somatosensory amplification. Girls: dysfunctional coping, anxiety sensitivity
	Pain catastrophizing	*OR 1.07 (0.66, 1.72) (boys)* OR 0.51 (0.30, 0.88) (girls) (adjusted for age)	
	Anxiety sensitivity	OR 1.47 (1.09, 1.99) (boys) (adjusted for age) *OR 0.86 (0.65, 1.14) (girls) (adjusted for age)*	
	Somatosensory amplification	*OR: 1.22 (0.91, 1.62) (boys)* OR: 1.78 (1.04, 3.05) (girls) (adjusted for age)	
Brattberg (1994)	Fear of schoolmates	OR 2.44 (1.13, 5.27)	Positive association to psychosocial features Fear of schoolmates, loneliness, difficulties to make friends, feelings of being an outsider, has been bullied, passive reactive to bullying, nervousness, difficulties verbalizing feelings No association Diffuse feelings of anger
	Loneliness	OR 3.64 (1.24, 11.09)	
	Difficulties to make friends	OR 2.11 (1.11, 4.01)	
	Feelings of being an outsider	OR 2.08 (1.14, 3.81)	
	Has been bullied	OR 2.11 (1.14, 3.60)	
	Passive reactive to bullying	OR 3.39 (1.59, 7.30)	
	Nervousness	OR 2.10 (1.27, 3.47)	
	Difficulties verbalizing feelings	OR 1.63 (1.01, 2.65)	
	Diffuse feelings of anger	*Not significant (results not reported)*	
Cheung (2010)	Low mood	OR 3.12 (1.31, 7.41) (adjusted age, gender, height)	Positive association Low mood, anxiety, feeling tense, under stress, fatigue, constant tiredness, headaches
	Anxiety	OR 4.61 (1.92, 11.08) (adjusted age, gender, height)	
	Feeling tense	OR 3.97 (1.65, 9.55) (adjusted age, gender, height)	
	Under stress	OR 4.52 (1.76, 11.62) (adjusted age, gender, height)	
	Fatigue	OR 4.10 (1.55, 10.85) (adjusted age, gender, height)	
	Constant tiredness	OR 5.09 (1.06, 24.43) (adjusted age, gender, height)	
	Headaches	OR 4.52 (1.78, 11.51) (adjusted age, gender, height)	
Coenen (2016)	Mental-health-related quality of life	Low pain and impact cluster as reference High pain and impact cluster: β −2.84 (−5.60, −0.07) (adjusted for sex)	Higher back pain cluster lower score on mental-health-related quality of life (poorer health-related quality of life)
Dunn (2011)	Depression	Higher back pain cluster high mean depression score	Somatization and depression scores lowest in cluster 1, the 'no pain problem' cluster. Largest improvements in depression in back pain cluster 2: decreasing probability of pain during follow-up
	Somatization	Higher back pain cluster high mean somatization score	
Feldman (2001)	Mental health score	*OR 0.98 (0.96–1.00)*	No association Mental health score
Gill (2014)	Externalizing and Internalizing	*OR 1.003 (0.995, 1.012) (LBP)* OR 1.020 (1.010, 1.030) (MBP) (adjusted for sex)	No association LBP: Psychosocial variables Positive association MBP: Internalizing and externalizing score, Depression index
	Depression	*OR 1.015 (0.989, 1.041) (LBP)* OR 1.051 (1.022, 1.081) (MBP) (adjusted for sex)	
Gustafsson (2018)	Daytime sleepiness	*(F4 = 14.62, p < 0.0001)*	No association Daytime sleepiness and psychological symptoms
	Psychological symptoms	*(F1 = 149.1, p < 0.0001)*	

Table 3 (continued)

Study	Potential risk factor for back pain	Results (95% CI)	Overall findings/alternative presentation of results
Hestbaek (2006)	Asthma	OR 1.34 (1.10, 1.62) (adjusted for age and sex)	Positive association Asthma, headache No association Atopic disease
	Atopic disease	*OR 1.08 (0.82, 1.42) (adjusted for age and sex)*	
	Headaches	OR 2.52 (1.56, 4.07) (adjusted for age and sex)	
Jones (2009)	Headaches	*RR 1.3 (0.5, 3.3)*	Positive association High level of peer problems No association Headaches, abdominal pain, high level of psychosocial difficulties overall, emotional problems, conduct problems, hyperactivity, prosocial behaviour, and daytime tiredness
	Abdominal pain	*RR 1.5 (0.7, 3.6)*	
	High level of psychosocial difficulties overall	*RR 1.1 (0.7, 1.9) (adjusted for age and sex)*	
	High level of peer problems	RR 2.3 (1.2, 4.2) (adjusted for age and sex)	
	Emotional problems	*RR: 1.5 (0.9, 2.6) (adjusted for age and sex)*	
	Conduct problems	*RR: 1.1 (0.7, 1.8) (adjusted for age and sex)*	
	Hyperactivity	*RR 1.0 (0.6, 1.6) (adjusted for age and sex)*	
	Daytime tiredness	*RR 1.1 (0.7, 1.9) (adjusted for age and sex)*	
	Prosocial behaviour	*RR 1.5 (0.9, 2.4) (Adjusted for age and sex)*	
Jones (2003)	Headaches	*RR 1.6 (0.97, 2.8) (adjusted for age and gender)*	Positive association Abdominal pain, high level of adverse psychosocial exposure, conduct problems No association Headaches, peer problems, emotional problems, hyperactivity, prosocial behaviour, and daytime tiredness
	Abdominal pain	RR 1.8 (1.1, 3.0) (adjusted for age and gender)	
	High level of adverse psychosocial exposure	RR: 1.6 (1.1, 2.3) (adjusted for age and sex)	
	High level of peer problems	*RR 1.3 (0.9, 1.9) (adjusted for age and sex)*	
	Emotional problems	*RR: 1.2 (0.8, 1.8) (adjusted for age and sex)*	
	Conduct problems	RR: 2.5 (1.7, 3.7) (adjusted for age and sex)	
	Hyperactivity	*RR 1.4 (0.98, 2.1) (adjusted for age and sex)*	
	Prosocial behaviour	*RR 0.9 (0.6, 1.3) (adjusted for age and sex)*	
Kanchanomai (2015)	Psychosocial factors	*Not significant (results not reported)*	No association Psychosocial factors
Lien (2011)	Mental distress	OR 1.6 (1.1, 2.4) (boys) (adjusted for ethnicity, family structure, socioeconomic) OR 1.5 (1.1, 1.9) (girls) (adjusted for ethnicity, family structure, socioeconomic)	Positive association Mental distress
Mikkonen (2016)	Externalizing behaviour	RR 3.62 (1.54, 8.50) (girls), *RR 1.12 (0.26, 4.76) (boys)*	Girls: externalizing behaviour cluster associated significantly with 'Consultation for LBP' at 18 years. Boy: none of the clusters associated with new LBP at 18 years

Table 3 (continued)

Study	Potential risk factor for back pain	Results (95% CI)	Overall findings/alternative presentation of results
Mustard (2005)	Chronic medical conditions[a]	*OR 1.01 (0.56, 1.82) (adjusted for age, sex, childhood conditions, childhood health status, and measures early adult health, behaviour, socioeconomic status, work environment)*	Positive association Psychological distress, emotional or behavioural disorders in childhood No association Chronic medical conditions
	Psychological distress (moderate/high)	OR 1.85 (1.07, 3.20) (adjusted for conduct problems age, sex, childhood conditions, childhood health status, and measures early adult health, behaviour, socioeconomic status, work environment)	
	Emotional or behavioural disorders in childhood	OR 1.87 (1.02, 3.41) (adjusted for age, sex, childhood conditions, childhood health status, and measures early adult health, behaviour, socioeconomic status, work environment)	
Muthuri (2018)	Serious illness 0–15 years	*RR 1.10 (0.79–1.52)*	Positive association Abdominal pain and conduct problems No association Serious illness in childhood and emotional problems
	Abdominal pain	RR 1.76 (1.28, 2.43) (adjusted for BMI, psychiatric disorders, education level, occupation, smoking status, parental back pain, sex)	
	Emotional problems	*RR 0.84 (0.56, 1.27)*	
	Conduct problems	RR 2.07 (1.28, 3.35) (adjusted for BMI, psychiatric disorders, education level, occupation, smoking status, parental back pain, sex)	
Power (2001)	Psychological distress high	OR 2.52 (1.65, 3.86) (adjusted for sex, ergonomic stress, and psychosocial work characteristics)	Positive association Psychological distress
Smith (2017)	Depression/Anxiety	*Not significant (results not reported)*	Positive association Somatic complaints, aggressive behaviour No association Depression/anxiety
	Somatic complaints	LBP with impact Vs no LBP: OR 1.30 (1.10, 1.54) (adjusted for sex and baseline BP)	
	Aggressive behaviour	LBP with impact versus no LBP: OR 1.37 (1.16, 1.62) (adjusted for sex and baseline BP)	
Stanford (2008)	Anxiety and/or depression	Start-point intercept: $\beta = 0.32$, $p < 0.001$, end-point intercept: $\beta = 0.16$, $p < 0.001$	Positive association Anxiety/depression and self-esteem with both the start- and end-point trajectories
	Self-esteem	Start-point intercept: $\beta = 0.22$, $p < 0.001$, end-point intercept: $\beta = 0.16$, $p < 0.01$).	

Italics No statistically significant difference

LBP low back pain, *MBP* mid-back pain, *BP* back pain, *OR* odds ratio (95% confidence intervals), *β* beta (95% confidence intervals), *RR* risk ratio (95% confidence intervals), *BMI* body mass index

Chronic medical conditions[a]: include asthma; heart problems; epilepsy or convulsions without fever; kidney disease; arthritis or rheumatism; cerebral palsy; diabetes; cancer; spina bifida; muscular dystrophy or another muscle disease; cystic fibrosis; missing fingers, hands, arms, toes, feet, or legs; deformity of the feet, legs, fingers, arms, or back; club foot or cleft palate; paralysis or weakness; blindness or chronic sight problems; deafness or chronic hearing problems; muteness or chronic speech problems; chronic pain or discomfort; or any other medical problem or condition

(Fig. 3) and (pooled OR [95% CI] = 1.4 [1.0, 1.8]; $n = 3062$; $I^2 = 86.99$) based on four cohort studies (Fig. 3) [28, 29, 33, 41]. There was no association between emotional coping problems and back pain (pooled RR [95% CI] = 1.0 [0.8, 1.3]; $n = 600$; $I^2 = 31.45$) (Fig. 3) based on data from four other cohort studies [35, 36, 39, 40]. Having a high level of 'peer problems' was not associated with back pain (pooled RR [95% CI] = 1.6 [0.9, 2.8]; $n = 1111$; $I^2 = 57.46$) (Fig. 4) [35, 36]. Conduct problems were associated with increased risk of back pain (pooled RR [95% CI] = 1.8 [1.1, 2.9]; $n = 4382$; $I^2 = 72.08$) (Fig. 4) [35, 36, 40]. Both studies that considered feeling 'tense' or 'stressed' or 'nervous' found increased odds of back pain (pooled OR [95% CI] = 2.7 [1.4, 5.2]; $n = 682$; $I^2 = 42.74$) (Fig. 4) [28, 29]. Hyperactivity was not associated with increased risk of back pain (pooled RR [95% CI] = 1.2 [0.9,1.7]; $n = 1111$; 11.31) (Fig. 4) [35, 36].

Discussion

Summary of evidence

This systematic review identified evidence from inception cohort studies that demonstrated the most likely risk factors for back pain are psychological distress, as well as psychological features including emotional coping problems and somatosensory amplification. Evidence from non-inception cohort studies cannot distinguish between potential risk factors or triggers for back pain. However, we identified several additional factors that are associated with back pain. Specifically, asthma, headaches, abdominal pain, depression, anxiety, conduct problems, somatization, and 'feeling tense' are potential risk factors or triggers for back pain. Results from the meta-analyses demonstrated the most likely risk factors for back pain in young people are psychological distress and emotional coping problems. Other factors identified in the meta-analyses as potential risk factors or triggers are headaches, abdominal pain, conduct problems, and 'feeling tense'.

The current results accord with related systematic reviews. A previous systematic review and meta-analysis reported negative emotional symptoms to be a potential risk factor for musculoskeletal pain during childhood and adolescence (pooled OR [95% CI] 1.54 (1.06, 2.24) [46]. Another systematic review found good evidence that psychological distress and psychosocial factors increase the risk of back pain in children [3]. Regarding physical illnesses, a systematic review and meta-analysis of cross-sectional twin studies reported that young people and adults with chronic conditions such as asthma, diabetes, and headaches were

Fig. 3 Forest plot of psychological features as potential triggers or risk factors for back pain. **a** Psychological distress overall (inception cohorts), **b** psychological difficulties overall, **c** emotional coping problems (inception cohorts), **d** emotional coping problems (OR), **e** emotional coping problems (RR) [outcome/subgroup results combined: studies reporting multiple outcomes or subgroups were first combined (through fixed effect models), accounting for lack of independence within study]

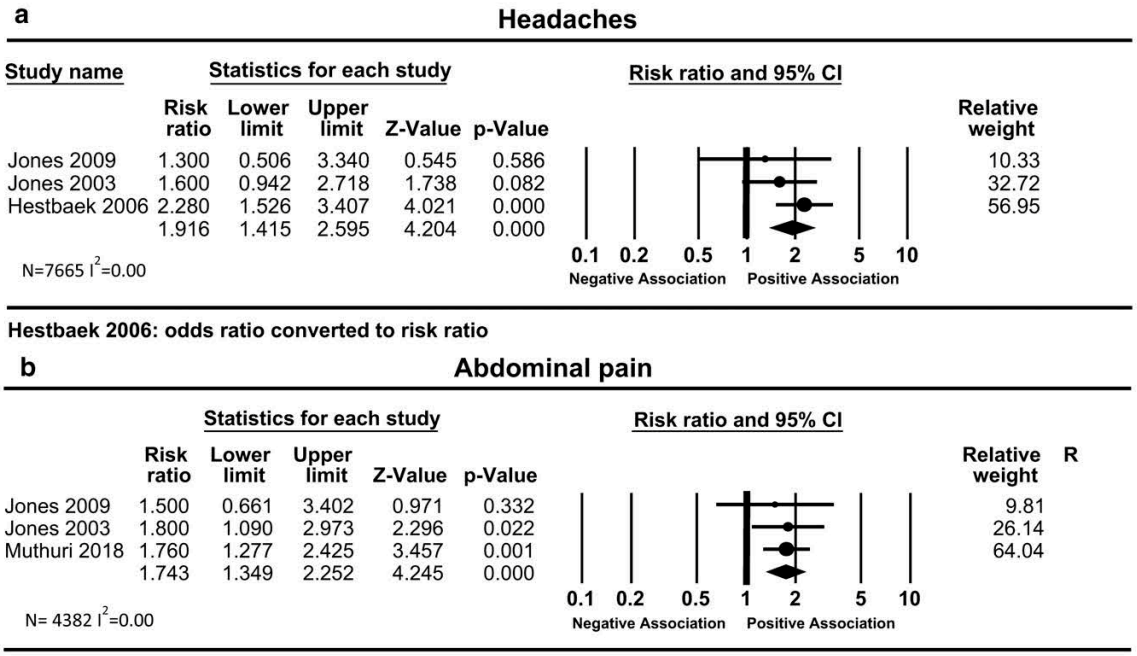
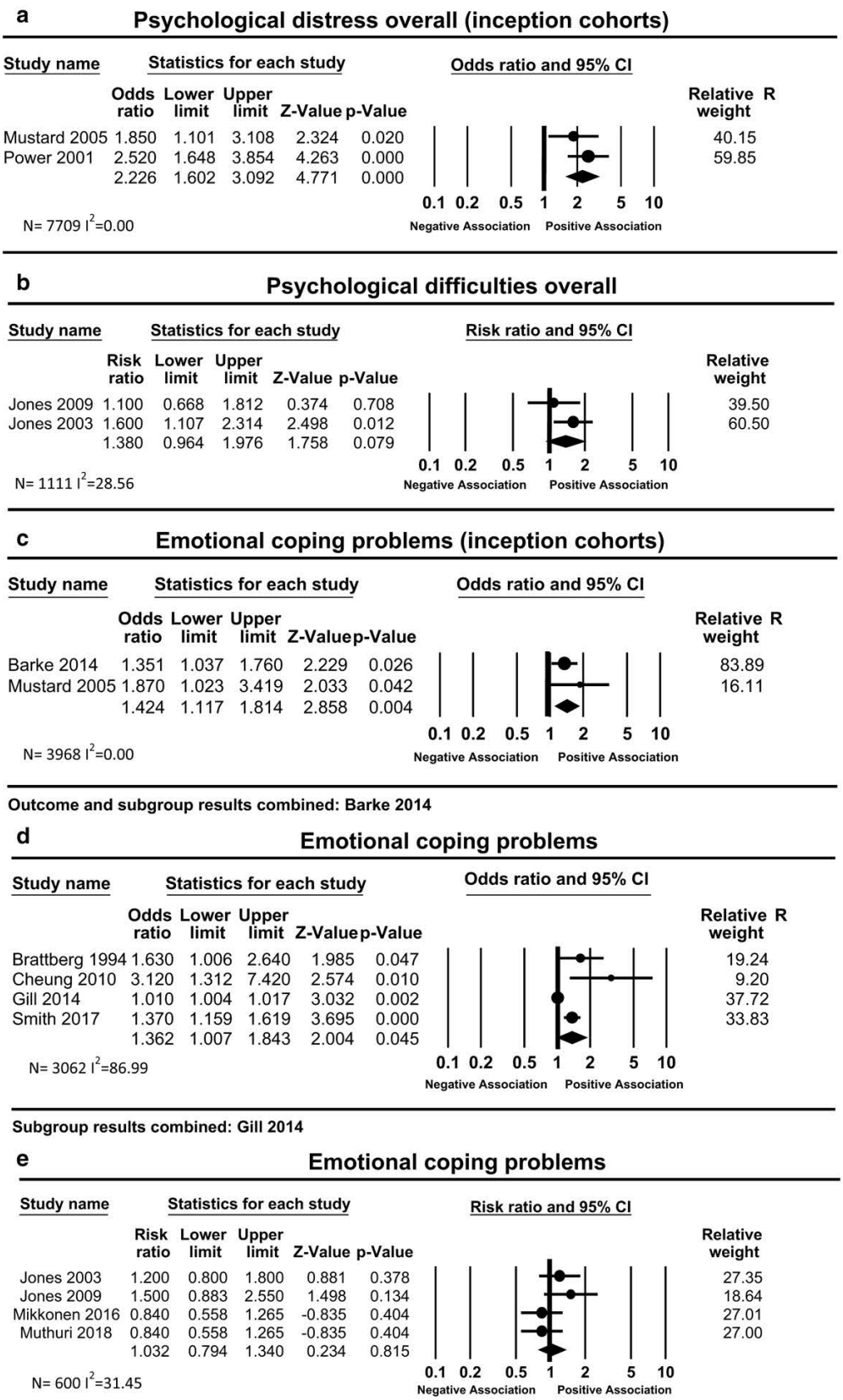


Fig. 2 Forest plots of physical illnesses as potential triggers or risk factors for back pain. **a** Headaches and **b** abdominal pain


a
Psychological distress overall (inception cohorts)
Study name
Statistics for each study
Odds ratio and 95% CI
Odds ratio
Lower limit
Upper limit
Z-Value
p-Value
Relative weight
Mustard 2005 1.850 1.101 3.108 2.324 0.020 40.15
Power 2001 2.520 1.648 3.854 4.263 0.000 59.85
2.226 1.602 3.092 4.771 0.000
0.1 0.2 0.5 1 2 5 10
Negative Association
Positive Association
N= 7709 I²=0.00
b
Psychological difficulties overall
Study name
Statistics for each study
Risk ratio and 95% CI
Risk ratio
Lower limit
Upper limit
Z-Value
p-Value
Relative weight
Jones 2009 1.100 0.668 1.812 0.374 0.708 39.50
Jones 2003 1.600 1.107 2.314 2.498 0.012 60.50
1.380 0.964 1.976 1.758 0.079
0.1 0.2 0.5 1 2 5 10
Negative Association
Positive Association
N= 1111 I²=28.56
c
Emotional coping problems (inception cohorts)
Study name
Statistics for each study
Odds ratio and 95% CI
Odds ratio
Lower limit
Upper limit
Z-Value
p-Value
Relative weight
Barke 2014 1.351 1.037 1.760 2.229 0.026 83.89
Mustard 2005 1.870 1.023 3.419 2.033 0.042 16.11
1.424 1.117 1.814 2.858 0.004
0.1 0.2 0.5 1 2 5 10
Negative Association
Positive Association
N= 3968 I²=0.00
Outcome and subgroup results combined: Barke 2014
d
Emotional coping problems
Study name
Statistics for each study
Odds ratio and 95% CI
Odds ratio
Lower limit
Upper limit
Z-Value
p-Value
Relative weight
Brattberg 1994 1.630 1.006 2.640 1.985 0.047 19.24
Cheung 2010 3.120 1.312 7.420 2.574 0.010 9.20
Gill 2014 1.010 1.004 1.017 3.032 0.002 37.72
Smith 2017 1.370 1.159 1.619 3.695 0.000 33.83
1.362 1.007 1.843 2.004 0.045
0.1 0.2 0.5 1 2 5 10
Negative Association
Positive Association
N= 3062 I²=86.99
Subgroup results combined: Gill 2014
e
Emotional coping problems
Study name
Statistics for each study
Risk ratio and 95% CI
Risk ratio
Lower limit
Upper limit
Z-Value
p-Value
Relative weight
Jones 2003 1.200 0.800 1.800 0.881 0.378 27.35
Jones 2009 1.500 0.883 2.550 1.498 0.134 18.64
Mikkonen 2016 0.840 0.558 1.265 -0.835 0.404 27.01
Muthuri 2018 0.840 0.558 1.265 -0.835 0.404 27.00
1.032 0.794 1.340 0.234 0.815
0.1 0.2 0.5 1 2 5 10
Negative Association
Positive Association
N= 600 I²=31.45
Subgroup results combined: Mikkonen 2016

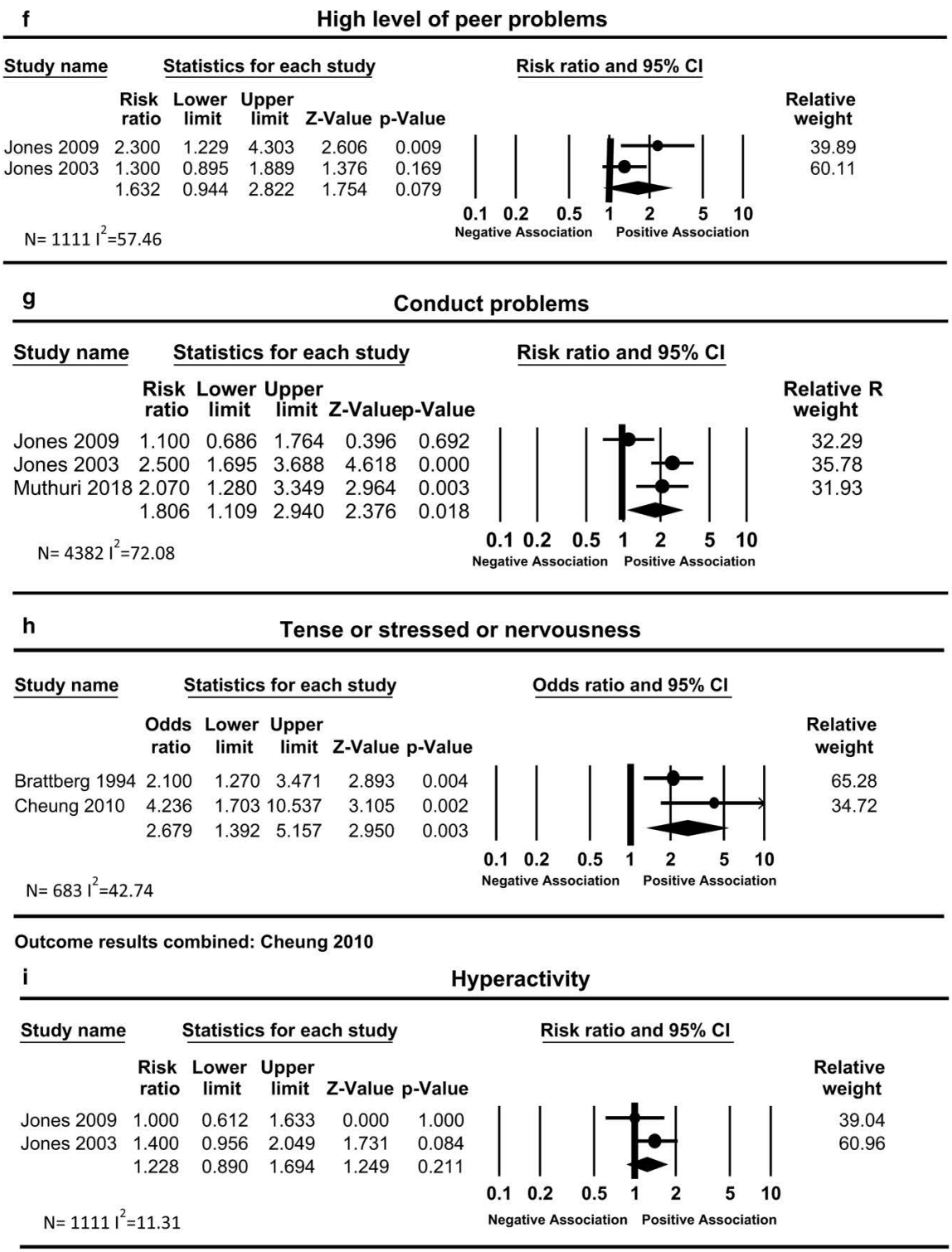


Fig. 4 Forest plot of psychological features as a potential predictor of back pain continued. **f** High level of peer problems, **g** conduct problems, **h** tense or stressed or nervousness, **i** hyperactivity [outcome/subgroup results combined: studies reporting multiple outcomes or subgroups were first combined (through fixed effect models), accounting for the lack of independence within study]

more likely to report low back pain (pooled OR range = 1.6 to 4.2) [7].

Methodological considerations for included studies

The majority of the included studies were not inception cohorts, meaning that back pain and potential risk factor data were collected concurrently, making the temporal relationship difficult to establish [13]. Many studies reported high attrition rates, and reasons for loss to follow-up were often unreported. Other common limitations were that the source population and/or the selection criteria were not well described. The outcome measurement (back pain) was often unclear. Many studies did not specify the temporal nature of the back pain (ongoing, episodic, or first time). While some studies applied a clear identification of the area of the back under study, such as through the use of pain diagrams, many other studies did not. We intended to convert odds ratios to risk ratios; however, this was not always possible owing to insufficient reporting (e.g. lack of information on back pain incidence or prevalence in the non-exposed participants).

Methodological considerations for this review

There are no established risk of bias tools for risk factor studies. We assessed risk of bias with a modified QUIPS tool that was originally designed for studies of prognosis. Due to methodological heterogeneity and that there were many different potential risk factors studied, few studies could be included together in the respective meta-analyses. Therefore, the syntheses are based on small numbers of studies and this lends itself to problems estimating between-studies variance [22]. Future studies are likely to change these estimates. Furthermore, we were unable to undertake sensitivity analyses or consider study subgroups (e.g. low risk of bias studies). Three meta-analyses demonstrated substantial-to-considerable statistical heterogeneity.

Recommendations for future research

Additional research is needed to understand the etiology of back pain. Future studies should better delineate between risk factors responsible for incident back pain cases and other factors that may be triggers for back pain episodes. Future research should also apply validated questionnaires and clearly identify and define the type of back pain under study (e.g. ongoing, episodic, or first time).

Conclusion

The most likely risk factors for back pain are psychological distress, as well as psychological features including emotional coping problems and somatosensory amplification. Due to the limitations of the literature, the role of some physical illnesses, mental health disorders, and psychological features as potential comorbidities, triggers, or risk factors for back pain remains unclear. Additional high-quality research is needed to better elucidate these relationships.

Acknowledgements We would like to thank Cody Davenport for his assistance with the study screening process.

Authors' contribution AB, JH, and BW were involved with the concept and design of the study. LB conducted the searches. AB and CH conducted study selection and data extraction. AB analysed and interpreted the data with the assistance of BW, JH, and CH. AB drafted the manuscript and performed revisions with substantial feedback and editing from all authors. All authors read and approved the final manuscript.

Funding This study was funded by a scholarship from Murdoch University, Western Australia and funding provided by Chiropractic Australia Research Foundation. JH receives salary support from the Canadian Chiropractic Research Foundation and the New Brunswick Health Research Foundation. The funding sources had no involvement in study design, analysis, interpretation, or manuscript preparation.

Data availability The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Summary of Chapter Three and link to next chapter

Using data from inception cohort studies, this systematic review and meta-analysis identified that the most likely risk factors for back pain in young people were psychological distress as well as psychological features including emotional coping problems. Non-inception cohort studies provided evidence that failed to differentiate between risk factors or triggers. Additional factors that were associated with back pain, based on the evidence of cohort studies, included asthma, headaches, abdominal pain, depression, anxiety, conduct problems, somatization, and 'feeling tense'. We considered these as potential triggers or risk factors for back pain.

Since most of the included studies were not inception cohorts and because in many studies the outcome measure for (back pain) was unclear, we concluded that it is not possible to definitively say if the identified factors were comorbidities, triggers, or risk factors for back pain. Consequently, the relationship between some physical illnesses, mental health disorders, and psychological features with back pain remains unclear. To better understand these relationships, additional high-quality research is needed.

Based on the limitations of the current studies, we decided to utilise methods in line with current conceptualisation of back pain by using repeated measures of back pain with clear definitions. There were limited studies that considered physical illnesses as potential risk factors for back pain in young people, therefore, in the next study we continued to focus on chronic physical illnesses as potential risk factors for back pain.

Chapter Four- Early life chronic inflammatory conditions predict low back pain in adolescence and young adulthood

There was limited research on physical illnesses as potential risk factors for back pain in young populations. A plausible biological link between certain illnesses and back pain is that there is an inflammatory-associated activation of the hypothalamic-pituitary-adrenal-axis [49]. Alternatively, inflammatory conditions and back pain may share a common aetiology [51]. Therefore, we investigated for associations between early life chronic or recurrent inflammatory conditions and low back pain by analysing data from the Raine Study.

This work underwent peer-review and is published as:

Beynon AM, Hebert JJ, Leboeuf-Yde C, Beales DJ, Jacques A, Walker BF. Early life chronic inflammatory conditions predict low back pain in adolescence and young adulthood. Eur J Pain (2020) DOI: 10.1002/ejp.1700

As of 24/02/2021: Citations: 0. Altmetric: 4

DOI: 10.1002/ejp.1700

ORIGINAL ARTICLE

EJP European Journal of Pain

Early life chronic inflammatory conditions predict low back pain in adolescence and young adulthood

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Funding information
The core management of the Raine Study is funded by The University of Western Australia, Curtin University, Telethon Kids Institute, Women and Infants Research Foundation, Edith Cowan University, Murdoch University, The University of Notre Dame Australia and the Raine Medical Research Foundation. The NHMRC for their long-term contribution to funding the study over the last 30 years. AB is supported by a scholarship from Murdoch University, Western Australia and a scholarship provided by Chiropractic Australia Research Foundation. JH receives salary support from the Canadian Chiropractic Research Foundation and the New Brunswick Health Research Foundation. The funding sources had no involvement in study design, analysis, interpretation or manuscript preparation.

Abstract

Background: Associations between inflammatory conditions and low back pain (LBP) have been found frequently in older populations. However, the nature of these relationships in younger populations is unknown. This study aimed to investigate the associations between early life chronic or recurrent inflammatory conditions and impactful LBP in adolescence and young adulthood.

Methods: In this longitudinal study, we used data from the Raine Study Gen2 participants at the 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22-year follow-ups ($N = 2,868$). Data were collected on inflammatory conditions from 1 to 22 years of age and occurrences of impactful LBP from 14 to 22 years of age. Longitudinal and cross-sectional associations between inflammatory conditions and impactful LBP occurrence were examined. Potential dose–response relationships between the number of inflammatory conditions and impactful LBP were also assessed. Logistic regression models were used in the analysis.

Results: Participants with respiratory or atopic conditions during childhood had increased odds of future impactful LBP in adolescence and young adulthood (odds ratio (OR) [95% confidence interval (CI)] = 1.29 [1.07, 1.54] and 1.23 [1.02, 1.49], respectively). There were cross-sectional associations between inflammatory conditions including respiratory, skin, musculoskeletal, autoimmune and atopic conditions, with impactful LBP. Participants with two illnesses and three or more illnesses had an increased odds (OR [95% CI] =1.68 [1.30, 2.18] and OR [95% CI] =2.12 [1.54, 2.89], respectively) of reporting impactful LBP.

Conclusions: Overall, longitudinal and cross-sectional associations of respiratory and atopic conditions with impactful LBP in adolescence and young adulthood were identified. More evidence is needed to determine whether there is a causal relationship between chronic inflammatory conditions and impactful LBP.

Significance: Low back pain (LBP) is a prominent and significant health problem and associations between inflammatory conditions and LBP have been found frequently in older populations. We found that children with respiratory or atopic conditions and those with several chronic inflammatory conditions are at increased odds of impactful LBP in adolescence and young adulthood. In clinical practice and future research, there is a need to consider comorbidities also in younger populations.

1 | INTRODUCTION

Low back pain (LBP) is a prominent and significant health problem. From early adolescence, LBP is ranked within the top 10 causes of years lived with disability (GBD, 2017 Disease, & Injury Incidence & Prevalence Collaborators, 2018). The LBP prevalence increases in adulthood when it becomes the leading cause of years lived with disability globally (GBD, 2017 Disease, & Injury Incidence & Prevalence Collaborators, 2018). Low back pain in adolescence is linked with LBP in adulthood (Hestbaek et al., 2006a). Many other chronic or recurrent inflammatory conditions commonly commence during childhood including respiratory disease, endocrine disorders and digestive system disorders. In addition, adults with both respiratory and digestive disorders have an increased prevalence of LBP compared to adults without respiratory and digestive disorders (Holmberg et al., 2005).

There are a couple of potential mechanisms in which inflammatory conditions could be associated with LBP. If we consider a temporal relationship, an inflammation-associated activation of the hypothalamic–pituitary–adrenal axis is a plausible biological link between chronic or recurrent inflammatory conditions and LBP (Hurwitz & Morgenstern, 1999). Early inflammatory conditions may alter hypothalamic–pituitary–adrenal axis function through direct action or via epigenetics (Polli et al., 2019; Shanmugam & Sethi, 2013), facilitating further mechanical or psychosocial stressors and overall hypersensitivity and pain. Early life is a critical period of development, and early life stresses can influence future nociceptive processing (Waller et al., 2020). These associations have been found previously between early life psychological stresses and increased incidence of chronic pain in later life (Burke et al., 2017), as well as between early life pain experiences and spinal pain in pre-adolescence (Joergensen et al., 2019).

Alternately, there may be another potential mechanism where comorbid inflammatory conditions and LBP could have a shared/common origin (Holmberg et al., 2005). A significant proportion of LBP itself could be an inflammatory condition. Hypothetically, the inflammatory conditions as well as LBP could therefore occur at any time during the lifetime and share a common cause.

Associations between chronic or recurrent inflammatory conditions and LBP have been found frequently in older populations (Heliövaara et al., 1991; Holmberg et al., 2005; Smith et al., 2009). However, the nature of these relationships in younger populations is unknown. Therefore, the overall aim of this study was to investigate the associations between early life chronic or recurrent inflammatory conditions with LBP in adolescence and young adulthood.

The specific objectives were (1) to investigate the longitudinal association between inflammatory conditions in childhood and impactful LBP occurrence from adolescence to young adulthood, (2) to investigate the cross-sectional association between inflammatory conditions from adolescence to young adulthood and impactful LBP occurrence and (3) to investigate potential dose–response relationships between the number of chronic inflammatory conditions and the occurrence of impactful LBP.

2 | METHODS

2.1 | Study design and ethics permissions

Data were used from the Raine Study Gen2 participants at the 1, 2, 3, 5, 8, 10, 14, 17, 20, and 22-year follow-ups. The Raine Study commenced as a Western Australian Pregnancy Cohort, with mothers recruited between May 1989 and Nov 1991 at King Edward Memorial Hospital for Women. There were 2,868 children recruited into the Raine Study Cohort. The children (Gen2) have been assessed at regular time points from birth, until present (27 years) (McKnight et al., 2012; Straker et al., 2017). The cohort at inception was predominantly Caucasian (93%).

All aspects of the Raine Study were approved by the Human Ethics Committees at King Edward Memorial Hospital, Princess Margaret Hospital, University of Western Australia and/or Curtin University. The adolescents/young adults and/or their parents or guardian provided written informed consent for data collection. Ethics approval for the current study was approved by Murdoch University Human Research Ethics Committee (Approval number: 2018/226).

2.2 | Exposure variables: Chronic or recurrent inflammatory conditions

Information on chronic inflammatory conditions was obtained at age 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22 years regarding any self-reported diagnosed conditions (by parents in early years and participants in later years) and, where possible, verified through medical records, medication use, hospital admissions, as well as ICD-9 codes. We included chronic or recurrent inflammatory conditions. Exclusion criteria included the following: neoplasms, blood conditions if not autoimmune or atopic, acute conditions or if unknown if acute or chronic, mental and neurological conditions caused by birth trauma or congenital defects, or if it was unknown to be an inflammatory condition due to insufficient information (e.g. hypothyroidism with unknown cause).

First, we categorized chronic inflammatory conditions using ICD-9 categories including the following: (1) endocrine system, (2) respiratory system, (3) digestive system, (4) skin and subcutaneous tissues (including the eye) and (5) musculoskeletal system and connective tissues. Second, additional categories (not mutually exclusive to the first five categories) included autoimmune and atopic conditions. These categories were utilized to determine the exposures to chronic inflammatory conditions within specific systems (e.g. endocrine, respiratory), as well as inflammatory

conditions of the same type (e.g. autoimmune, atopic). Third, all chronic inflammatory illnesses were included together in a final exposure category of 'any inflammatory condition'. The Appendix shows each of the exposure categories.

For objective one, we included inflammatory conditions from 1 to 10 years of age to capture inflammatory conditions in childhood that were likely to precede the onset of back pain (Smith et al., 2017). For objective two, inflammatory conditions from 14 to 22 years were included to investigate the cross-sectional association between inflammatory conditions and LBP from adolescence to young adulthood. For objective three, we included inflammatory conditions from 1 to 22 years, as this considers inflammatory conditions at any point from childhood to young adulthood. Participants were considered to have a condition if they reported that they were diagnosed with that condition at least once within the respective timeframe, that is, for objective one (1–10 years).

2.3 | Low back pain outcomes

The occurrence of LBP was assessed at 14, 17, 20 and 22 years of age. Participants self-reported LBP occurrences within the last month, including the impact of LBP on care-seeking and activity participation. At each time point, participants answered five questions: 'Has your low back been painful at any time in the last month?', 'Have you missed work or school due to low back pain?', 'Has low back pain interfered with your normal activities?', 'Has low back pain interfered with recreational physical activities?', 'Have you sought professional advice or treatment for low back pain?', 'Have you taken medication to relieve low back pain?' At the 14-year follow-up, questions were asked about any 'back pain' rather than specifically 'low back pain'.

The outcome variable of low back pain for our analysis was 'impactful LBP', which we defined as having LBP plus answering affirmatively to at least one of the LBP impact questions (i.e. questions 2–5) (Coenen et al., 2017) at least once at 14, 17, 20 or 22 years of age. Merely having back pain in adolescence may be a normal life experience and potentially of benign nature with no long-term problems (Burton et al., 1996). Impactful LBP was used as the outcome variable of LBP in an attempt to exclude trivial occurrences of LBP.

2.4 | Potential confounders

Potential confounders included sex, body mass index and pubertal status. The trend in the literature shows a higher prevalence of back pain with advancing age, more advanced pubertal status and female sex (Beynon et al., 2019a, 2019b). There are mixed results in the literature regarding the relationship between body mass index and back pain (Beynon et al., 2019a, 2019b).

Pubertal status was assessed at 14 and 17 years of age using the Tanner stages (Tanner, 1962). Tanner stages were reported on a scale of 1–5, with higher scores representing later pubertal status, based on self-assessments of pubic hair development in boys and breast development in girls (Marshall & Tanner, 1969, 1970). Height was measured with a Holtain Stadiometer (nearest 0.1 cm); body weight was measured using a Wedderburn Chair Scale (nearest 100g). Body mass index was calculated by taking weight (kg)/height $(m)^2$. Age and sex-specific body mass index categories for normal weight, overweight and obesity were calculated for all participants (Vidmar et al., 2013).

2.5 | Statistical analysis

Demographic data were reported descriptively. We conducted analyses to determine the associations between chronic or recurrent inflammatory conditions and impactful LBP, using univariate and adjusted logistic regression models with robust standard errors. Covariates were introduced into the model and kept within the model if it was associated with back pain, or if it made significant changes to the association between the exposure variable and back pain. For each exposure variable, a minimum of 10 cases (people with the condition of interest) were needed to run the model. The effects of risk factors were summarized using odds ratios (OR) with 95% confidence intervals [95% CI] and p values. Data were analysed using Stata S/E version 15 (StataCorp, TX).

3 | RESULTS

The demographic characteristics of participants at each follow-up are presented in Table 1. From the ages of 14 to 22 years, 1,152 participants (59%) reported at least one episode of impactful LBP. Pubertal status and body mass index were not univariately associated with LBP and therefore not included in the models. Sex was found to be a significant covariate; therefore, all models are adjusted for sex.

3.1 | Objective 1: Longitudinal association between inflammatory conditions in childhood and impactful low back pain occurrence from adolescence to young adulthood

Figure 1 demonstrates the relationship between participants with chronic or recurrent inflammatory conditions from 1 to 10 years of age and subsequently whether impactful LBP manifests in adolescence or young adulthood. There were only eight and five participants with endocrine and musculoskeletal conditions (1–10 years of age), respectively; therefore, these models

TABLE 1 Number of participants with data

Follow-up	Total participants: *n*	Age (years): mean (*SD*)	Female: *n* (%)
1	2,430	1.2 (0.1)	1,193 (49.1)
2	1974	2.1 (0.1)	945 (47.9)
3	2,260	3.1 (0.1)	1,110 (49.1)
5	2,236	5.9 (0.2)	1,082 (48.4)
8	2,142	8.1 (0.3)	1,042 (48.6)
10	2048	10.6 (9.8)	989 (48.3)
14	1865	14.1 (0.2)	906 (48.6)
17	1693	17.1 (0.3)	849 (50.2)
20	1577	20.0 (0.5)	787 (49.9)
22	1,235	22.2 (0.8)	640 (51.8)

SD: standard deviation

could not be created. The odds ratios with 95% confidence intervals to develop future LBP for participants with respiratory conditions, atopic conditions, and any inflammatory condition, respectively, were (1.29 [1.07, 1.54]), (1.23 [1.02, 1.49]) and (1.25 [1.03, 1.52]). No associations were found between digestive, skin or autoimmune conditions and LBP (Figure 1).

3.2 | Objective 2: Cross-sectional associations between inflammatory conditions and impactful low back pain occurrence from adolescence to young adulthood

Participants with respiratory, skin, musculoskeletal, autoimmune or atopic conditions at 14–22 years of age had an increased odds of impactful LBP (Figure 2). Furthermore, participants with any inflammatory condition compared to those with no inflammatory condition had increased odds of LBP (OR [95% CI] = 1.45 [1.20, 1.76]). There was no association found between endocrine and digestive conditions, and LBP (Figure 2).

3.3 | Objective 3: Dose–response relationship between number of chronic inflammatory conditions and impactful low back pain

Participants with a greater number of chronic inflammatory conditions from 1 to 22 years had increased odds of impactful LBP at 14–22 years (Figure 3). Participants with two illnesses and three or more illnesses had an increased odds (OR [95% CI] = 1.68 [1.30, 2.18]) and (OR [95% CI] = 2.12 [1.54, 2.89], respectively) of reporting LBP (Figure 3). The increased odds ratios demonstrate evidence of a potential dose–response relationship.

4 | DISCUSSION

In longitudinal analysis, participants with respiratory or atopic conditions during childhood had increased odds of future impactful LBP in adolescence/young adulthood. However, there were no associations found between digestive, skin or autoimmune conditions during childhood and LBP in adolescence and young adulthood (objective 1). There were cross-sectional associations between chronic inflammatory conditions including respiratory, skin, musculoskeletal, autoimmune and atopic conditions, and LBP in adolescence to

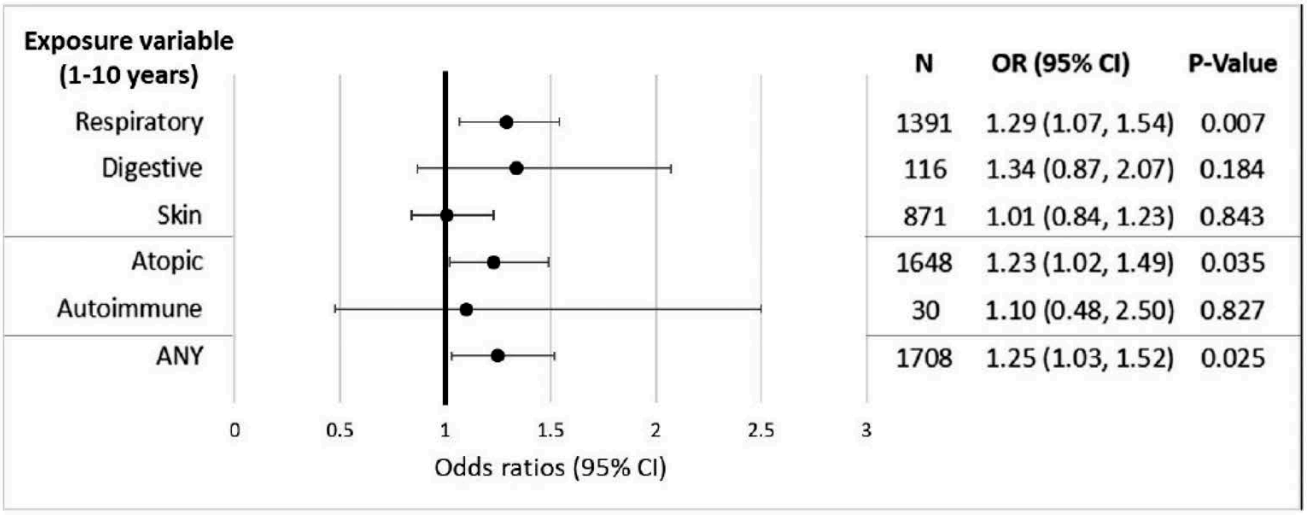

FIGURE 1 Longitudinal association between chronic inflammatory conditions from 1 to 10 years and impactful low back pain occurrences 14 to 22 years. Abbreviations: N: number of participants with the condition, OR: odds ratio, 95% CI: 95% confidence intervals, Any: any inflammatory condition. Note: All models adjusted for sex

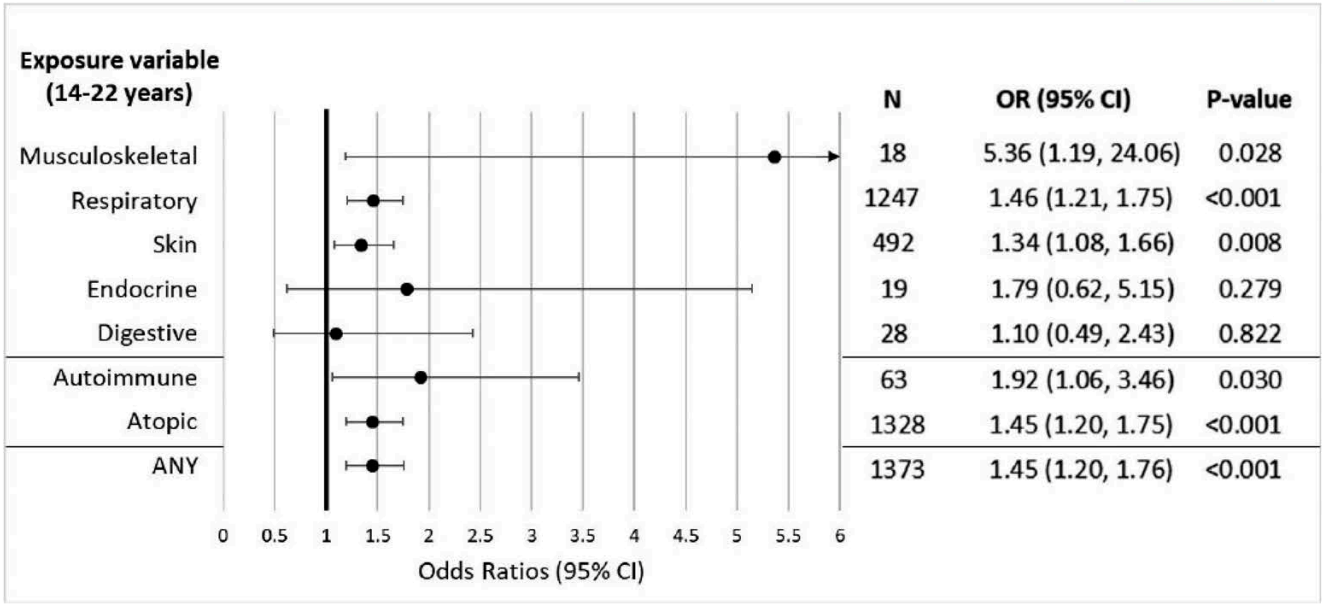

FIGURE 2 Cross-sectional association between inflammatory conditions and low back pain occurrences from 14 to 22 years. Abbreviations: N: number of participants with the condition, OR: odds ratio, 95% CI: 95% confidence intervals, Any: any inflammatory condition. Note: All models adjusted for sex

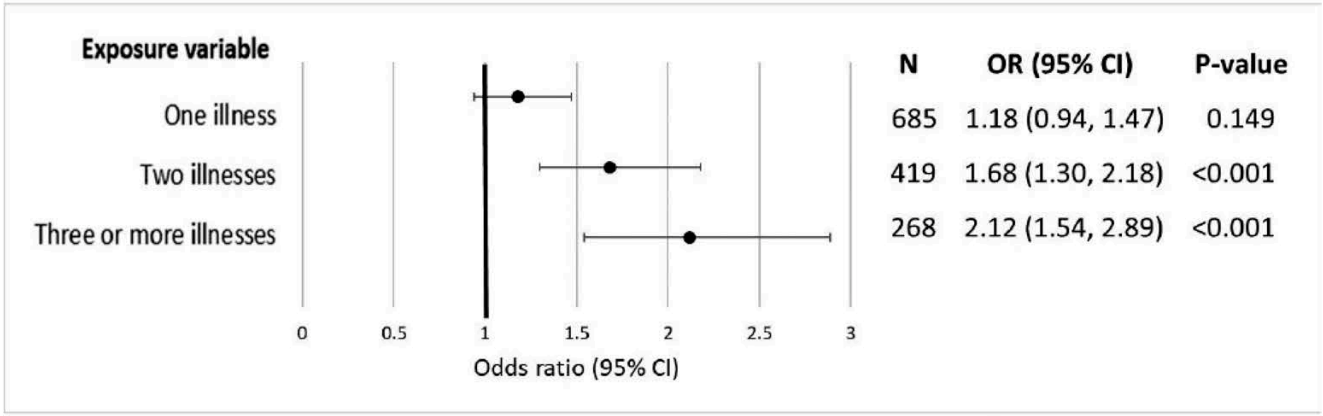

FIGURE 3 Dose–response relationship between number of chronic inflammatory conditions and impactful low back pain. Abbreviations: N: number of participants with the condition/s, OR: odds ratio, 95% CI: 95% confidence intervals. Note: All models adjusted for sex

young adulthood (objective 2). Participants with a greater number of chronic inflammatory conditions had increased odds of LBP in adolescence and young adulthood (objective 3). Use of the Raine Study data has enabled a comprehensive look at comorbidity of chronic inflammatory conditions and impactful LBP over a long period of time.

4.1 | Potential mechanisms

In objective one, we investigated whether there was a temporal relationship between early inflammatory conditions and later impactful LBP, in children not reporting LBP at the time of having reported other inflammatory conditions. Such a finding could support the theory that early life inflammation, of any type of inflammatory condition, could explain why LBP is likely to occur through a change of the hypothalamic–pituitary–adrenal axis (Hurwitz & Morgenstern, 1999; Polli et al., 2019; Shanmugam & Sethi, 2013).

In objective two, we investigated the cross-sectional association between inflammatory conditions and LBP. Such comorbidity could indicate a shared underlying (inflammatory) mechanism for both the comorbidity and LBP, thus indicating that LBP would be an inflammatory condition. Association between inflammatory conditions and impactful LBP was more consistent in the cross-sectional analysis than in the longitudinal analysis, suggesting that when the inflammatory condition is active, LBP may be yet another of its manifestations.

We cannot infer causation based on these analyses but rather consider whether chronic inflammatory conditions could predict LBP in adolescence and young adulthood. The association between respiratory conditions and LBP is consistent with the broader literature. Cross-sectional studies have shown that adults with breathing difficulties (Smith et al., 2006), respiratory diseases including asthma (Heliövaara et al., 1991; Hurwitz & Morgenstern, 1999; Wright et al., 1995) or allergies (Hurwitz & Morgenstern, 1999) had higher odds of having back pain compared to those without the condition. Additionally, asthma in adolescence has been found to be associated with future LBP (Hestbaek et al., 2006b). Our analysis supports these findings and expands them using both cross-sectional and longitudinal analyses.

In considering temporality, we considered childhood chronic illnesses diagnosed in early childhood in LBP-free individuals and subsequently whether LBP manifests in adolescence or young adulthood (objective 1). Back pain with impact generally does not originate until around pubertal or after puberty. In considering this longitudinal association, only respiratory or atopic conditions had increased odds of future LBP.

The dose–response relationship was examined in objective three. Participants with a greater number of chronic inflammatory conditions had increased odds of LBP in adolescence and young adulthood. This dose–response relationship has also been consistently seen within the previous literature. Adults with both respiratory and digestive (Holmberg et al., 2005), or respiratory and gastrointestinal disorders (Smith et al., 2009) had an increased risk of developing back pain as compared to those without the conditions.

More evidence is needed to elucidate if there is a causal relationship, but there is an association between some chronic inflammatory conditions and LBP. The associations found in this study suggest further investigations related to causality are a reasonable thing to do.

4.2 | Research and clinical implications

The results from this study show the need to consider comorbidities in clinical practice and future research. Clinicians and researchers tend to work in clinical silos. Musculoskeletal clinicians and researchers should consider other conditions that are potentially having a role in the musculoskeletal complaint. Musculoskeletal clinicians may ask about past and current medical history, but they should also consider this medical history within the treatment plan potentially through interprofessional collaborations.

Low back pain is known to be complex and multifactorial (Hartvigsen et al., 2018). For example, in the Raine Study participants, exposure to pain, physical factors, psychological factors, social factors and lifestyle factors at 14 years of age have been shown to be associated with the reporting of LBP at 17 (Smith et al., 2017). The results should be interpreted within the broader understanding of LBP as a complex disorder.

4.3 | Strengths and limitations

The population is a community-dwelling sample, rather than just a clinical population which increases the external validity. Merely having back pain in adolescence may be a normal life experience and potentially of benign nature with no long-term problems (Burton et al., 1996). Impactful LBP was considered in this study. This definition captures the population that could be associated with an increasing health and societal burden from LBP.

At 14 years of age, questions were asked about back pain rather than specifically LBP. Back pain covers a bigger part of the spine potentially leading to a larger prevalence estimate at the 14-year time point. Additionally, the severity and duration of LBP were unknown. In considering inflammatory conditions during childhood, certain conditions had a low prevalence. For example, there were only 30 participants diagnosed with chronic autoimmune inflammatory conditions from 1 to 10 years of age when compared with 1,391 participants diagnosed with chronic respiratory inflammatory conditions from 1 to 10 years of age. The low prevalence of certain conditions could lead to a type two error, failing to reject the null hypothesis. For objective one, we included inflammatory conditions from 1 to 10 years of age to capture inflammatory conditions in childhood that were likely to precede the onset of back pain. However, it is possible that different, or stronger, results might be found if a longer period of childhood was considered. Additionally, the chronic inflammatory conditions were self-reported and, where possible, verified through medical records. No information was included on the duration of the condition, age at the time of diagnosis or severity of conditions. Therefore, there could have been a difference between participants with the same diagnosis as well as under- or over-diagnosis based on self-reported data. While we did attempt to control for confounding by including covariates in our models, we were unable to account for every possible source of confounding. Therefore, there is a potential for residual confounding.

5 | CONCLUSION

Overall, longitudinal and cross-sectional associations of respiratory and atopic conditions, with impactful LBP in adolescence and young adulthood were identified. More evidence is needed to determine whether there is a causal

relationship between chronic inflammatory conditions and impactful LBP, or if there is a common origin for these conditions.

ACKNOWLEDGEMENTS

We would like to acknowledge the Raine Study participants and their families for their ongoing participation in the study and the Raine Study team for study coordination and data collection.

CONFLICT OF INTEREST

None declared.

AUTHORS' CONTRIBUTIONS

AB, JH, CLY, DB and BW were involved with the concept and design. Statistical analysis was performed by AB, JH and AJ. All authors were involved with interpretation of the results and drafting the manuscript. All authors reviewed and approved the final manuscript.

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How to cite this article: Beynon AM, Hebert JJ, Leboeuf-Yde C, Beales DJ, Jacques A, Walker BF. Early life chronic inflammatory conditions predict low back pain in adolescence and young adulthood. *Eur J Pain*. 2020;00:1–8. https://doi.org/10.1002/ejp.1700

APPENDIX

Exposure categories of chronic or recurrent inflammatory conditions with included conditions (conditions reported by participants)

1. Endocrine system:
   - Diabetes mellitus type 1
   - Addison's disease
   - Hashimoto's disease
   - Autoimmune lymphoproliferative syndrome

2. Respiratory system:
   - Chronic or allergic rhinitis
   - Chronic sinusitis
   - Chronic tonsillitis
   - Simple chronic bronchitis
   - Bronchiectasis
   - Asthma

3. Digestive system:
   - Oesophageal reflux
   - Gastritis
   - Crohn's disease
   - Eosinophilic gastroenteritis
   - Chronic pancreatitis
   - Celiac disease

4. Skin and subcutaneous tissues(including the eye):
   - Atopic dermatitis
   - Psoriasis
   - Chronic conjunctivitis
   - Eczematous dermatitis – eyelid

5. Musculoskeletal system and connective tissues:
   - Systemic lupus erythematosus
   - Juvenile rheumatoid arthritis
   - Ankylosing spondylitis
   - Polymyalgia rheumatica

6. Autoimmune conditions:
   - Diabetes mellitus type 1
   - Addison's disease
   - Hashimoto's disease
   - Autoimmune lymphoproliferative syndrome
   - Immune thrombocytopenic purpura
   - Wegener's granulomatosis
   - Celiac disease
   - Psoriatic arthropathy
   - Psoriasis
   - Systemic lupus erythematosus
   - Juvenile rheumatoid arthritis
   - Ankylosing spondylitis

7. Atopic conditions:
   - Atopic dermatitis
   - Chronic conjunctivitis
   - Eczematous dermatitis – eyelid
   - Chronic or allergic rhinitis
   - Asthma

8. Any:
   - Includes any of the above conditions

Summary or Chapter Four and link to next chapter

Through this Raine Study analysis, we found longitudinal and cross-sectional associations of respiratory and atopic conditions, with impactful low back pain in adolescence and young adulthood. There was also a dose-response relationship between the number of chronic inflammatory conditions and impactful low back pain.

Through the analysis of longitudinal data we considered if there was a temporal relationship between chronic inflammatory conditions during childhood and future impactful low back pain during adolescence and young adulthood. We found that participants with respiratory, atopic, or any chronic inflammatory condition in childhood (1-10 years of age) had increased odds of low back pain during adolescence and young adulthood.

Through the cross-sectional analysis, we examined the associations between chronic inflammatory conditions and impactful low back pain during adolescence and young adulthood. We found that the presence of any chronic inflammatory condition albeit musculoskeletal, respiratory, skin, autoimmune, or atopic in nature resulted in increased odds of impactful low back pain during the years in question. This concurrent association may indicate that the conditions could be comorbid with a shared underlying origin or mechanism [51], with low back pain itself being an inflammatory condition.

Based on these results we do not know if there is a causal relationship between chronic inflammatory conditions and impactful low back pain, or if there is a common origin for these conditions. Nevertheless, we found cross-sectional and longitudinal evidence of associations between some chronic inflammatory conditions and low back pain.

From the findings of this study, we further investigated the potential link between chronic inflammatory conditions and low back pain by considering the relationship between CRP and low back pain within this same population.

Chapter Five- Multi-trajectory analysis of C-reactive protein and low back pain from adolescence to early adulthood

We identified a link between inflammatory conditions and low back pain. However, the reasons behind this link are still unknown. Individuals with certain pathological conditions may secrete greater amounts of pro-inflammatory cytokines. C-reactive protein (CRP) is a sensitive biomarker of inflammation [69]. Previous cross-sectional studies have reported associations between CRP and low back pain in adult populations [89, 90]. However, this relationship is unclear in younger populations.

Trajectory modelling is useful for developing an understanding of complex longitudinal relationships and can assist when exploring the relationships between exposures and outcomes that develop over time. Trajectory modelling can also demonstrate the recurrent and fluctuating nature of pain conditions [94].

First, as a preliminary study we identified trajectories of CRP and investigated the longitudinal association between trajectories of CRP and body mass index (Appendix One). Secondly, we identified the trajectories of low back pain from early adolescence through to early adulthood and investigated the associations between trajectories of CRP and low back pain.

This work underwent peer-review and is published as:

Beynon AM, Hebert JJ, Beales DJ, Jacques A, Walker BF. Multi-trajectory analysis of C-reactive protein and low back pain from adolescence to early adulthood. Eur Spine J (2021). DOI : 10.1007/s00586-020-06677-0

As of 24/02/2021: Article accesses: 93. Citations: 0. Altmetric: 2

European Spine Journal
https://doi.org/10.1007/s00586-020-06677-0

ORIGINAL ARTICLE

Multi-trajectory analysis of C-reactive protein and low back pain from adolescence to early adulthood

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Received: 16 July 2020 / Revised: 5 October 2020 / Accepted: 22 November 2020

Abstract

Purpose To identify low back pain (LBP) trajectories from early adolescence through to early adulthood and to investigate whether sustained levels of elevated subclinical C-reactive protein (CRP) are linked with these LBP trajectories.

Methods We analysed longitudinal data from 1513 participants who were enrolled in the Raine Study cohort. Data on LBP with impact on daily living and CRP were collected at the ages of 14, 17, 20, and 22. We constructed group-based trajectory models to identify discrete trajectories of LBP with impact. We then evaluated how the CRP trajectories and the LBP with impact trajectories evolved jointly over time using a multi-trajectory analysis.

Results The model identified three LBP trajectories. One subgroup included almost half the participants (46.1%) who had a consistently low probability of LBP. Another subgroup comprising 43.5% of participants had an increasing probability of LBP, while one in ten participants (10.4%) had a decreasing probability of LBP. There were no associations between elevated CRP and LBP trajectory subgroup membership.

Conclusion Although young people follow distinct trajectories of LBP, CRP trajectories do not appear to be a distinguishing factor of the LBP trajectories. Previously reported associations between CRP and LBP may be explained by comorbidity or other factors. Future studies undertaking trajectory analysis should consider comorbidity clusters.

Level of Evidence I Diagnostic: individual cross-sectional studies with the consistently applied reference standard and blinding

Keywords "Low Back Pain" · "C-reaction protein" · Trajectories · Adolescence · "Early adulthood"

Introduction

Low back pain (LBP) is the leading cause of disability worldwide affecting people of all ages [1]. Low back pain has many potential contributors, including psychosocial, physical, and genetic factors [2]. Further, some comorbidities [2], including asthma [3, 4], allergies [4], and depression [4], are reportedly associated with LBP from adolescence to adulthood.

A plausible biological link between these comorbid disorders may be that those with certain conditions secrete greater amounts of pro-inflammatory cytokines than those without the condition [4]. Potentially, this leads to inflammation-associated activation of the hypothalamic–pituitary–adrenal axis [4]. Such activation can lead to axis dysregulation and hyperresponsiveness to mechanical or psychosocial stressors that may contribute to pain [4].

C-reactive protein (CRP) is a sensitive but nonspecific inflammatory biomarker [5]. Healthy adults usually have stable CRP levels (median concentration of 0.8 mg/l), except for infrequent elevations related to minor infections, inflammation, or trauma [5]. Preliminary evidence points to a potential link between CRP and LBP. Recent systematic reviews investigating the relationship between pro-inflammatory biomarkers and LBP found moderate-quality evidence for a positive association of CRP with the presence and severity of LBP [6, 7]. A cross-sectional analysis of a

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-020-06677-0) contains supplementary material, which is available to authorised users.

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Published online: 03 January 2021

population-based sample (N = 15,322) reported high CRP levels to be associated with increased odds of reporting LBP, particularly in participants living with obesity (odds ratio [95% CI] = 2.86 [1.18–6.96]) [8]. Other studies [9, 10] have reported higher CRP to be associated with higher cold-pressor sensitivity, suggesting a link between pain sensitivity and inflammation.

Taken together, these findings show that increased inflammation may alter the experience of LBP by modulating underlying sensitisations. However, this hypothesis is based on cross-sectional evidence [6, 8–10]. The longitudinal nature of the relationship between inflammation and LBP is unclear. Trajectory modelling is useful for understanding complex longitudinal relationships and may help to elucidate the potential relationship between chronic, subclinical levels of CRP and the course of LBP.

The aim of this study was to investigate the longitudinal associations between CRP levels and LBP from adolescence to early adulthood. Specifically, we (1) identified the trajectories of LBP from early adolescence through to early adulthood, (2) examined for differences in mean CRP between LBP trajectory subgroups, and (3) investigated the associations between trajectories of CRP and trajectories of LBP from early adolescence through to early adulthood.

Methods

Study design and participants

This longitudinal study used data from the Raine Study Gen2 participants at 14-, 17-, 20-, and 22-year follow-ups. The Raine Study is a multi-generation, longitudinal cohort study from Western Australia. It commenced as a pregnancy cohort with mothers recruited between May 1989 and November 1991 from King Edward Memorial Hospital for Women and from surrounding private practice clinics. There were 2868 children recruited into the Raine Study cohort. These child participants (Gen2) have been followed at regular time points from birth to the present day (i.e. for 27 years) [11]. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement guidelines [12].

C-reactive protein

High-sensitivity CRP was measured from blood samples by PathWest at 14, 17, 20, and 22 years of age, using an immunoturbidimetric method on an Architect c16000 Analyser. This method correlates well with representative immunonephelometric assays [13]. The immunoassays for CRP are reproducible, robust, and well standardised [5]. High-sensitivity CRP (hs-CRP) refers to the lower detection limit of the assay. Data points with hs-CRP > 10 mg/L were excluded because this was assumed to indicate acute inflammation or current infection [14].

Low back pain

Questionnaire items of the Raine Study assessed back pain at 14, 17, 20, and 22 years of age. Data were collected on participants' self-reported occurrences of LBP within the last month along with the impact of back pain, including any treatment or interference with daily activities. Specific questions were as follows: "Has your low back been painful at any time in the last month?", "Have you missed work or school due to low back pain?", "Has low back pain interfered with your normal activities?", "Has low back pain interfered with recreational physical activities?", "Have you sought professional advice or treatment for low back pain?", and "Have you taken medication to relieve low back pain?" At age 14, the questions were asked about any "back pain" rather than specifically "low back pain".

We constructed a "LBP with impact" variable defined as reporting back pain and answering affirmatively to at least one of the LBP impact questions (questions 2–5).

Statistical analysis

Demographic data were reported descriptively. All analyses were performed using Stata S/E version 15 (StataCorp, TX).

To address objective 1, the identification of LBP trajectories from early adolescence through to early adulthood, we constructed a group-based trajectory model [15] to identify latent classes of LBP with impact. Group-based trajectory modelling is a special application of finite mixture modelling used to estimate discrete trajectory subgroups with maximum likelihood [16, 17]. Group-based trajectory modelling is a person-centred approach aiming to identify groups of individuals who share certain attributes, as compared to variable-centred analyses which aim to describe associations between variables [18]. Unlike latent class analysis or growth-mixture modelling, covariates are not required as unspecified group-based trajectory models are not prone to bias [16, 17].

We included participants with two or more assessments of LBP over the four time points. This model accounts for missing data at random with robust maximum likelihood estimation methods resulting in asymptotically unbiased parameter estimates [17]. Model selection decisions were made using the Bayesian Information Criterion (BIC) statistic. In building the model, we first decided on the number of groups and then determined the shape of the polynomial

trajectories (zero-order, linear, or quadratic). We started with the simplest solution (two groups) and increased the number of groups and complexity of polynomial shapes until the BIC plateaued, and with a minimum subgroup size of 30 participants [16, 17].

Accordingly, the decision of the number of groups was directed by the goal of analysis and confirmation based on posterior probability diagnostics. We applied five a priori diagnostic criteria to determine model fit: (1) mean posterior probability ≥ 70% for each group, (2) odds of correct classification ≥ 5 for each group, (3) meaningful distinction between the groups, (4) close correspondence between the estimated group proportions and the assigned membership proportions, and (5) reasonably narrow confidence intervals around estimated values [16, 17].

For objective 2, to examine for differences in mean hs-CRP between LBP trajectory subgroups, multinomial logistic regression was used. We reported the mean and standard deviation of hs-CRP at each time point and the relative risk ratios with 95% confidence intervals. The LBP trajectory 1 (consistently low probability of LBP) was used as the reference category. Sex, pubertal status, and body mass index were found not significant as covariates; therefore, no covariates were added to the model.

To address objective 3, to investigate the associations between trajectories of CRP and trajectories of LBP from early adolescence through to early adulthood, we constructed group-based multi-trajectory models to evaluate the co-development of hs-CRP and the LBP trajectories over time. Multi-trajectory modelling identifies the concurrent development of multiple outcomes of interest simultaneously [19]. As multi-trajectory models assess the co-development of multiple outcomes as a function of age, the model may differ from the univariate trajectory model. We included participants with two or more assessments of hs-CRP (≤ 10 mg/L) and LBP over the four time points. The same criteria of the best model fit were used as above. Sensitivity analyses were completed for both the univariate LBP trajectory model and the multi-trajectory model including stratified sex-specific analyses, only including the 17–22 year time points, and only including participants with all four time points.

Results

The demographic characteristics and descriptive LBP and hs-CRP data for all four follow-up time points are presented in Table 1. Data from 1513 participants with at least two LBP measurements were included in the trajectory model. In total, 942 participants had two or more measures of hs-CRP (≤ 10 mg/L) and LBP, and they were included in the multi-trajectory model (Fig. 1).

Low back pain with impact trajectories

The three-group trajectory model demonstrated the optimal fit and met all a priori diagnostic criteria (Online Resource 1). There were three distinct LBP trajectory subgroups from ages 14–22 years. Trajectory groups were categorised according to their probability of LBP and labelled as follows: "consistently low" (46.1%,$n = 746$), "decreasing" (10.4%,$n = 151$), and "increasing" (43.5%,$n = 616$) (Fig. 2). All sensitivity analyses yielded similar results (Online Resource 2).

Low back pain with impact trajectories and mean C-reactive protein levels

As demonstrated by the multinomial logistic regression analysis, there were no differences in the mean hs-CRP between LBP trajectory subgroups (Table 2).

Multi-trajectory model of C-reactive protein and low back pain with impact

Multi-trajectory modelling assessed the potential interrelationship between the co-development of hs-CRP trajectories and the LBP trajectories. The three-group trajectory model demonstrated the optimal fit and met all a priori diagnostic criteria (Online Resource 1). Figure 3 demonstrates the

Table 1 Number of participants with data

Age: mean (SD)	Total Participants:n (% female)	Back pain data: n (%)	Reported having LBP with impact n (%)	Valid hs-CRP (≤ 10 mg/L)[a]: n (%)	Mean hs-CRP (mg/L): mean (SD)
14.1 (0.2)	1865 (49)	1596 (85.6)	479 (30.0)	1355 (72.6)	0.8 (1.3)
17.1 (0.3)	1693 (50)	1289 (76.1)	321 (24.9)	1239 (73.2)	1.3 (1.9)
20.0 (0.5)	1577(50)	1241 (78.7)	395 (31.8)	1118 (70.9)	1.6 (2.0)
22.2 (0.8)	1235 (52)	1115 (90.3)	468 (42.0)	938 (75.9)	1.6 (1.9)

SD: standard deviation, *LBP*: low back pain, *hs-CRP*: High-sensitivity *C*-reactive protein, *hs-CRP* (≤ 10 mg/L)[a]: those with hs-CRP (≤ 10 mg /L), as this could indicate acute inflammation rather than chronic inflammation state

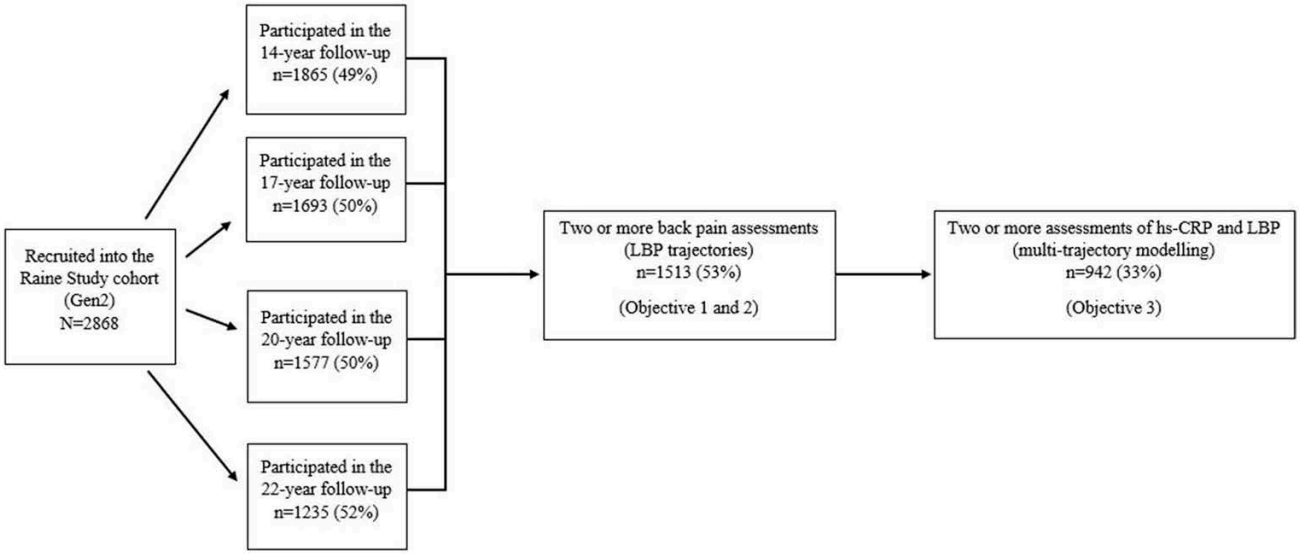

Fig. 1 Study flow diagram

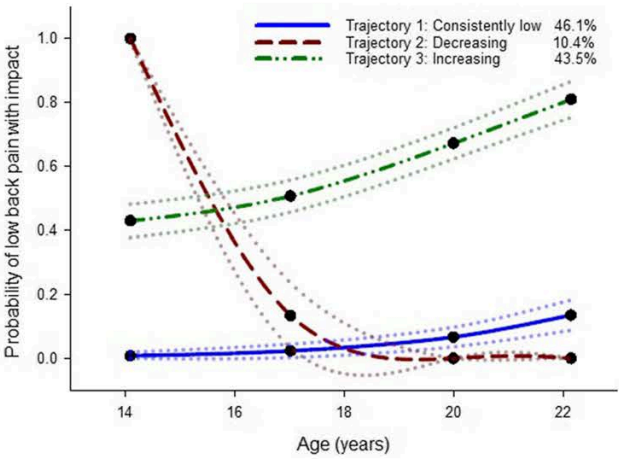

Fig. 2 Trajectories of the probability of low back pain with impact from 14 to 22 years with 95% confidence intervals

multi-trajectory analysis of hs-CRP and LBP from 14 to 22 years with 95% confidence intervals. Group 1 ("low CRP, low LBP" 52.4%) had stable-low hs-CRP and a consistently low probability of LBP. Group 2 ("low CRP, increasing LBP" 39.9%) had again stable-low hs-CRP but an increasing probability of LBP over time. Group 3 ("increasing CRP, moderate LBP" 7.7%) had an increasing level of hs-CRP over time and a moderate probability of LBP. The multi-trajectory model revealed no obvious association between hs-CRP and LBP from adolescence to early adulthood. All sensitivity analyses yielded similar results (Online Resource 2).

Table 2 Low back pain with impact trajectories and the mean hs-CRP at each time point

hs-CRP at ages	LBP Trajectory 1 ("Consistently low") REFERENCE	LBP trajectory 2 ("Decreasing")		LBP trajectory 3 ("Increasing")	
	mean (SD)	mean (SD)	RRR (95% CI)	mean (SD)	RRR (95% CI)
Age 13	0.85 (1.51)	0.66 (0.98)	0.89 (0.70, 1.12)	0.70 (1.03)	0.89 (0.70, 1.12)
Age 16	1.39 (1.87)	1.16 (1.68)	0.93 (0.78, 1.09)	1.22 (1.71)	0.95 (0.86, 1.05)
Age 20	1.73 (2.05)	1.67 (1.89)	0.98 (0.86, 1.12)	1.58 (1.98)	0.96 (0.88, 1.05)
Age 23	1.65 (1.90)	1.70 (2.03)	1.01 (0.87, 1.17)	1.72 (2.93)	1.01 (0.93, 1.11)

hs-CRP: high-sensitivity *C*-reactive protein, *LBP*: low back pain, *SD*: standard deviation, *RRR*: relative risk ratio, 95% *CI*: 95% confidence interval

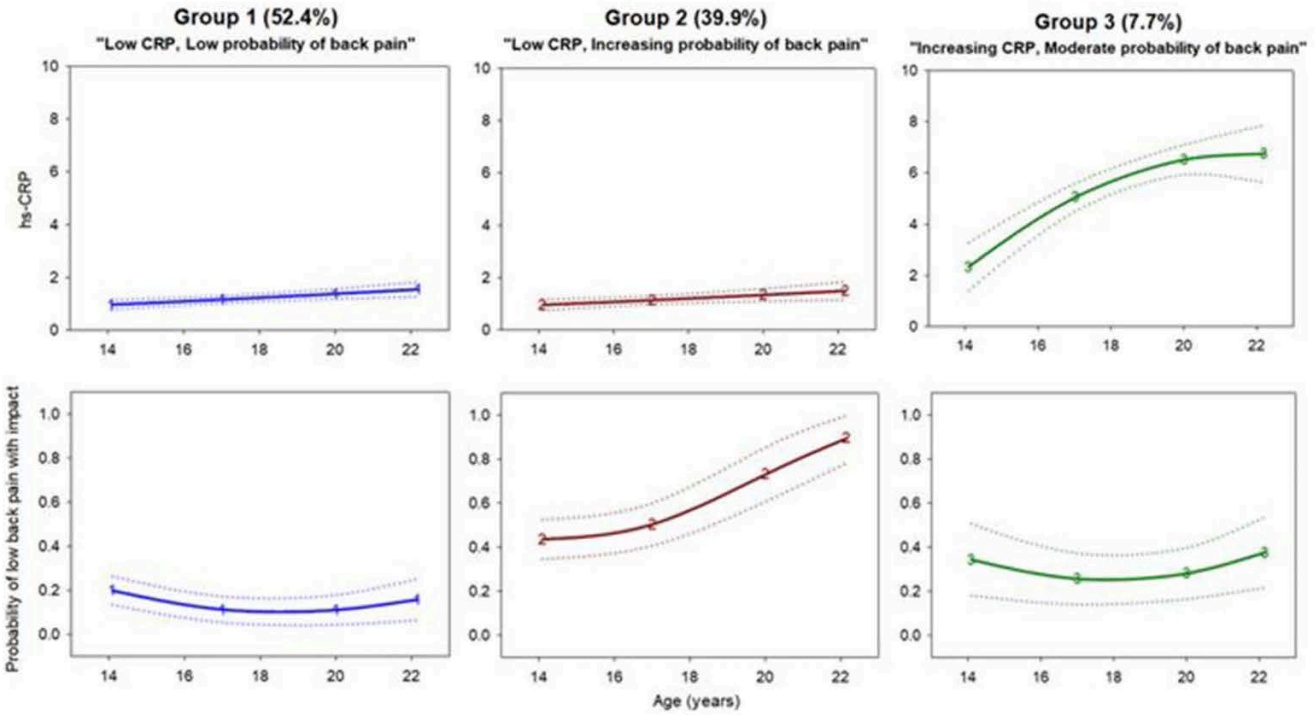

Fig. 3 Multi-trajectory analysis of hs-CRP and low back pain with impact from 14 to 22 years with 95% confidence intervals

Discussion

We identified three LBP trajectories from 14 to 22 years of age. One group of participants had a "consistently low" probability of LBP with impact (46.1%), another group had an "increasing" probability of LBP with impact (43.5%), and the final group had a "decreasing" probability of LBP with impact (10.4%). There were no differences in the mean hs-CRP between LBP trajectory subgroups. Additionally, the multi-trajectory model revealed that elevated hs-CRP over time is not associated with LBP. Taken together, these results indicate a lack of a relationship between the patterns of hs-CRP and LBP development over time. In other words, CRP does not appear to play a role in the development of impactful LBP in adolescents and young adults.

Comparison to the literature

Similar longitudinal LBP clusters have been previously created within the Raine Study Gen2 participants from 17 to 22 years using repeated measures latent class analysis that clustered multiple LBP indicator variables [20]. However, Coenen et al. [20] identified four clusters: low (53%), increasing (22%), decreasing (15%), and high (10%) prevalence of LBP and its impact [20]. This reflects two different statistical and methodological ways of dealing with similar data. The difference in age and type of modelling accounted for the different results. The low trajectory/cluster was similar across both studies, as was the decreasing trajectory/cluster. When combining the increasing and high cluster within the previous study [20], it represented approximately 30% of the cohort, approximating this current study. While there are differences in terms of the type of analysis and the number of trajectory classes reported in these studies, the results seem complementary and confirmatory.

A recent systematic review synthesised the results of four trajectory studies, including Coenen et al. [20], and found that there were three common patterns of LBP in children and adolescence. The majority of children (49–53%) reported no or low probability of LBP, the second pattern in children and adolescents reported fluctuations of LBP (16–37%), and a minority of children and adolescents repeatedly reported LBP (< 1–10%) [21]. This again shows complementary results within not only the same study population but also different study populations.

This study found that elevated levels of hs-CRP over time were not directly related to LBP. This finding conflicts with the results of a cross-sectional study by Briggs et al. [8] who found that high hs-CRP levels increased the odds of reporting LBP, particularly in individuals who were obese. However, their sample population included a mixture of ages including adolescents and older adults. It may be that a direct relationship between CRP and LBP emerges after the age of 22. Therefore, it could be of value to continue to track populations further into adulthood. The link is potentially

more about comorbidities rather than just back pain and inflammation. In younger people perhaps, the relationship between CRP and comorbidity, with LBP being a feature of a cluster of poor health conditions, might be more meaningful than when taken in isolation. Future research could consider comorbidity clusters rather than just LBP in isolation.

Another future direction may be to consider pain sensitivity in conjunction with the pain itself. Mechanistic links have been proposed between inflammatory mediators and pain sensitivity [9, 10]. Potentially underlying inflammation may contribute to a pro-nociceptive state [22], without directly influencing the report of pain and disability itself which might be driven by other factors [23].

Strengths and limitations

We considered LBP and its impact in this study. Merely having nonspecific LBP (without disc herniation or other abnormal findings on MR or CT) in adolescence is potentially of a benign nature and a normal life experience [24]. Therefore, our augmented definition captures the population of young people with LBP with the potential to increase the societal burden of LBP. Another strength was that the population is a community-dwelling sample. Having measures of both back pain and CRP at up to four time points across adolescence into early adulthood seem to be a unique data set.

There were some limitations in the way the LBP measurement was undertaken. At 14 years, questions were asked about back pain rather than specifically LBP, as back pain potentially covers a bigger part of the spine; this may have led to a larger prevalence estimate at the 14-year time point. This difference in back pain reporting could have played a role in the "decreasing" LBP trajectory where there was a decreased back pain probability from 14 to 17 years. However, this "decreasing" trajectory could also be consistent with the evidence of pubertal development and growth as potential risk factors for spinal pain [25]. Only four time points with two to three years between measurements were used to assess LBP and hs-CRP. This may not have the accuracy of truly representing the potential recurrent nature of LBP that would be achieved by having more frequent time points. Low back pain measured in this may oversimplify participants' pain experience. Low back pain is dynamic and difficult to capture with dichotomous outcomes. To better understand the trajectories of LBP, more frequent measurements should be undertaken and this may yield different results. Additionally, the severity and duration of LBP were unknown.

Conclusion

In young people, surveyed four times between the ages of 14 and 22, three trajectories of LBP with impact were identified. Almost half had a "consistently low" probability of LBP with impact. Another 43% had an "increasing" probability of LBP with impact, whereas a small percentage had a "decreasing" probability of LBP with impact. There was no association between the LBP trajectories and the mean hs-CRP level at each time point nor with the hs-CRP trajectories. Future research in adolescents and young adults might focus on inflammation in pain-related comorbidity groups, or as a contributor to a pro-nociceptive state that moderates the pain experience rather than directly affecting the pain experience itself.

Acknowledgements We would like to acknowledge the Raine Study participants and their families for their ongoing participation in the study and the Raine Study team for study co-ordination and data collection. In relation to the biological essay data used in this study, we acknowledge the in-kind support provided by the following institutions for biosample storage and curation: The University of Western Australia, School of Women's and Infants' Health, King Edward Memorial Hospital; The University of Western Australia, Medical School, Royal Perth Hospital; and Telethon Kids Institute. We would like to acknowledge Professor Charlotte Leboeuf-Yde for her assistance in design and supervision. We would also like to acknowledge Professor Anne Smith for her assistance with the revision of the manuscript.

Authors' Contributions All authors contributed to the study conception and design. Statistical analysis was performed by AB, JH, and AJ. All authors were involved with the interpretation of the results and drafting the manuscript. All authors reviewed and approved the final manuscript.

Funding The core management of the Raine Study is funded by The University of Western Australia, Curtin University, Telethon Kids Institute, Women and Infants Research Foundation, Edith Cowan University, Murdoch University, The University of Notre Dame Australia, and the Raine Medical Research Foundation. The Raine Study Gen2 14-, 17-, 20- and 22-year follow-ups were funded by NHMRC Project Grants (211912, 003209, 403981, 323200, 353514, 1021105, 1027449, 1044840, and 1021858), Safe Work Australia, and the WA Department of Health (G06302). AB is supported by a scholarship from Murdoch University, Western Australia, and a scholarship provided by Chiropractic Australia Research Foundation. JH receives salary support from the Canadian Chiropractic Research Foundation and the New Brunswick Health Research Foundation. The funding sources had no involvement in study design, analysis, interpretation, or manuscript preparation. For the remaining authors, none was declared.

Availability of data and materials The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request and with permission of the Raine Study.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The Raine Study received ethical approval from the Human Ethics Committees at King Edward Memorial Hospital, Princess Margaret Hospital, University of Western Australia, and/or Curtin University. Ethics approval for the current study was granted by the Murdoch University Human Research Ethics Committee (Approval Number: 2018/226).

Consent to participate Informed consent to participate in the study was to be obtained from participants (or their parent or legal guardian).

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Summary of Chapter Five and link to next chapter

We identified three distinct trajectories of low back pain with impact from 14 to 22 years of age. One subgroup had a consistently low probability of low back pain (46.1%), another subgroup had an increasing probability of low back pain (43.5%), and the final subgroup had a decreasing probability of low back pain (10.4%). There was no association between CRP and the low back pain trajectories. This finding conflicts with the results of a large cross-sectional study of a general population by Briggs et al. [93] who found that elevated levels of CRP increased odds of reporting low back pain, particularly in individuals who were obese. The relationship between CRP and back pain could develop in older populations and may not be apparent in young populations. Additionally, this link could be more about comorbidities rather than just back pain and inflammation.

Within this study there was potential bias due to the study attrition. There were 2868 children (at birth) recruited into the Raine Study, follow-up data were collected for approximately 50% of participants at 14 through 22 years. Low back pain trajectories were based on data from 53% of the original sample, and multi-trajectory modelling was based on data from 33% of the original sample. When first recruited into the Raine Study it was the parents who were recruited, as time went on and the children became teenagers and young adults, it is understandable that there would be a certain degree of missing data and dropouts. While, we cannot provide information about distribution of risk and/or prognostic factors in participants with and without complete follow-up data, we do acknowledge the potential bias that this high attrition rate may bring.

Cardiovascular disease does not typically manifest in childhood, as these conditions generally present in later life, therefore it is useful to consider cardiovascular disease risk factors during childhood. Clustering of cardiovascular disease risk factors can manifest in children and then continues into adulthood [55-57]. It has been reported that cardiovascular disease risk factors in children predict metabolic syndromes later in life [106, 107]. This leads to our next study where we sought to investigate the association between cardiovascular disease risk factors and spinal pain in young people.

Chapter Six- Association between cardiovascular disease risk factors and future spinal pain with the potential moderating role of health-related physical activity (CHAMPS Study-DK)

In adults, cardiovascular disease has been shown to be significantly associated with back pain [54, 108]. In children it is important to consider cardiovascular disease risk factors that can lead to metabolic syndromes later in life [106, 107].

This next study aimed to 1) investigate the prospective associations between childhood cardiovascular disease risk factors and spinal pain occurrences, and 2) examine for the potential moderating role of health-related physical activity in this relationship. We hypothesized that children with greater cardiovascular disease risk factors would have an increased risk of developing spinal pain.

This manuscript has been prepared for publication and formatted for publication in the European Journal of Pain.

Beynon AM, Wedderkopp N, Walker BF, Leboeuf-Yde C, Hartvigsen J, Hebert JJ. Association between cardiovascular disease risk factors and future spinal pain with the potential moderating role of health-related physical activity (CHAMPS Study-DK)

Study: Association between cardiovascular disease risk factors and future spinal pain with the potential moderating role of health-related physical activity (CHAMPS Study-DK)

Short title: Cardiovascular disease risk factors and spinal pain

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Original article

Funding/Support: Funding for the CHAMPS Study-DK: The TRYG Foundation, University College Lillebaelt, University of Southern Denmark, The Nordea Foundation, The IMK foundation, The Region of Southern Denmark, The Egmont Foundation, The A.J. Andersen Foundation, The Danish Rheumatism Association, Østifternes Foundation, Brd. Hartmann's Foundation, TEAM Denmark, The Danish Chiropractor Foundation, and The Nordic Institute of Chiropractic and Clinical Biomechanics. AB is supported by a scholarship from Murdoch University, Western Australia and a scholarship provided by Chiropractic Australia Research Foundation. JJH receives salary support from the Canadian Chiropractic Research Foundation and the New Brunswick Health Research Foundation. The funding sources had no involvement in study design, analysis, interpretation, or manuscript preparation.

Conflict of interest: None declared

What's already known about this topic?

- Spinal pain is a significant public health problem.
- Spinal pain has been previously linked with cardiovascular disease risk factors in children.

What does this study add?

- There may be an association between cardiovascular disease risk factors and future spinal pain, however this relationship is dependent on sex, age, and health-related physical activity behaviour.
- Further research is needed to better understand the reasons for and implications of these relationships.

Abstract

Background: Spinal pain is a significant public health problem. Spinal pain has been previously linked with cardiovascular disease risk factors in children. This study aimed to investigate any prospective associations between childhood cardiovascular disease risk factors and spinal pain occurrences, and to examine for a moderating role of health-related physical activity in these relationships.

Methods: In this prospective study, we used data from the Childhood Health, Activity, and Motor Performance School Study Denmark (CHAMPS Study-DK) participants. The exposure variables were clustered cardiovascular risk score and homeostasis assessment model-estimated insulin resistance (HOMA-IR) score collected in 2008 and 2010. The spinal pain outcome comprised the number of weeks of non-traumatic spinal pain from 2008-2010 and 2010-2012. Mixed negative binominal regression models were created to investigate the prospective associations of cardiovascular disease risk factors and non-traumatic spinal pain, along with the potential moderating role of health-related physical activity in these relationships.

Results: Girls with low HOMA-IR scores and boys with low clustered cardiovascular disease risk score who engaged in higher levels of moderate-to-vigorous physical activity reported more weeks of spinal pain. Also, boys with higher clustered cardiovascular disease risk who had less time in moderate-to-vigorous physical activity reported more weeks of spinal pain.

Conclusion: Our results suggest that there may be an association between cardiovascular disease risk factors and future spinal pain. However, this relationship is dependent on sex, age, and health-related physical activity behaviour. Further research is needed to better understand the reasons for and implications of these relationships.

Background

Spinal pain is a significant public health problem. Even during adolescence low back pain is ranked as one of the top ten causes of years lived with disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018) and adolescents with low back pain have a higher risk of reporting low back pain in adulthood (Hestbaek et al., 2006). Musculoskeletal conditions commonly co-occur with other chronic diseases as part of multimorbidity (van der Zee-Neuen et al., 2016; Williams et al., 2018). Multimorbidity is the co-existence of two or more diseases within an individual with the assumption that none of the diseases are more central or take precedence over the others (Fortin et al., 2004; Lefèvre et al., 2014; Orueta et al., 2013; van den Akker et al., 1996; van den Akker et al., 2001).

One such multimorbidity is cardiovascular disease, which has been shown to be associated with low back pain in adults (Ha et al., 2014) and cardiovascular disease risk factors contributing to metabolic syndromes are more prevalent in those reporting high-intensity chronic pain (Goodson et al., 2013). Spinal pain has been longitudinally linked with cardiovascular disease risk factors in children (Hebert et al., 2019) and a causal relationship between cardiovascular disease and musculoskeletal conditions has been suggested (Williams et al., 2018). Clustering of cardiovascular disease risk factors begins to manifest in childhood and continues into adulthood (Khoury et al., 1980; Strong et al., 1992; Webber et al., 1979). Childhood could, therefore, be the time to reduce modifiable cardiovascular disease risk factors not only to reduce risk of cardiovascular disease but, if a causal link exists, potentially also other conditions such as spinal pain.

This study aimed to 1) investigate any prospective associations between childhood cardiovascular disease risk factors and spinal pain occurrences, and 2) examine for a moderating role of health-related physical activity in these relationships. We hypothesized that children with greater cardiovascular disease risk factors would be at increased risk of developing spinal pain and that health-related physical activity would moderate this relationship.

Methods

Study design and Ethics Permissions

In this prospective cohort study, we used data from the participants of the Childhood Health, Activity, and Motor Performance School Study Denmark (CHAMPS study-DK) (Wedderkopp et al., 2012). Participating children from ten schools were enrolled into the study on a rolling basis starting from October 2008. The sample comprised children from 6 years to 11 years of age at the time of enrolment who were followed until June 2014 (Franz et al., 2014; Fuglkjær et al., 2017).

This current analysis was conducted in two phases (including the same participants in both phases). Phase one included cardiovascular disease risk factors sampled in September – October 2008 and spinal pain data collected from November 2008 to November 2010. Phase two included cardiovascular disease risk factors sampled in September – October 2010 and spinal pain data collected from November 2010 to November 2012.

Ethics approval was obtained from the Regional Scientific Committee of Southern Denmark for the CHAMPS study-DK (ID S20080047) and the study was registered with

the Danish Data protection Agency, as stipulated by Danish law J.nr 2008-41-2240. Written informed consent was obtained from parents. Every child and parent also gave verbal consent for all clinical examinations. Ethics approval for the current analysis was also given by Murdoch University Human Research Ethics Committee (Approval number: 2019/012).

Cardiovascular disease risk factors

Blood samples and other measurements of cardiovascular disease risk were taken in 2008 and 2010, including fasting blood samples and systolic blood pressure. Fasting blood samples were obtained between 8.00 – 10.30 AM, stored on ice, and transported to the laboratory within four hours, where they were pipetted, centrifuged, and stored at -80 degrees Celsius (Hebert et al., 2017). Biochemical serum markers included: total cholesterol, high-density lipoprotein cholesterol (HDL-C), total cholesterol: HDL-C ratio, triglycerides, glucose, and insulin (Hebert et al., 2017). The homeostasis assessment model-estimated insulin resistance (HOMA-IR) score was calculated as insulin (µU/ ml) × glucose (mmol/l)/22.5 (Hebert et al., 2017; Matthews et al., 1985). The HOMA-IR assessment has been found to be reliable and valid within a population of children and adolescents with obesity (Conwell et al., 2004; Keskin et al., 2005).

Systolic blood pressure was measured with an automated blood pressure monitor [Welch Allyn® (New York, USA) vital signs monitor 300 series with FlexiPort™]. Blood pressure was taken seated after the participants had rested for five minutes and were recorded at 1-minute intervals until three stable measurements or five total measurements were obtained. The mean of the final three measurements was used for analysis (Hebert et al., 2017).

The primary exposure variable was a clustered cardiovascular risk score, which has been reported as a better measure of cardiovascular health in children than a single risk factor (Andersen et al., 2003). The clustered cardiovascular risk score was calculated by summing the standardized values of systolic blood pressure, total cholesterol: HDL-C ratio, log triglycerides, and log HOMA-IR (Klakk et al., 2014). All scores were then converted to positive values, with larger scores representing higher levels of cardiovascular disease risk (Hebert et al., 2017). The secondary exposure variable was the HOMA-IR score. We calculated tertiles for each exposure variable to be able to distinguish between the group of children with low and high-risk values.

Spinal pain outcome

Spinal pain was defined as any pain during the past week in either the neck, mid-back, and/or low back. Spinal pain data were collected through an automated text message each Sunday over 5.5 years. The average weekly response rate was 96.5% (Franz et al., 2014). When pain was reported, the parents were called by phone the following day. If pain persisted at that time, the child had an examination with a clinician (Franz et al., 2014). ICD codes were used to classify the spinal pain diagnosis at the time of examination and occurrences were classified as traumatic or non-traumatic (Franz et al., 2017). Additionally, research staff examined linked medical records for additional information.

In the current analyses, we excluded all occurrences of diagnosed spinal pain arising from a traumatic aetiology (e.g., fracture, sprain, contusion). Therefore, the spinal pain outcome comprised the number of weeks of non-traumatic spinal pain occurring in each of the two study phases. To be included in the analysis, participants needed to have at

least 60% valid reporting of spinal pain data during the respective two-year phase. For example, to be included in phase one, participants needed at least 60% valid reporting of spinal pain data in phase one, irrespective of reporting in phase two. We divided the analysis into two phases because the collection of the cardiovascular disease risk factors were collected at two timepoints, two years apart.

Covariates

Demographic information was collected through a questionnaire at baseline. Potential moderators and confounders included age, sex, and time spent in moderate-to-vigorous intensity physical activity. Physical activity was measured objectively every second year using Actigraph GTX3 accelerometers (Hebert et al., 2015; Wedderkopp et al., 2012). Participants wore the accelerometer at the right hip, using a customised elastic belt, for seven consecutive days during waking hours (except when swimming or bathing). Data on physical activity were included if the participant accumulated at least ten hours of wear time on four or more days. Physical activity was measured as counts per minute and minutes spent in different intensities (sedentary, light, moderate, and vigorous) of physical activity, which gave an estimate of the overall mean physical activity for an average day. We applied standard cut-points to identify moderate and vigorous physical activity intensities, and isolated the proportion of the day in moderate-to-vigorous intensity physical activity (Hebert et al., 2015; Wedderkopp et al., 2012). These covariates were chosen due to their potential associations with back pain (Beynon et al., 2019a; Beynon et al., 2019b) and cardiovascular disease risk factors (Andersen et al., 2006).

Statistical analysis

Demographic data were reported descriptively including mean and standard deviation (SD), or median and interquartile range (IQR) depending on the nature of the variable distribution. We log-transformed exposure variables with non-normal distributions.

In the first analysis (phase one), we used the baseline cardiovascular disease risk factors sampled in September – October 2008 as predictors for the number of weeks with at least some non-traumatic spinal pain from November 2008 to November 2010. In the second analysis (phase two), we used the cardiovascular disease risk factors variables sampled in September – October 2010 as predictors for the number of weeks with at least some non-traumatic spinal pain from November 2010 to November 2012.

To examine prospective associations between childhood cardiovascular disease risk factors and spinal pain occurrences (aim one), we constructed separate, mixed negative binominal regression models to investigate the prospective associations of cardiovascular disease risk factors and non-traumatic spinal pain for each risk factor at each of the two study phases. Negative binomial models are well suited for zero-inflated count data (weeks with spinal pain) (Hardin and Hilbe, 2014). To account for the hierarchical nature of this school-based study, we included each child's school class identifier as a random effect in all models. Age was added as a covariate and sex as a potential modifier by adding an interaction term with the cardiovascular disease risk factor. Model results were reported with unstandardized beta coefficients (β) and 95% confidence intervals (CI), stratified by sex. The lowest tertile groups (i.e., tertile one) was used as the reference for the HOMA-IR and clustered cardiovascular disease risk factor exposure groups.

To examine the potential moderating role of health-related physical activity in the relationship between cardiovascular disease risk factors and spinal pain (aim two), we repeated the same modelling procedure and included a three-way interaction between clustered risk, sex, and moderate-to-vigorous physical activity. We examined the nature of these interactions by stratifying model results on sex, estimating the predicted margins, and plotting these results graphically.

Data were analysed using and Stata/SE version 15 (StataCorp, TX). *P* values <0.05 were considered statistically significant.

Results

Overall, 1630 participants (52% female) participated in the study. In the first study phase, the study sample consisted of 1099 children (52% female) with a mean (SD) age of 8.4 (1.4) years and the second phase included 1129 children (52% female) with a mean (SD) age of 10.4 (1.4) years (Table 1).

The prevalence of any kind non-traumatic spinal pain was very similar between phase one and two. However, there was a higher mean duration for weeks with spinal pain in phase two compared to phase one. In phase one, 62% of the 1104 children reported no non-traumatic spinal pain, 19% reported one week with at least some spinal pain, 6% reported two weeks, 4% reported three weeks, and 9% reported four or more weeks with spinal pain. In phase two, 60% of the 1291 children reported no non-traumatic spinal pain, 15% reported one week, 5% reported two weeks, 4% reported three weeks, and 15% reported non-traumatic spinal pain in four weeks or more (Table 2).

<u>Cardiovascular disease risk factors and future spinal pain</u>

In phase one, when children had a mean age of 8-10 years, we found that girls with moderate log HOMA-IR scores (tertile two) were less likely to experience non-traumatic spinal pain compared to girls with low log HOMA-IR scores (tertile one) (β [95% CI]= -0.83 [-1.57, -0.08]). In phase two, when children had a mean age of 10-12 years, girls with high log HOMA-IR scores (tertile three) were less likely to experience non-traumatic spinal pain than girls with low log HOMA-IR scores (tertile one) (β [CI]= -1.57 [-2.63, -0.51]). There were no other associations between the cardiovascular disease risk factors and spinal pain (please see Appendix A for reporting of all estimates).

Cardiovascular disease risk factors, future spinal pain, and the moderating role of physical activity

In phase one, there were no associations between the cardiovascular disease risk factors and non-traumatic spinal pain when accounting for the moderating role of health-related physical activity (Figure 1).

In phase two, there was a significant three-way interaction with log-HOMA-IR, moderate-to-vigorous physical activity, and sex (p= 0.009). Overall, girls with low HOMA-IR scores who engaged in higher levels of moderate-to-vigorous physical activity reported more weeks of spinal pain. Also, boys with lower clustered cardiovascular disease risk and more time in moderate-to-vigorous physical activity reported more weeks with spinal pain. Further, boys with higher clustered cardiovascular risk who had less time in moderate -to-vigorous physical activity reported more weeks of spinal pain (Figure 2).

Specifically, girls with low (tertile one) log HOMA-IR risk scores and more moderate-to-vigorous physical activity had a higher likelihood of non-traumatic spinal pain than girls

with moderate (tertile two) and high (tertile three) log HOMA-IR scores (significant two-way interaction p= 0.009 and 0.001 for tertile two and three respectively) (Figure 2, A1). Boys with low (tertile one) log HOMA-IR scores and more time in moderate-to-vigorous physical activity had a higher likelihood of non-traumatic spinal pain than boys with moderate (tertile two) log HOMA-IR scores (significant two-way interaction p= 0.033) (Figure 2, A2).

Boys with low (tertile one) clustered cardiovascular disease risk scores and more time in moderate-to-vigorous physical activity reported more weeks with non-traumatic spinal pain than boys with high (tertile three) cardiovascular disease risk scores (significant two-way interaction p= 0.024) (Figure 2, B2). Furthermore, boys with a high (tertile three) clustered cardiovascular disease risk score and less moderate-to-vigorous physical activity were more likely to experience non-traumatic spinal pain than boys with low (tertile one) clustered cardiovascular disease risk score (significant two-way interaction p= 0.024) (Figure 2, B2), this association was not found in girls (Figure 2, B1).

Discussion

Girls with low HOMA-IR scores and boys with low clustered cardiovascular risk score who engaged in higher levels of moderate-to-vigorous physical activity reported more weeks of spinal pain. Also, boys with higher clustered cardiovascular risk who had less time in moderate-to-vigorous physical activity reported more weeks of spinal pain. We only observed the moderating effect in the oldest cohort (phase two). Thus, our results suggest that there may be an association between cardiovascular risk factors and future spinal pain, however this relationship is dependent on sex, age, and health-related physical activity behaviour.

Comparisons to previous literature

We are unaware of studies that have investigated the moderating role of health-related physical activity in the relationship between cardiovascular disease risk factors and spinal pain. However, several studies have evaluated these relationships separately. Previous research found that girls with spinal pain had greater clustered cardiovascular risk compared to girls without spinal pain, independently of health-related physical activity (Hebert et al., 2019). Similarly, adults with higher levels of cardiovascular risk factors or a history of cardiovascular disease reported more low back pain (Ha et al., 2014; Leino-Arjas et al., 2006). Considering other illnesses within comparable young populations, previous associations have been identified between early life chronic illnesses and back pain in young populations, with individuals with chronic inflammatory conditions reporting more back pain in adolescence and young adulthood compared to those without the condition (Beynon et al., 2020a; Beynon et al., 2020b).

There is inconsistent evidence regarding the nature of the relationship between spinal pain and physical activity (Beynon et al., 2019a; Beynon et al., 2019b; Heneweer et al., 2011). It has been suggested that the association between physical activity and low back pain should be considered on a continuum, a 'U-shape distribution' (Campello et al., 1996). This has been supported by results from a population-based study which found cross-sectional associations between extremes of physical activity (too much or too little) with chronic low back pain, particularly in women (Heneweer et al., 2009). However, this was contradicted by Heuch et al. (2016) who reported no evidence of a U-shaped relationship between physical activity and low back pain. Schiltenwolf and Schneider (2009) called for longitudinal studies to consider this relationship between

low back pain and physical activity, and in our longitudinal analyses we found that physical activity moderates the association of cardiovascular disease risk factors and spinal pain in older children. This finding supports the idea that depending on an individual's cardiovascular disease risk score, age and sex, too much or too little exercise may be associated with increased spinal pain.

Methodological considerations

Strengths of the current study include its longitudinal design and large, representative cohort of children. We used uniquely robust measurements of spinal pain, cardiovascular disease risk factors, and physical activity. Spinal pain data were collected with weekly text messaging which likely reduced recall bias with high levels of participant engagement and clinical examinations.

Although models were adjusted for some potential modification and confounding there might have been other factors not included, as a source of confounding. Consequently, there is potential for residual confounding. The severity of the spinal pain was also unknown.

Our study was an exploratory hypothesis generating study that requires confirmation before considering clinical or policy-related implications. Thus, we cannot make confident judgements about causation, as the temporality has not been established. However, as spinal pain is uncommon in very young children (Franz et al., 2014), we expect that relatively few children had established spinal pain prior to enrolment in the study. Nevertheless, additional evidence is needed to judge the causal nature of these relationships between cardiovascular disease risk factors, physical activity, and spinal pain.

Conclusion

This study considered the prospective associations between cardiovascular disease risk factors with future non-traumatic spinal pain, and the moderating role of health-related physical activity. Girls with low insulin resistance and boys with low clustered cardiovascular risk score at baseline, when children were approximately 10-12 years of age, and who spent high amounts of time doing moderate-to-vigorous physical activity reported more weeks with spinal pain during the two year follow up. Boys with higher clustered cardiovascular risk who had low amounts of time doing moderate-to-vigorous physical activity also reported more weeks with spinal pain. Thus, there appears to be a relationship between insulin resistance, cardiovascular risk factors and future spinal pain in older children and this relationship might be moderated by physical activity. Further research is needed to better understand the reasons for and implications of these relationships.

Acknowledgments

The authors acknowledge all the members of the CHAMPS Study-DK and the clinicians taking part in this study. We also thank the participating children, their parents, and teachers in the schools involved in the project.

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Table 1: Baseline descriptive demographics and cardiovascular risk variables for each study phase.

Variable	2008 (phase 1)		2010 (phase 2)	
	(n)	Mean (SD)	(n)	Mean (SD)
Age (yr.)	Girls (572)	8.3 (1.4)	Girls (588)	10.3 (1.4)
	Boys (527)	8.4 (1.4)	Boys (541)	10.4 (1.4)
Body mass index (kg/m^2)	Girls (571)	16.4 (2.1)	Girls (588)	17.5 (2.5)
	Boys (522)	16.3 (2.0)	Boys (540)	17.1 (2.3)
Insulin (µU/mL)	Girls (479)	3.9 (2.9)	Girls (447)	5.1 (2.9)
	Boys (447)	3.4 (2.1)	Boys (429)	5.0 (6.6)
Glucose (mmol/L)	Girls (478)	4.5 (0.4)	Girls (447)	4.7 (0.3)
	Boys (447)	4.7 (0.8)	Boys (429)	4.9 (0.8)
HOMA-IR	Girls (478)	0.8 (0.6)	Girls (447)	1.1 (0.7)
	Boys (447)	0.7 (0.6)	Boys (429)	1.3 (4.5)
Systolic BP (mm Hg)	Girls (555)	101.1 (8.1)	Girls (588)	102.0 (8.2)
	Boys (510)	101.5 (8.7)	Boys (541)	102.3 (8.1)
Total Cholesterol (mg/dL)	Girls (478)	174.5 (28.8)	Girls (447)	167.8 (26.2)
	Boys (447)	167 (25.7)	Boys (429)	163.2 (25.3)
HDL Cholesterol (mg/dL)	Girls (478)	63.0 (13.7)	Girls (447)	62.1 (12.8)
	Boys (447)	66.1 (13.3)	Boys (429)	64.3 (14.1)
Total:HDL-C (mg/dL)	Girls (478)	2.9 (0.7)	Girls (447)	2.8 (0.7)
	Boys (447)	2.6 (0.6)	Boys (429)	2.6 (0.6)
LDL Cholesterol (mg/dL)	Girls (478)	99.3 (26.7)	Girls (447)	93.5 (23.8)
	Boys (447)	90.6 (23.7)	Boys (428)	87.4 (22.4)
Triglycerides (mg/dL)	Girls (478)	60.8 (23.7)	Girls (447)	59.0 (26.6)
	Boys (447)	52.1 (20.9)	Boys (428)	54.4 (27.6)
Clustered CV risk score	Girls (467)	12.8 (2.6)	Girls (447)	16.1 (2.6)
	Boys (433)	11.8 (2.5)	Boys (428)	15.4 (2.9)
MVPA (% of day)	Girls (591)	7.4 (2.3)	Girls (608)	7.2 (2.6)
	Boys (519)	9.0 (2.5)	Boys (532)	9.6 (3.1)

HOMA-IR: homeostasis assessment model-estimated insulin resistance, BP: blood pressure, HDL-C: high-density lipoprotein cholesterol, LDL-Cholesterol: low-density lipoprotein cholesterol, CV: cardiovascular, MVPA: moderate-to-vigorous physical activity.

Table 2: Number of weeks of reported non-traumatic spinal pain for each study phase.

		Phase 1 (Nov 2008-Nov 2010)				
	(n)	Mean (SD)	Median	IQR	Range	n (%) ≥ 1-week with pain
Number of weeks with non-traumatic spinal pain	Girls (587)	1.7 (5.4)	0	1	0 to 62	241 (41)
	Boys (517)	1.3 (5.9)	0	1	0 to 75	179 (35)
		Phase 2 (Nov 2010-Nov 2012)				
	(n)	Mean (SD)	Median	IQR	Range	n (%) ≥ 1-week with pain
Number of weeks with non-traumatic spinal pain	Girls (676)	3.1 (8.5)	0	2	0 to 91	284 (42)
	Boys (615)	1.9 (6.8)	0	1	0 to 90	230 (37)

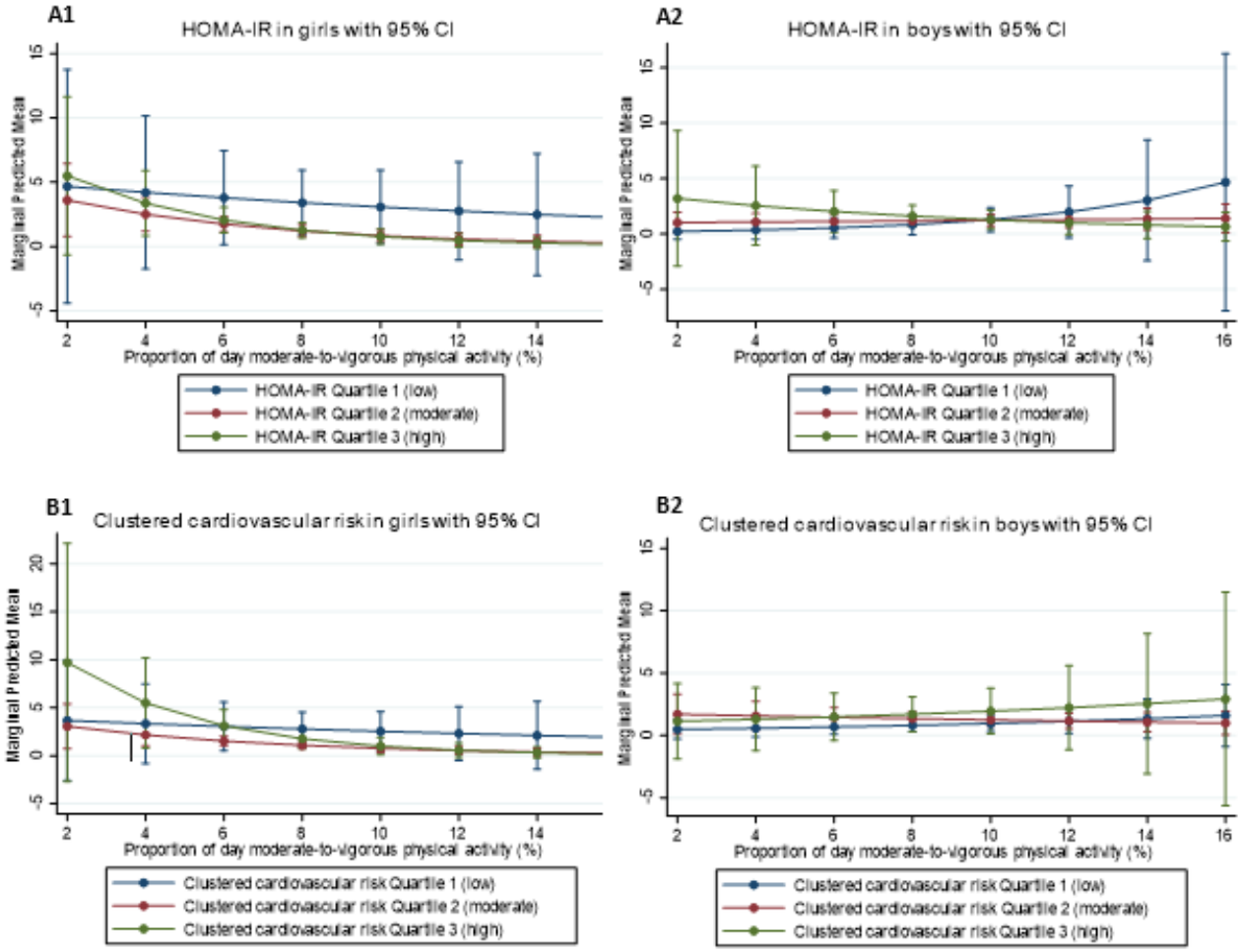

Figure 1: Predictive margins of HOMA-IR and clustered cardiovascular risk for phase 1
No significant 2-way interaction with cardiovascular disease risk factor and moderate-to-vigorous physical activity

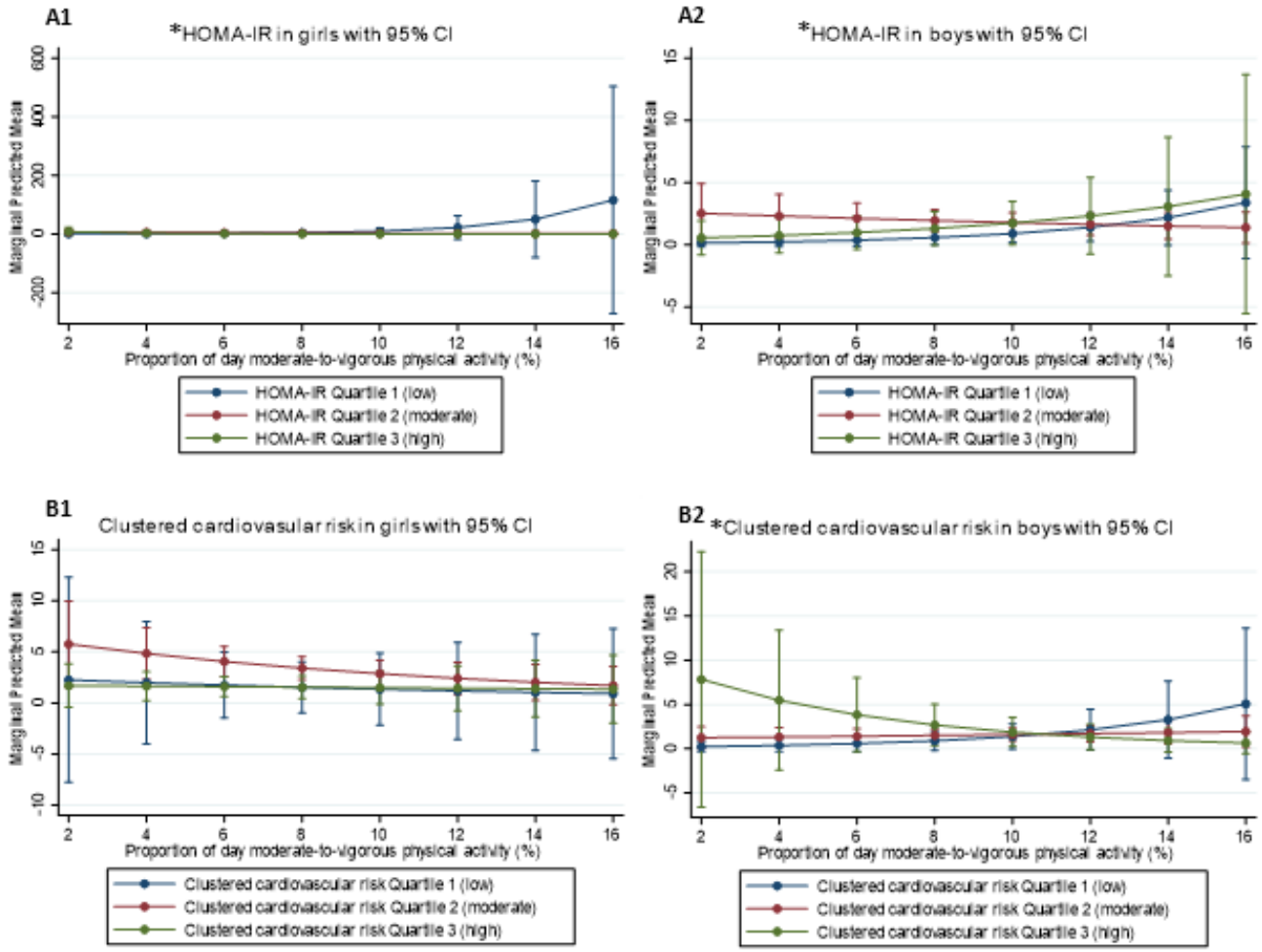

Figure 2: Predictive margins of HOMA-IR and clustered cardiovascular risk for phase 2
*Significant 2-way interaction with cardiovascular disease risk factor and moderate-to-vigorous physical activity

Summary of Chapter Six and link to next chapter

This CHAMPS Study-DK analysis found that girls with low insulin resistance score (HOMA-IR) and had a high amount of time doing moderate-to-vigorous physical activity reported more weeks with spinal pain. Additionally, boys with low clustered cardiovascular disease risk who had high amounts of time doing moderate to vigorous physical activity and higher clustered cardiovascular disease risk who had low amounts of time doing moderate to vigorous physical activity reported more weeks with spinal pain.

As far as we know, no other study in any other study population has considered the moderating role of health-related physical activity in the relationship between cardiovascular disease risk factors and spinal pain. Therefore, this was an exploratory study about hypothesis generation. To better understand the relationship between these factors the results require replication in different populations.

We then moved on to consider the potential relationship between CRP and spinal pain within this cohort.

Chapter Seven- No association between sub-clinical elevation of C-reactive protein levels and spinal pain trajectories in children (CHAMPS Study-DK).

The aim of this study was to investigate the associations between sub-clinical elevation of CRP levels and spinal pain from childhood to adolescence. Specifically, we examined for differences in mean CRP levels between spinal pain trajectory subgroups.

This manuscript has been prepared for publication and formatted for publication in the Pediatrics.

Beynon AM, Wedderkopp N, Walker BF, Leboeuf-Yde C, Hartvigsen J, Hebert JJ. No association between sub-clinical elevation of C-reactive protein levels and spinal pain trajectories in children (CHAMPS Study-DK).

Study: No association between sub-clinical elevation of C-reactive protein levels and spinal pain trajectories in children (CHAMPS Study-DK).

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Short title: C-reactive protein levels and spinal pain trajectories

Conflict of Interest Disclosures: The authors have no conflicts of interest relevant to this article to disclose.

Funding/Support: Funding for the CHAMPS Study-DK: The TRYG Foundation, University College Lillebaelt, University of Southern Denmark, The Nordea Foundation, The IMK foundation, The Region of Southern Denmark, The Egmont Foundation, The A.J. Andersen Foundation, The Danish Rheumatism Association, Østifternes Foundation, Brd. Hartmann's Foundation, TEAM Denmark, The Danish Chiropractor Foundation, and The Nordic Institute of Chiropractic and Clinical Biomechanics. Amber Beynon is supported by a scholarship from Murdoch University, Western Australia and a scholarship provided by Chiropractic Australia Research Foundation. Jeffrey Hebert receives salary support from the Canadian Chiropractic Research Foundation and the New Brunswick Health Research Foundation.

Role of Funder/Sponsor: The funder/sponsor did not participate in the work

Abbreviations: CRP: C-reactive protein; OR: odds ratio; CI: confidence intervals; CHAMPS: The childhood health, activity and motor performance school study; MVPA: moderate-to-vigorous intensity physical activity; SD: standard deviation.

Article Summary: Through group-based trajectory modelling, this study identified distinct trajectory of spinal pain in children and investigated the association between CRP and spinal pain trajectories.

What's Known on This Subject: Spinal pain is the leading cause of disability and can affect children. Preliminary evidence points to a link between CRP and spinal pain. Prospective data are needed to study the relationship between CRP levels and spinal pain in young populations.

What This Study Adds: Most children repeatedly reported no spinal pain or spinal pain rarely, with a minority of children repeatedly reporting spinal pain, which increases with age towards adolescence. There were no differences in mean CRP levels between spinal pain trajectory subgroups.

Data Sharing Statement: Deidentified individual participant data will not be made available.

Acknowledgments: The authors acknowledge all the members of the CHAMPS Study-DK and the clinicians taking part in this study. We also thank the participating children, their parents, and teachers in the schools involved in the project. We acknowledge Professor Bobby Jones for his assistance with creating the trajectory models. We also acknowledge Dr Chinchin Wang and Professor Ian Shrier for providing the inputted datasets.

Abstract:

Background and Objectives: Spinal pain is the leading cause of disability worldwide and can affect children. Preliminary evidence points to a link between C-reactive protein (CRP) and spinal pain. The aim of this study was to investigate the associations between sub-clinical elevation of CRP and different trajectories of spinal pain frequency from childhood to adolescence.

Methods: We used data from the Childhood Health, Activity, and Motor Performance School Study Denmark (CHAMPS study-DK). High-sensitivity CRP (hs-CRP) was measured from blood samples. The outcome variable was the number of weeks of non-traumatic spinal pain. Group-based spinal pain trajectories were generated using group-based trajectory modelling. The association between hs-CRP and spinal pain trajectory subgroup membership was investigated with multinominal logistic regression.

Results: Based on data from 1556 participants, there were five distinct spinal pain trajectory subgroups from 6 to 17 years of age: “no pain” (55.3%), “rare” (20.3%), “rare, increasing” (10.9%), “moderate, increasing” (6.0%), and “early onset, decreasing” (1.3%). There were no differences in mean hs-CRP at baseline between spinal pain trajectory subgroups.

Conclusions: Whilst there were some fluctuations in of spinal pain frequency between the trajectory groups, most children reported spinal pain rarely or not at all. There was no significant association between the hs-CRP levels and the spinal pain trajectories. Future studies should consider including follow-up of children into adulthood, assessments of other inflammatory markers, and measurements of outcome based on other types and definitions of spinal pain.

Introduction

Globally, spinal pain is the leading cause of disability[1] and affects people across their life-course including children and adolescents.[2,3] Spinal pain is complex and has been found to have many possible contributors, including genetic, physical, and psychosocial factors,[4] and follow different trajectories in sufferers.[5-7] Low-grade persistent inflammation has been proposed as a biological mechanism for an array of health conditions[8,9] and there is some evidence that points to a link between elevated levels of pro-inflammatory biomarkers and spinal pain.[10,11]

C-reactive protein (CRP) is a sensitive marker of inflammation in the human body. Adults generally have relatively stable levels of CRP with a median concentration of 0.8mg/l, with occasional increased levels usually linked to infections or trauma.[12] CRP levels greater than 10 mg/L (clinical levels) are likely to indicate current infection and acute inflammation.[13] Sub-clinical levels of CRP, between 1-3 and 10mg/L, have been associated with multiple factors for poor health,[9] such as metabolic syndromes,[14,15] coronary heart disease,[16-19] and diabetes.[20,21] In children, CRP has been correlated with cardiovascular risk factors such as fibrinogen, HDL-cholesterol, heart rate and systolic blood pressure, as well as measures of adiposity.[22,23]

There is also preliminary evidence that points to a potential link between CRP and spinal pain. For example, there is moderate quality evidence showing positive associations between CRP and the presence and severity of low back pain in adult populations,[10,11] and authors of a large cross-sectional population-based study (N=15,322) reported that participants with obesity and high CRP levels had an almost three-fold increased odds of reporting low back pain (odds ratio [95% CI] = 2.86 [1.18 to 6.96]).[24] Data from cross-sectional studies in older or mixed general populations indicate that increased inflammation may alter the experience of spinal pain by altering underlying

sensitisations.[10,24-26] However, longitudinal data are needed to study the relationship between CRP levels and spinal pain over time in particular in children and adolescents.

Thus, the aim of this study was to investigate any associations between sub-clinical CRP levels and different courses of spinal pain from childhood to adolescence. Specifically, we examined for differences in mean CRP levels at baseline between spinal pain trajectory subgroups.

Methods

Study design and Ethics Permissions

We analysed data from the Childhood Health, Activity, and Motor Performance School Study Denmark (CHAMPS study-DK).[27] Participating children from ten schools were enrolled into the study on a rolling basis starting from October 2008, and comprised children from 6 to 11 years of age at the time of enrolment, and were followed until 2014.[28,29]

Ethics approval was obtained by the Regional Scientific Committee of Southern Denmark for the CHAMPS Study-DK (ID S20080047) and the study was also registered with the Danish Data protection Agency, as stipulated by Danish law J.nr 2008-41-2240. Written informed consent was obtained from every parent. Every child and parent also gave verbal consent for all clinical examinations. Ethics approval for the current analysis was also approved by Murdoch University Human Research Ethics Committee (Approval number: 2019/012).

C-reactive protein

High-sensitivity CRP was measured from blood samples obtained at baseline. Fasting blood samples were obtained in the morning (8.00 – 10.30 AM), stored on ice and

transported within 4 hours to a laboratory, where they were pipetted, centrifuged, and stored at -80 degrees Celsius.[30] High-sensitivity CRP (hs-CRP) refers to the lower detection limit of the assay compared to CRP. The immunoassays for CRP have been shown to be well-standardized, robust, and reproducible.[12] Data points with hs-CRP > 10 mg/L were excluded because this is likely to indicate current infection or acute inflammation rather than chronic inflammation.[13]

Spinal pain outcome

Spinal pain was defined as pain in the neck, mid-back and/or lower back. Spinal pain data were reported by parents each week over five and a half years (November 2008 to June 2014) via text messaging. Specifically asking the parent: "Has [NAME OF CHILD] during the last week has any pain in: 1. Neck, mid back and/or lower back, 2. Shoulder, arm or hand, 3. Hip, leg or foot and 4. No my child has not had any pain." Additionally, diagnosed spinal pain was identified through clinical examination and audit of linked medical records. Diagnosed spinal pain was classified as traumatic or non-traumatic in origin.[31]

We excluded all incidents of diagnosed spinal pain occurring from a traumatic aetiology (e.g., contusions, sprains, strains, fracture). The outcome variable of non-traumatic spinal pain comprised the number of weeks of spinal pain excluding spinal pain with a traumatic diagnosis. The follow-up data were grouped into 6-month timepoints starting from baseline. The number of weeks with reported spinal pain per 11 half years were used to create 11 timepoints on which we modelled the non-traumatic spinal pain trajectories. For spinal data to be included at a particular timepoint, participants needed to report at least 60% valid data during that six-month period (i.e. they had to respond to the weekly text message at least 60% of the time).

96 Covariates

97 Potential moderators and confounders included: sex, pubertal status, body mass index,
98 and health-related physical activity (proportion of waking time in moderate-to-vigorous
99 intensity physical activity [MVPA]). Demographic information was collected through a
100 questionnaire at baseline. Puberty status was assessed at baseline and once a year through
101 a self-reported Tanner stage in structured interviews. Tanner stages were reported on a
102 scale of 1 to 5, with higher scores representing later pubertal status, based on self-
103 assessments of pubic hair development in boys and breast development in girls.[32,33]
104 Anthropometric measurements were taken at baseline and twice a year for five years.
105 Height was measured with a portable stadiometer (SECA 214, Seca Corporation,
106 Hanover, MD, USA) to the nearest .5 cm, and body weight was measured using a
107 calibrated Tanita BWB-800S digital scale (Tanita Corporation, Tokyo, Japan) to the
108 nearest 100g. Age- and sex-specific BMI categories for underweight, normal weight,
109 overweight, and obese were calculated for all participants according to the International
110 Obesity Task Force criteria.[34] Physical activity was measured objectively every second
111 year using Actigraph GTX3 accelerometers and we applied standard cut-points to identify
112 moderate and vigorous physical activity intensities, and isolated the proportion of the day
113 in MVPA.[27,35]

114 These covariates were chosen due to their associations with spinal pain [31,36,37] and
115 CRP.[22,38-40] Previous research demonstrates a higher prevalence of spinal pain in females
116 and with advanced pubertal status.[36,37] There are mixed results regarding the relationship
117 between body mass index and spinal pain.[36,37] Physical activity has been found within the
118 CHAMPS Study-DK cohort to be associated with future spinal pain.[31] Physical exercise
119 has been shown to reduce CRP levels in adults, which could in turn lower the risk of
120 coronary heart disease by moderating inflammation.[40] There are mixed results regarding

sex differences but females have been found to overall have higher levels of CRP in a general population,[38,39] additionally in children girls have also been found to have higher levels of CRP than boys.[22]

Statistical analysis

Demographic data were reported descriptively including mean and standard deviation (SD) of hs-CRP. Data were analysed using Stata S/E version 15 (StataCorp, TX).

Missing data on spinal pain were imputed by multiple imputation using random hot deck imputation. Random hot deck imputation is a logic-based approach in which a pool of 'donors' with similar characteristics are identified and used to impute the missing value. This method allows for the uncertainty of imputation to be accounted for. Five imputed datasets of spinal pain were created and used within the analyses to create the spinal pain trajectories.[41]

Group-based spinal pain trajectories were first generated using group-based trajectory modelling to identify trajectory subgroups for spinal pain. Spinal pain was modelled as a function of age. Compared to variable-centered analyses that endeavour to find associations between variables (e.g., regression), person-centered approaches such as group-based trajectory modelling identify subgroups of individuals who share particular attributes (e.g. course of spinal pain over time).[42] Group-based trajectory modelling is a specialised application of finite mixture modelling that delivers an empirical method of classifying meaningful subgroups of individuals, based on their patterns of change (i.e., trajectories) in outcome over time.[43,44] Dissimilar to growth mixture modelling, group-based trajectory modelling uses maximum likelihood estimation to estimate and create an unknown distribution of trajectories across individuals.[43] In this way, group-based trajectory models are well-suited to identify meaningful but unknown homogeneous

subgroups (i.e., classes) that follow distinct trajectories within a heterogeneous population.[13]

Firstly, single class models were constructed and the number of classes, and complexity of polynomial distributions (e.g., linear, quadratic, cubic) were increased until optimal models were identified.[43] A best model fit was selected using all available data estimating two to eight latent trajectory groups with zero-order, linear, quadratic and cubic terms for each group. The initial modelling decisions were based on a combination of statistical and clinical judgments that were subsequently tested with several diagnostic approaches. We used the Bayesian Information Criterion (BIC) statistic to find clinically relevant trajectories. Models were then subsequently evaluated with 4 *a priori* diagnostic criteria: 1) an average posterior probability of individual group membership of ≥ 70 per cent for each group; 2) obtaining close correspondence between the estimated probability of group membership and the proportion of participants assigned to each group based on the posterior probability; 3) reasonably tight confidence intervals around estimated group membership probabilities and 4) minimum odds of correct classification ≥5.[43,44]

To investigate for differences in mean hs-CRP (at baseline) between spinal pain trajectory subgroups, multinominal logistic regression was used. Hs-CRP was used in its original scale because after excluding values over 10 mg/L its distribution approximated normality.[13] We reported the mean and standard deviation (SD) of hs-CRP at each time point and the beta coefficients with 95% confidence intervals. The spinal pain trajectory 1 (No pain) was used as the reference category. Covariates were introduced into the model initially individually and then in combination, also assessing for any interaction effects between the variables. Covariates were included, if they were associated with spinal pain and/or they made >10% changes in the main exposure variable of interest (hs-CRP) when added or subtracted from the model.

Results

At baseline, the study sample included 572 females (52%) and 527 males with a mean (SD) age of 8.4 (1.4) years, and of these, 916 participants had valid hs-CRP (≤10mg/L) results (Table 1). Data from 1556 participants were included in the non-traumatic spinal pain trajectory model, and mean CRP was calculated among those with valid CRP measurements at baseline (n=916). Sex and level of health-related physical activity were found as significant covariates and included in the final model. Body mass index and pubertal status were not found to be significant covariates nor to make any changes to the magnitude of association and were therefore not included in the final model.

Non-traumatic spinal pain trajectories

The five-group trajectory model demonstrated the optimal fit and met all *a priori* diagnostic criteria (Appendix A). There were five distinct non-traumatic spinal pain trajectory subgroups from ages 6 to 17 years of age, which were labelled as follows: "no pain" (55.3%), "rare" (20.3%), "rare, increasing" (10.9%), "moderate, increasing" (6.0%), and "early onset, decreasing" (1.3%) (Figure 1).

Non-traumatic spinal pain trajectories and mean C-reactive protein levels

There were no differences in mean hs-CRP at baseline between spinal pain trajectory subgroups (Table 2).

Discussion

We identified five non-traumatic spinal pain trajectories from 6 to 17 years of age. Whilst there were some fluctuations in the amount of spinal pain within three of the trajectory groups, three-quarters of children were within the "no pain" or "rare pain" trajectory

groups. This aligns with results from a recent systematic review, which found three common patterns of low back pain in adolescence and young adulthood.[45]

Contrary to our expectations, there were no significant differences in the mean hs-CRP between spinal pain trajectory subgroups. This finding is supported by a recent study on another young cohort study that also found no association between hs-CRP and low back pain in adolescence and young adulthood.[7] However, these findings conflict with the results of a large cross-sectional study of a general population by Briggs et al.[24] who found that elevated levels of hs-CRP increased odds of reporting low back pain, particularly in individuals who were obese. The sample population within Briggs et al. [24] included a mixture of ages including adolescents and older adults. It may be that a direct relationship between CRP and spinal pain emerges in older populations and is not evident in young populations. Further, this link could be potentially about comorbidities rather than just spinal pain and one inflammatory biomarker, CRP. Otherwise, there may simply not be a link between CRP and spinal pain in younger populations. Future research could continue to track the population further into adulthood, examine other potential inflammatory markers, or study other types/definitions of spinal pain.

Strengths and limitations

The main strengths of this study include its longitudinal design over 5.5 years with a large representative cohort of children, and the robust measurements of spinal pain and CRP. Spinal pain data were collected with weekly text messaging data which reduced recall bias and the diagnosis of traumatic/non-traumatic spinal pain enabled spinal pain with a traumatic diagnosis to be excluded. There was also an extremely high response rate (96%) to the weekly spinal pain text messages.[28] Additionally, the utilisation of imputation methods ensured there were limited missing spinal pain data.

Some potential limitations were that although models were adjusted for some potential confounding there could have been other factors not considered as potential source of residual confounding. The quality of our spinal pain variable was considered high but severity of the spinal pain was not measured. Some occurrences of traumatic spinal pain may not have been diagnosed, therefore included in the spinal pain trajectories. However, this is not extremely likely because whenever possible there was a medical examination to diagnosis the spinal pain.

Conclusion

We identified five non-traumatic spinal pain trajectories from 6 to 17 years of age. Whilst there were some fluctuations of the amount of spinal pain within three of the trajectory groups, the majority of children reported spinal pain rarely or not at all. There was no significant association between the spinal pain trajectories and the mean hs-CRP level at baseline. Future research within this area should consider continuing tracking children/adolescents into adulthood, examine other potential inflammatory markers or study other types/definitions of spinal pain.

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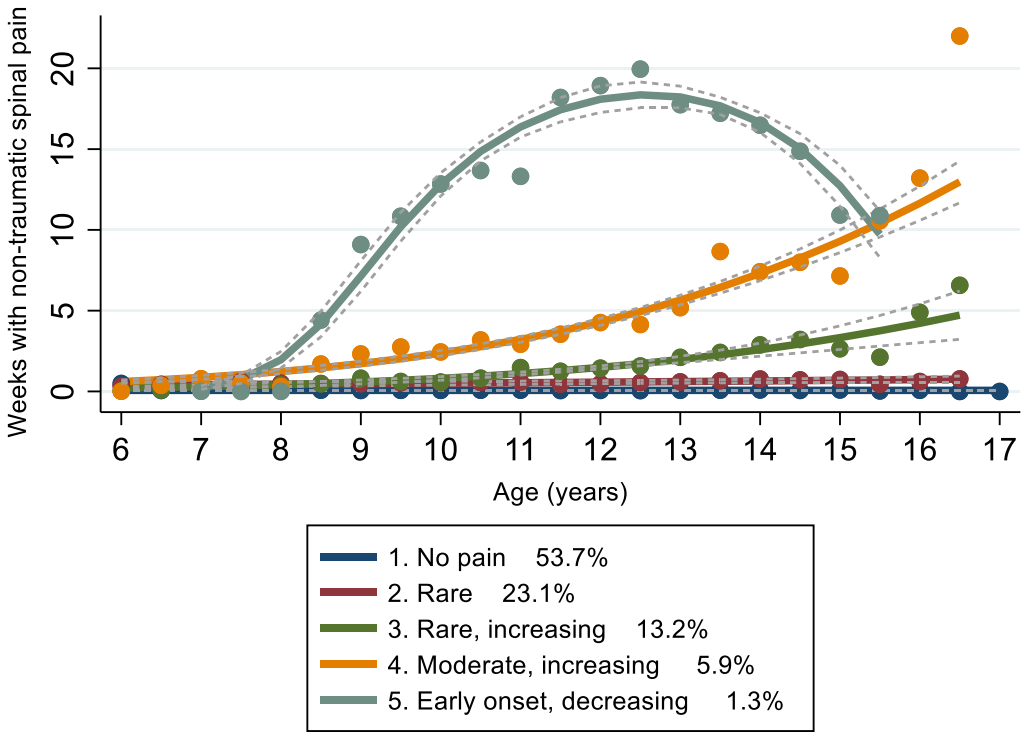
Table 3: Number, age and sex of participants at baseline, plus the number of participants with available data for hs-CRP

Timepoint		Total number of participants: n	Age (years) Mean (SD)	Valid hs-CRP (≤10mg/L)[a]: n	Mean hs-CRP (mg/L): Mean (SD)
Baseline	**All**	1099	8.4 (1.4)	916	0.47 (0.86)
	Girls	572	8.3 (1.4)	470	0.53 (0.88)
	Boys	527	8.4 (1.4)	446	0.42 (0.83)
SD: standard deviation, hs-CRP: High sensitivity C-reactive protein, hs-CRP (≤10mg/L)[a]: those with hs-CRP (≤10mg /L), which indicates acute inflammation					

Table 4: Mean hs-CRP estimates at baseline by the non-traumatic spinal pain trajectory in children.

hs-CRP at timepoint	Spinal pain trajectory 1 ("No pain") REFERENCE	Spinal pain trajectory 2 ("Rare")		Spinal pain trajectory 3 ("Rare, increasing")		Spinal pain trajectory 4 ("Moderate, increasing")		Spinal pain trajectory 5 ("Early onset, decreasing")	
	Mean (SD)	Mean (SD)	β (95% CI)	Mean (SD)	β (95% CI)	Mean (SD)	β (95% CI)	Mean (SD)	β (95% CI)
Baseline	0.52 (0.98)	0.37 (0.43)	-0.27 (-0.56, 0.02)	0.47 (0.87)	-0.05 (-0.31, 0.21)	0.44 (0.71)	-0.11 (-0.56, 0.34)	0.32 (0.33)	-0.41 (-1.76, 0.93)
hs-CRP: high sensitivity C-reactive protein, SD: standard deviation, **β**: beta coefficients 95% CI: 95% confidence interval. Models adjusted for health-related physical activity level and sex									

Figure 1 Non-traumatic spinal pain trajectories from 6 to 17 years of age



Summary of Chapter Seven

Within this final CHAMPS Study-DK analysis, through trajectory analysis we identified five distinct non-traumatic spinal pain trajectory subgroups from childhood to adolescence. The largest subgroup (53.7%) was the 'no pain' subgroup, followed by 23.1% of participants in the 'rare' spinal pain subgroup. Another subgroup with 13.2% of participants was the 'rare, increasing' spinal pain subgroup. The final two smallest subgroups were the 'moderate, increasing' and 'early onset, decreasing' spinal pain subgroups with 5.9% and 1.3% of participants respectively. This shows that most of the children repeatedly reported no spinal pain or spinal pain rarely, with a minority of children repeatedly reporting spinal pain, which increases with age towards adolescence.

Finally, there were no differences in mean hs-CRP levels between spinal pain trajectory subgroups within this cohort.

Chapter Eight- Thesis discussion

Overall aim and summary of main findings

The overarching aim of this thesis was to explore aspects of the aetiology of spinal pain in young populations. Specifically, the aim of this thesis was to investigate if early life illness factors such as childhood gastrointestinal, cardiovascular and respiratory illnesses, or cardiovascular disease risk factors are risk factors for back pain in adolescence or young adulthood. Also, to investigate if there is a link between CRP and back pain in young population.

Based on the review articles (chapter two and three) the most likely risk factors for back pain in children and young adults are female sex, older age towards adolescence and young adulthood, later pubertal status, positive family history of back pain, and psychological factors [109-111]. In the assembled literature between-study comparisons were hampered by a lack of clarity of definitions for back pain. Consequently, the results are mainly restricted to associations. To assist the analyses we adopted the methodology of using repeated measures of back pain with clear definitions and applied it to risk factors of back pain in young populations.

These reviews informed our investigative processes as we drew on high quality databases to explore our hypotheses. We found:

a) Longitudinal and cross-sectional associations of respiratory and atopic conditions, with impactful low back pain occurrences in adolescence and young adulthood (chapter four) [112].

b) A dose-response relationship between the number of chronic inflammatory conditions and impactful low back pain (chapter four) [112].

c) Girls with low insulin resistance scores and boys with low cardiovascular disease risk scores who engaged in high amounts of time in moderate to vigorous physical activity reported more weeks with spinal pain (chapter six).

d) Boys with higher clustered cardiovascular disease risk and low time in moderate to vigorous physical activity reported more weeks with spinal pain (chapter six).

e) An explanation for an underlying mechanism was not found by the presence of a relationship between the inflammatory blood marker CRP and back pain (chapter five and seven) [113].

Existing risk factor literature in a new light

The first step in working towards our aim was to systematically search and summarise the existing literature. Previous systematic reviews have mostly looked at individual risk factors, lacked adequate definitions of back pain, or had not considered the issue of temporality between exposure and outcome. Taking these parameters into consideration, our findings [109, 110] agreed with previous systematic reviews identifying female sex [24, 28, 114] and older age approaching young adulthood [24, 25, 28] as the most common risk factors for back pain in young populations. While we did account for sex within our analyses, exploring the reasons for sex differences is beyond the scope of this thesis. It has also been found that adolescent girls with low back pain have an increased burden of impact when compared to boys with low back pain [35]. It has been proposed that the reason females are at increased risk of back pain is because of differences in pain modulation due to oestrogen [115]. However, others have suggested that these sex differences are likely to be more complex, with neurophysiological, psychosocial, as well as hormonal factors playing a role [116]. Nonetheless, the findings of this thesis highlight the notion that back pain is complex and multifactorial.

Previous systematic reviews have similarly identified other likely risk factors of back pain in young people as being advanced pubertal status [117], a positive family history of back pain [118], and a prior history of back pain [114, 119]. The common thread for these risk factors or triggers being that they are predominantly biological in nature. This theme of risk factors, and in particular, a familial history of back pain, points to a possible genetic or social component. However, the literature surrounding the role of genetics in back pain is mixed [50]. Overall, there appears to be at least some genetic component [120-125]. But, it is worth posing the question, how much of an effect? A systematic review of twin studies found the heritability effects on low back pain ranged from 21% to 67% [50]. It was also found that the heritability effects were dependent on the chronicity and severity of low back pain, with an increased effect of heritability with

more chronic and disabling low back pain compared to acute and inconsequential low back pain [50]. This is similar across all spinal regions [123].

One of the important unresolved issues within this field of research is the relative contributions of the role of 'nurture', as opposed to that of 'nature'. One twin study of children found no difference in the frequency of low back pain between monozygotic and dizygotic twins which suggests little genetic effect [126]. However, 41% of the risk of low back pain was attributed to shared environment and the other 59% to unshared environmental factors [126]. Similarly, another twin study on monozygotic and dizygotic twins found that among children shared environmental factors were strong components in the aetiology of low back pain, but this was not found in older age groups [120]. After 15 years of age, the shared environmental component appeared to be unimportant, rather the effect of unshared environment components increased, but also the genetic effect became more evident, indicating the genetic interactions seem likely to increase as age increases [120]. Our findings of the association between atopic and respiratory conditions with low back pain (OR [95% CI] = 1.2 [1.0,1.5] and OR [95% CI] = 1.3 [1.1,1.5] respectively) suggest that one avenue to better quantify the nature and nurture debate may be to use monozygotic and dizygotic twins with and without these conditions.

We found that psychological features are risk factors for back pain in young people [111]. These results agree with related systematic reviews. A previous systematic review also found that children with psychological distress have an increased risk of back pain [28] and there is moderate-quality evidence that negative emotional symptoms are associated with later in life musculoskeletal pain (pooled OR [95% CI] = 1.5 [1.1,2.2]) [27]. Also, previous systematic reviews on adult populations found that psychological factors may play a role in the aetiology of spinal pain [127], but they also appear to impact the transition to chronicity [127, 128]. More recently children were found to be at an increased odds (girls: OR [95% CI] = 4.6 [2.1,10.4]; boys: OR [95% CI] = 8.7 [3.9,19.2]) of reporting spinal pain when experiencing multiple physiological factors in higher frequencies [129]. These consistent findings, across multiple sources, highlight the considerable weight of evidence for psychological factors playing a role in the aetiology of back pain, even in younger populations. Further considering psychological

factors as risk factors for back pain in young populations was outside the scope of this thesis.

Also within chapter three, other factors, namely asthma, headaches, abdominal pain, depression, anxiety, conduct problems, somatization, and 'feeling tense' were found to be associated with back pain [111]. Comparably, previous studies found that adolescents who reported medium and high levels of stress had an increased likelihood (OR [95% CI] = 2.2 [2.1,2.3] and OR [95% CI] = 4.4 [4.3,5.2] respectively) of spinal pain compared to adolescents who reported no stress [130]. Similarly, increased likelihood for spinal pain is also seen in adolescents with lower levels of general well-being (OR [95% CI] = 2.5 [2.3,2.7]) [130]. Based on our systematic review, it is not possible to say whether illness factors are comorbidities, triggers, or risk factors for back pain. However, when considered as a whole, the evidence suggests that there appears to be a relationship between these chronic conditions and back pain.

One limitation of the existing literature that we encountered was the lack of consistent and adequate definitions of back pain. The consequence being an inability to directly compare studies and reach more definitive conclusions. Most of the previous studies considered back pain at single time points, which does not accurately represent its recurrent and fluctuating nature [131, 132]. The dynamic nature of back pain is difficult to capture with dichotomous outcomes [132]. The inadequacy of prior back pain studies in this way further highlights the limitations of cross-sectional studies when attempting to understand the experiences of people with back pain. Of note is that in this thesis, to mitigate these inadequacies we used methodological approaches in line with current conceptualisation of back pain through the use of longitudinal back pain data and applying clear definitions of back pain.

Contributing to the search for back pain risk factors

In order to say a variable is a risk factor for a condition, a causal relationship must be established [95]. Even though there are differing opinions on the "Bradford Hill criteria" and its usefulness [133, 134], it is still one of the most cited concepts in health research [134]. Although first proposed in 1965, the Bradford Hill criteria are still relevant and assist researchers in making connections based on a body of research, to

either aid in identifying causal relationship or to highlight potential avenues for future research to understand possible causality [133]. These criteria provide a mechanism by which the findings of this thesis can be placed within the context of the search for back pain “causes” or risk factors.

There are nine tenets in the Bradford Hill criteria that are used to determine if a causal pathway potentially exists, namely: 1) strength of association, 2) consistency, 3) specificity, 4) temporality, 5) biological gradient, 6) plausibility, 7) coherence, 8) experiment, and 9) analogy [97]. In considering if there is a potential causal relationship between chronic illnesses and back pain, this thesis undertook analyses to explore several of the important of the Bradford Hill criteria.

1. Based on the results from the systematic review (chapter three) and from the Raine Study analysis (chapter four), the strength of the association was found to be low for individual risk factors with most of the odds ratios just above one.

2. Consistency was found. The results from chapters three and four for all included conditions were found to be in the same direction, showing positive associations between illness factors and back pain. These results are consistent with the broader literature where musculoskeletal conditions have been found to increase the risk of chronic disease [38]. They also align with studies of twins where people with chronic conditions such as asthma, diabetes, headaches, or were in poor general health, compared to people in good health, were more likely to report low back pain [50].

3. Due to the complex and multifactorial nature of back pain uncertainty remains about the specificity of association. For specificity of association to be shown ideally the outcome would only have one cause. For example, if the association was observed only in a specific population or in a specific geographic place, and the outcome variable has no other valid explanation then specificity of association could be shown. As we cannot say only one factor alone causes back pain, we cannot say there is specificity of association.

4. The longitudinal analysis conducted in chapter four revealed a temporal relationship between respiratory and atopic conditions during childhood with future impactful low back pain in adolescence and young adulthood [112].

5. Biological gradient or the dose response relationship was also examined within chapter four. This revealed that participants who reported a greater number of chronic inflammatory conditions had an increased odds of impactful low back pain in adolescence and young adulthood [112]. This result supports reports of a dose-response relationship between the number of early postnatal life pain exposures (infantile colic and otitis media) and the risk of pre-adolescent spinal pain [67].

6. In terms of the plausibility between inflammatory conditions and back pain, the proffered causal link from early life inflammation and inflammatory conditions to back pain, is inflammation-associated activation of the hypothalamic-pituitary-adrenal axis [49, 60, 61]. Dysregulation of this axis can lead to overactive responses to later psychosocial or mechanical stressors and overall hypersensitivity, resulting in pain [49]. However, it remains that an equally plausible explanation could be that inflammatory conditions and back pain are comorbid and share a underlying common origin or mechanism [51, 132], with back pain itself being a result of an inflammatory condition.

   Additionally, when we further consider the results from chapter six, it is plausible there is some form of relationship between cardiovascular disease risk factors, physical activity, and spinal pain. The possible biological mechanism being that inflammation is an important component in pathogenesis of cardiovascular disease [135] and potentially with spinal pain as well. However, within this thesis, we found no association between CRP and back pain in younger populations (chapters five and seven). The activation in the hypothalamic-pituitary-adrenal axis has been found to be associated with higher levels of cardiovascular disease risk factors [136]. Physical activity has been found to reduce inflammation [88, 137]. However,

this is not the case for all types of activity as high intensity training has been found to induce an inflammatory response [138]. Also, very low levels of physical activity could be problematic, as children who had lower levels of physical activity have been found to have increased levels of cardiovascular disease risk factors compared to children in the most active quintile [139]. This "sweet spot" is also seen in spinal pain where moderate-to-vigorous physical activity has been found to be protective for spinal pain, whereas vigorous intensity physical activity was associated with increased spinal pain [104]. Vigorous physical activity may be related to injuries. Viewed together, these findings build a case for the likely existence of a relationship between cardiovascular disease risk factors, physical activity, and spinal pain. This shows a complex interaction between biological and behaviour factors, and the frequency of spinal pain reported by young people.

7. Although, we found no association between the inflammatory blood marker CRP and back pain, other potential biomarkers exist, and to date there are no conflicting results that contradict this association based on previous studies or basic science concepts, therefore it cannot be said that there is a lack of coherence.

8. There is no known experimental evidence testing the relationship between chronic illnesses and back pain.

9. There is no known specific analogy to support or refute this association.

More evidence is needed to say if there is a causal relationship, a common origin, or another potential mechanism, but overall, we found associations between some chronic inflammatory conditions and low back pain. Further exploration of these relationships is warranted.

Searching for the underlying mechanism

As previously discussed, it remains plausible that there is a link between the identified inflammatory conditions and back pain. CRP has been shown to be a sensitive biomarker of inflammation [69] and cross-sectional associations have been demonstrated between CRP and low back pain but mainly in adult populations [89, 90].

However, we found no evidence of such a link for low back pain occurrence or trajectories of spinal pain in younger populations (chapters five and seven).

Future research could continue to track the populations further into adulthood to determine if the relationship emerges in older populations. It could also be beneficial to consider other inflammatory biomarkers such as interleukin-6 or tumour necrosis factors. This recommendation is supported by a recent systematic review that reported positive associations between CRP, tumour necrosis factors, and interleukin-6 with nonspecific low back pain in adults [90]. A narrative review article discussing mechanisms of the adverse effects of early life trauma and long-term risk for disease susceptibility in later life, found that of all proinflammatory cytokines evaluated, interleukin-6 findings were the most robust [140]. Interleukin-6 has been described as one of the most appropriate inflammatory markers to determine the level of inflammation within individuals [141] and is a relevant stress biomarker [142]. Finally, interleukin-6 directly stimulates the hypothalamic-pituitary-adrenal axis [143-145] and this may highlight the role of inflammation in inflammatory related changes to pain sensitivity.

Methodological considerations

This thesis presents a comprehensive analyses of early life illnesses as potential risk factors for back pain in adolescence and young adulthood. It comprised a two-part scoping review, a systematic review, and four longitudinal studies based on two representative populations of children from different hemispheres of the world. In addition, innovative statistical approaches were used. Given the above, we contend that we have contributed to the existing literature in the search for potential childhood risk factors for back pain.

This thesis has many methodological strengths. Within chapters four and five, impactful low back pain was measured at four timepoints from adolescence to young adulthood. This represents a population of young people with low back pain with the potential to have an increasing health burden of low back pain, to address concerns around the inadequate definition of back pain. Within chapters six and seven we used intensive measures of data collection about spinal pain collected weekly over five and a

half years. This approach reduces the possibility of recall bias. Classifications of spinal pain were confirmed through clinical examination which enabled us to exclude spinal pain with a traumatic diagnosis [101]. By undertaking trajectory modelling we were able to better demonstrate the fluctuating nature of back pain, even within younger populations, compared to methods that define outcomes at a single time point [94]. This work contributes towards the literature for risk factors by employing a contemporary understanding of the chronic and recurrent nature of back pain.

We are also cognizant of several limitations within the thesis. The cohorts the data were extracted from used differing definitions of back pain. Within chapters four and five (Raine Study analyses) the outcome variable was impactful low back pain. Within chapters six and seven (CHAMPS Study-DK analyses) the outcome variable was non-traumatic spinal pain. Consequently, despite clearly defining these outcome measures within the respective studies, they cannot be directly compared. Additionally, within both the Raine Study and the CHAMPS Study-DK cohorts the severity of 'back pain' was not measured. Nonetheless, we are confident that the measures we have taken around impactful back pain and non-traumatic spinal pain make the findings of the thesis robust. While we did make an attempt to control for confounding there may have been other factors not considered. We have also only focused on singular risk factors as opposed to a more comprehensive assessment of risk factors from multiple domains. For example, a more comprehensive assessment of risk factors could include; considering factors together such as sex, psychological distress, chronic illnesses, with the level of physical activity. In this way we could consider the interaction effect between biological, lifestyle, and psychosocial factors.

Within chapter two, only two key databases were searched (PubMed and Cochrane databases), and articles were limited to the English language. Consequently, some non-English studies may have been missed. However, as this type of research is quite stereotyped, it is doubtful that any missed articles would have changed the overall results.

Within chapter three, due to methodological and/or clinical heterogeneity, few studies could be included together in the respective meta-analyses. Therefore, the syntheses are based on a small number of studies. Furthermore, we were unable to

undertake sensitivity analyses or subgroup analyses. Three meta-analyses demonstrated substantial-to-considerable statistical heterogeneity. Only two of the included studies were rated as low risk of bias. Whereas, twelve studies were at moderate risk of bias, and five studies were at high risk of bias. Many of the included studies reported high attrition rates with poor reporting of drop-outs, and had unclear descriptions of the source population, the selection criteria and/or the outcome variable (back pain). We used the best available data at the time. However, future larger studies may change these results.

Future research and implications of future research

To better understand the aetiology of back pain, future research should carefully consider how back pain is defined. Validated questionnaires that clearly identify and define the type of back pain under study (e.g. ongoing, episodic, or first time) should be utilized. In order to identify a risk factor back pain, data should be collected on the exposure variable before the onset of back pain. Therefore, it is of value to start following a population from early life.

Within the literature, there is increasing evidence that the aetiology back pain is multifactorial, with risk factors from multiple domains, including biological, lifestyle, and psychosocial factors [20, 31-37, 146]. This thesis further highlights the fact that the aetiology of back pain is complex and multifactorial. Setting aside frank trauma, it could be that a combination of risk factors, rather than a single risk factor, leads to the onset of back pain [35]. Consequently, as demonstrated within this thesis, we must continue to be more innovative in future investigations of the aetiology of back pain. This should involve the consideration of cumulative exposures, twin studies, and/or use or longitudinal approaches such as multi-trajectory methods. Future studies should look at multiple risk factors from multiple domains together.

This concept of multiple factors contributing to the aetiology of disorders has been suggested previously through a dynamic, multifactorial, and recursive model of aetiology in sports injury [147]. This model emphasises the value of investigating intrinsic predisposing factors along with extrinsic factors, which interact together and increase the risk of injury [147]. Certain intrinsic risk factors predispose an individual to injury,

then exposure to extrinsic risk factor/s leaves the individual susceptible, and an 'inciting' event leads to injury [147]. In addition, this model further highlights that it is not a linear model, as once was proposed [148], but rather a dynamic recursive (cyclic) model in which the outcome may differ with repeated exposure to risk factor/s, and whether the exposure leads to adaption, maladaptation, injury or recovery [147].

In considering back pain, specific predictive risk factors may predispose individuals to back pain, and then in combination with other possibly causal risk factors, the individual could develop back pain. For example, girls (factor 1) with a higher level of psychological distress (factor 2) could be susceptible to back pain that is consequently caused by vigorous physical activity (factor 3). The outcome could also change due to repeated exposures. Consequently, from a clinical point of view, it might be important to also consider multidimensional interventions, even within young populations.

The complex nature of back pain suggests that prevention and treatment will require multidimensional interventions. A previous study found that a multimodal approach including physiotherapy screening, back pain education, individualised specific exercises, and strength and conditioning training was most effective at reducing the incidence of low back pain in adolescent female rowers compared to a control group who just did their usual training [149]. This multidimensional thinking was voiced in a recent editorial making recommendations for the management of musculoskeletal pain [150]. Recommendations were made to screen for and address health comorbidities and other biopsychosocial factors when managing musculoskeletal pain [150]. This thesis, along with previous research, points to the fact that susceptibility for chronic back pain could develop during childhood [132]. Therefore, based on the findings of this thesis, it makes logical sense that these recommendations for adults should also be applied to younger populations.

In clinical practice and future research there is a need to screen for and address comorbidities in younger populations. Clinicians tend to work in clinical silos and this mindset may permeate their conceptualising of the body regions as also being silos [150]. Musculoskeletal clinicians and researchers may need to consider algorithms that include conditions or factors that run across multiple domains, such as biopsychosocial factors and health co-morbidities that could be playing a role in the clinically presenting

musculoskeletal complaint. Pragmatically this will mean that musculoskeletal clinicians should enquire about past and current medical history including co-morbidities, and interventions may require interprofessional collaborations to optimize patient outcomes [132]. An example is physical activity counselling which could help in the prevention and/or management of back pain and many of the comorbid conditions.

Conclusion

This thesis has summarised the literature surrounding risk factors for back pain in young people. This has highlighted the necessity of a contemporary definition of back pain and informed investigations of data bases to explore relationships between early life illness factors and back pain. Overall, there is some evidence that early life illness factors are risk factors for back pain in young populations, but more evidence is needed to determine if this involves a causal relationship. There appears to be an association between cardiovascular disease risk factors and spinal pain, however this relationship is dependent on sex, age, and health-related physical activity behaviour. We did not find any associations between the inflammatory blood marker CRP and back pain within these young populations.

The findings of this thesis should inform future investigations that seek to further elucidate mechanisms to reduce this global financial burden attributed to back pain. The emerging picture appears to be one of complexity. The continued search for an answer may lie in identifying early life risk factors for back pain and considering multiple risk factors from multiple domains together.

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APPENDICES

Appendix One- Insight into the longitudinal relationship between chronic subclinical inflammation and obesity from adolescence to early adulthood: a dual trajectory analysis

As a preliminary study to chapter five we identified C-reactive protein trajectories from adolescence to early adulthood and determined if they were related to body mass index trajectories.

This manuscript has been submitted for publication to Inflammation Research.

Beales DJ, Beynon AM, Jacques A, Smith A, Cicuttini F, Straker L, Insight into the longitudinal relationship between chronic subclinical inflammation and obesity from adolescence to early adulthood: a dual trajectory analysis

Appendix one: Co-Authorship Statement

Submitted manuscript: Beales DJ, Beynon AM, Jacques A, Smith A, Cicuttini F, Straker L, Insight into the longitudinal relationship between chronic subclinical inflammation and obesity from adolescence to early adulthood: a dual trajectory analysis

Author	Authors' contribution			
	Design	Data analysis	Interpretation	Manuscript
Darren J. Beales	45%	N/A	40%	40%
Amber M. Beynon	5%	50%	20%	20%
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Study: Insight into the longitudinal relationship between chronic subclinical inflammation and obesity from adolescence to early adulthood: a dual trajectory analysis

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AUTHOR CONTRIBUTIONS

DB, AS and LS conceived the study. All authors contributed further to the design. AB, AJ, and AS performed the analysis. All authors contributed to preparation of the manuscript.

ABSTRACT

Objectives and Design:

This study aimed to identify C-reactive protein (CRP) trajectories from adolescence to early adulthood and determine if they were related to body mass index (BMI) trajectories.

Methods:

CRP and BMI were collected from participants of the Raine Study Gen2 at 14, 17, 20 and 22 year follow-ups (n=1312). A dual trajectory analysis was conducted to assess the association between CRP and BMI trajectories, providing conditional probabilities of membership of CRP trajectory membership given BMI trajectory membership. Best model fit was assessed by systematically fitting two to eight trajectory groups with linear and quadratic terms and comparing models according to the Bayesian Information Criterion statistic.

Results:

Three CRP trajectories were identified; “stable-low” (71.0%), “low-to-high” (13.8%) and “stable-high” (15.2%). Participants in a “high-increasing” BMI trajectory had a higher probability of being in the “stable-high” CRP trajectory (60.4% of participants). In contrast, individuals in the “medium-increasing” BMI trajectory did not have a significantly increased probability of being in the “stable-high” CRP trajectory.

Conclusions:

These findings support that chronic sub-clinical inflammation is present through adolescence into early adulthood in some individuals. Targeting chronic sub-clinical inflammation though obesity prevention strategies may be important for improving future health outcomes.

KEY WORDS

C-reactive protein; sub-clinical inflammation; body mass index; dual trajectory modelling; The Raine Study

Introduction

Globally childhood and adolescent obesity is on the rise [1], which is likely to contribute to escalating negative impact on individuals' current and future health [1, 2]. Chronic, sub-clinical pro-inflammation status is one potential biological link between obesity and poor health across a wide range of health conditions [3, 4]. One potential mechanism suggested is that hypoxia related death of adipocytes in obese individual precipitates an immune response resulting in the upregulation of adipocytokine production and facilitated expression of pro-inflammatory genes [5, 6]. The negative health effects of chronic, sub-clinical inflammation in children and adolescents who are obese include higher prevalence of the metabolic syndrome [7-9] and diabetes [10]. Additionally, there is some indication this may continue to future negative health outcomes in adulthood [7, 11]. A need for a deeper understanding of the longitudinal relationship between a chronic, sub-clinical pro-inflammatory status and obesity early in the lifespan has been recognised [8] as this has the potential of informing novel approaches to prevention [12, 13].

C-reactive protein (CRP) is a sensitive marker of inflammation in the human body. It is used as a screening tool for many diseases, and for monitoring responses to treatment of infection and inflammation [14]. C-reactive protein levels are unaffected by food, and the only known condition that impairs the production of CRP is liver failure. Additionally, there are limited drugs that reduce the level of CRP unless they also affect the underlying pathology [14]. C-reactive protein is a useful inflammatory marker in children and adolescents [15]. The use of trajectory modelling of CRP levels has offered a longitudinal approach to better understand chronic, sub-clinical inflammation in adults. Prior research has identified four CRP trajectories over a 10 year period in people aged 47-87 years at baseline (n=2437); "stable-low" (baseline of 1.33mg/L and <3mg/L throughout, 71.3%), "medium-to-high" (baseline 2.7mg/L increasing to 5.3mg/L, 14.3%), "high-to-medium" (baseline 6.6mg/L decreasing to 2.4mg/L, 9.9%) and "stable-high" (5.7mg/L to 7.5mg/L, 4.6%) [16]. People in the "medium-to-high" or the "stable-high" trajectories had an increased risk of 'adverse aging outcomes', such as poor cardiometabolic health, reduced respiratory and physical function, increased depressive symptoms, and arthritis, confirming the importance of chronic, sub-clinical inflammation

trajectories in older adults. This trajectory modelling approach could be utilised in younger populations.

There have been associations found between CRP and obesity in all ages [17, 18]. Obesity trajectories in early life [19, 20] could potentially relate to CRP trajectories. Dual trajectory modelling can provide insights into complex longitudinal relationships, extracting potential developmental linkages between measures [21]. For example, dual trajectory modelling can assist in determining if a chronic, sub-clinical pro-inflammation status and obesity emerge contemporaneously or at different times. While longitudinal assessments of CRP levels in childhood and early adulthood have been reported [11, 22], to date trajectory modelling of CRP early in the life-course has not been published.

Thus, the aims of this study were; (Aim 1) to identify CRP trajectories from adolescence to early adulthood and (Aim 2) to determine any association between CRP trajectories and body mass index (BMI) trajectories during this period. The novel application of dual trajectory modelling to investigate these relationships from adolescence into early adulthood would enhance understanding of the development of chronic, sub-clinical inflammation during the life span, during a time where other research is either cross-sectional or if longitudinal has only limited data at multiple time points [11, 22]. We applied group-based trajectory modelling in line with the broader clinical concept of identifying groups of at-risk individuals.

Materials and Methods

Study design

A longitudinal study using data from the Raine Study Gen2-14, 17, 20 and 22 year follow-ups was performed. All aspects of the study were approved by the Human Research Ethics Committees of King Edward Memorial Hospital, Princess Margaret Hospital, University of Western Australia and/or Curtin University. Participants and/or their parent/guardian provided written informed consent for data collection. This specific project was approved by The Raine Study Scientific Review Committee (Project Number RES0417). Reporting was aligned to the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) checklist [23] (Online Resource 1).

The Raine Study

In the Raine Study, mothers were recruited between May 1989 and Nov 1991 from the public antenatal clinic at King Edward Memorial Hospital for Women, and from nearby private practice clinics. A total of 2868 live births were recruited into the Raine Study cohort [24]. These children (Gen2) have been followed from birth, with ongoing regular reassessment. Information has been collected on environmental, developmental and health information covering an extensive range of health areas (www.rainestudy.org.au). At inception the cohort was predominantly Caucasian (93%). The characteristics of the Raine Study participants were quite similar to the general Western Australian population [24].

Data collection

At ages 14, 17, 20 and 22 years the Raine Study Gen2 participants completed questionnaires and physical assessments including measures of height, weight and fasting blood samples. Table 1 presents the total number of participants, their sex and their age at each of the four follow-up time points. It also provides the number of participants with available data for each variable and the mean hs-CRP at each time point. Overall there were 1312 participants who had at least two measurements of CRP and also two measurements of BMI, to enable the dual trajectory modelling.

C-reactive protein

High-sensitivity CRP (hs-CRP) was measured from the Raine Study blood samples [25] using an immunoturbidimetric method on an Architect c16000 Analyser. Blood samples were frozen at -80 degrees Celsius and batch processed soon after collection. High-sensitivity CRP refers to the lower detection limit of the assay procedures being used. This has been found to correlate well with representative immunopheloetric assays [26]. The immunoassays for hs-CRP have been shown to be robust, well standardized, reproducible and readily available [14]. In healthy young adults, the median concentrations of serum hs-CRP has been reported as 0.8 mg/L [14]. Data points with hs-CRP > 10 mg/L were excluded, because this was likely to indicate acute inflammation and current infection rather than a chronic inflammation state [16].

Body mass index

Measurements were taken in a standardised manner by experienced research staff [27]. Height was measured using a Holtain Stadiometer (nearest 0.1 cm), body weight using a Wedderburn Chair Scale (nearest 100g). BMI was calculated by taking weight/height2 for all timepoint.

Other variables

Additional variables were obtained to provide demographic description of the cohort (see Table 2) including birth weight, ethnicity, waist girth (measured with a non-elastic tape in cm), socioeconomic status, diet patterns and total metabolic equivalent. Ethnicity and socioeconomic status were reported at birth. Socioeconomic status was based on economic resources as well as education and occupation, reported as quartiles [28]. Data on diet type were collected at 14 and 17 years of age. Diet types included heathy patterns and western patterns dichotomised into more (high) and less (low) patterns for the two diet types [29]. Data on total metabolic equivalent were collected at 17 and 22 years of age and reported as minutes per week.

Statistical Analysis

Data were analysed using Stata S/E version 15 (StataCorp, TX). Data were screened for invalid observations and corrected accordingly. Demographic data on age and sex was reported descriptively. Descriptive statistics were calculated for the whole cohort and the CRP trajectory groups. Correlation of BMI and waist girth were assessed at each age.

For the first phase of the analysis, group-based trajectory modelling [30] was performed to identify hs-CRP trajectories separately to BMI trajectories. Estimating hs-CRP trajectories addressed Aim 1 (identify CRP trajectories from adolescence to early adulthood). However, estimating BMI trajectories was also a necessary preparatory step for the dual trajectory analysis to address Aim 2 (associations between CRP trajectories and BMI trajectories). Absolute continuous values for CRP and BMI were used to construct the trajectories. Both CRP and BMI trajectory models were modelled using censored normal distribution. The trajectories were generated using group-based trajectory modelling with the Stata TRAJ plug-in module [30]. Group-based trajectory

modelling is a form of finite mixture modelling which uses maximum likelihood to estimate and create trajectories of average values within homogenous subgroups of individuals from the study population, based on distinct groups of trajectory parameters and excluding within-person variability [21, 31]. Group-based trajectory modelling utilises a person-centered approach with the aim of identifying groups of individuals with certain attributes, as opposed to variable-centered analyses which aims to describe associations between variables [32]. Therefore, this analysis was consistent with our stated aims.

Participants were included if they had at least two valid measures of hs-CRP and BMI over the four follow-ups. Missing data was at random. Group-based trajectory modelling accounts for missing data at random with robust maximum likelihood estimation methods resulting in asymptotically unbiased parameter estimates [21]. Model selection decisions were made using Bayesian Information Criterion (BIC) statistic. Models were identified by systematically deciding on the number of trajectory groups and then determining the shape of the polynomial trajectories (zero-order, linear or quadratic). Model selection began with the simplest solution (two groups) and increased the number of groups and complexity of polynomial shapes until the BIC plateaued, and every group comprising at least 30 participants [21, 31]. The decision as to the number of groups was also guided by the goal of analysis [21, 31] with confirmation based on posterior probability diagnostics [19]. The 5 a priori diagnostic criteria for best fit included: 1) mean posterior probability ≥70% for each group, 2) odds of correct classification ≥ 5 for each group, 3) close approximation between the estimated group proportions and the assigned membership proportions, 4) reasonably tight confidence intervals around estimated values, and 5) meaningful distinction between the groups [21, 31]. Model validity was confirmed by conducting parametric bootstrap sampling on model parameters to obtain the confidence intervals for group sizes. Models were estimated using sex as an active covariate given indications female children/adolescents seem to have higher levels of CRP than males [33]. Sensitivity analyses were completed for both univariate CRP and BMI trajectory models only including participants with all four timepoints.

For Aim 2, the framework of the group-based trajectory analyses was expanded using dual trajectory modelling [30]. Dual trajectory modelling estimates the trajectory groups for two outcomes, the probability of membership in the identified trajectory groups, and conditional probabilities linking membership across the trajectory groups of the two outcomes [30]. This provided conditional probabilities of membership of hs-CRP trajectory membership, given BMI trajectory membership.

Results

There was one participant who had three timepoints excluded due to hs-CRP >10, and 17 participants who had two timepoints excluded due to hs-CRP >10. Otherwise, only single timepoints were excluded from participants due to hs-CRP >10. Overall there were 1312 participants who had at least two measurements of CRP and also two measurements of BMI, to enable the dual trajectory modelling. Table 2 presents descriptive statistics for the whole cohort included in this analysis (N=1312) and for the CRP trajectory groups. Very high correlation between BMI and waist girth were noted (between 0.867-0.900).

C-reactive protein trajectories (Aim 1)

The three-group trajectory model for CRP demonstrated the optimal fit and met all a priori diagnostic criteria (Online Resource 2). The three-trajectory group model demonstrated good model fit with the average posterior probabilities of membership for each class above 75%. Trajectory group 1 with the majority of individuals (71.0%) were “stable-low”, trajectory group 2 (13.8%) were “low-to-high” and trajectory group 3 were “stable-high” (15.2%) (Figure 1).

Body mass index trajectories

The four-group trajectory model for BMI demonstrated the optimal fit and met all a priori diagnostic criteria (Online Resource 2). The four-trajectory group model demonstrated good model fit with the average posterior probabilities of membership for each class ≥ 89%. Trajectory group 1 were “low” (53.0%), group 2 (32.8%) were “medium”, trajectory group 3 were “medium-increasing” (11.0%) and trajectory group 4 were “high-increasing” (3.1%) (Figure 2).

Dual trajectories of C-reactive protein and body mass index (Aim 2)

The probability of being in the 3 different hs-CRP trajectories differed significantly depending upon the assigned BMI trajectory (chi-sq=136.41, p<0.001), displaying a longitudinal relationship between these measures (Figure 3, Table 3). For example, of those in the "high-increasing" BMI trajectory, 68.9% were estimated to belong to the 'stable-high' hs-CRP trajectory, with only 9.1% and 22.1% estimated to be it the "stable-low" or "low-to-high" hs-CRP trajectories respectively. In contrast, of those in the "low" BMI trajectory, 81.7% were estimated to belong to the "stable-low" hs-CRP trajectory with a minority estimated to be in the "stable-high" and "low to high" hs-CRP trajectories. In the "medium-increasing" BMI trajectory, there was not a higher probability of being in the "stable-high" hs-CRP trajectory versus the other hs-CRP trajectories.

Sensitivity analyses were completed for both the univariate trajectory models of BMI and CRP only including participants with all four timepoints, without a discernible change to results (see Online Resource 3 for sensitivity analysis results).

Discussion

Three trajectories of hs-CRP ("stable-low", "low-to-high", "stable-high") were identified from adolescence into early adulthood, with the "stable-high" suggesting the potential existence of chronic, sub-clinical inflammation earlier in life than previously reported. This is a novel finding for this period of the life span, having only previously been identified in older adults [16]. Additionally, the trajectory with higher hs-CRP levels over time was associated with the trajectory with a "high-increasing" BMI over time, but not those in the "low" trajectory. This aligns to recent suggestion of a group of high-risk individuals identified in a cross-sectional design [34]. The identification of the association between hs-CRP and BMI trajectories demonstrates a longitudinal relationship, which will be important to consider in the context of developing protocols for risk-profiling, disease prevention and monitoring of treatment effectiveness [8, 12, 13].

Trajectories of C-reactive protein (Aim 1)

It has been suggested that CRP levels tend to be stable over time [14], though with an overall increase with increasing age [35]. However, the identification of trajectories of hs-CRP suggests that levels of sub-clinical inflammation are more complex than previously thought. One prior study utilized hs-CRP trajectory modelling in older adults, and identified three trajectories in common with groups in our study [16]. A "stable-low" trajectory represented 71% of participants in both samples, and the ascending trajectories about 14% in both samples. A difference was an absence of a descending trajectory in our data, which might be related to the different age profiles of the two studies. Continued tracking of CRP levels/trajectories in our now young adult sample over time will be valuable, with ongoing data collections occurring.

Relationship between C-reactive protein trajectories and BMI trajectories (Aim 2)

Using dual trajectory analysis we found a link between higher levels of hs-CRP and higher BMI. No previous study using this approach to assess the relationship between chronic, sub-clinical inflammation and obesity has been reported. More broadly in the literature, longitudinal investigations of the relationship between chronic inflammation show links between sub-clinical inflammation and obesity at all ages [17, 18], supporting mechanistic links between obesity and a pro-inflammatory state [3, 4]. Our results provide new insight into this relationship.

The association of higher levels of CRP with higher BMI is consistent with this broader literature. Using data from late adolescence (age 18, n=3877) and early adulthood (age 22, n=3483), positive associations between CRP levels and a broad array of adiposity measures were documented in a birth cohort in Brazil [22]. A positive association has also been shown from childhood (age 6-8 years) to adolescence (age 12-16 years) in Spanish schoolchildren (n=272) [36]. Our trajectory analysis supports these findings, while expanding them using data from four time points rather than two, providing data at multiple times not only for adiposity but also for inflammation, and specifically investigating sub-clinical inflammation. Taken together these studies indicate that an overall pro-inflammatory state is more likely to be present in individuals with higher BMI as they transition from childhood, through adolescence and into early adulthood.

Strengths, limitations and methodological considerations

Use of community-dwelling participant data from the Raine Study enables the extrapolation of the results to the general population. Having participants of the same age with data collected from them at four separate timepoints allows for a fidelity in the trajectory patterns during this period of the lifespan that has not been previously possible. The Raine Study cohort is predominantly Caucasian [24], and ethnicity can influence CRP levels (highest to lowest levels: African Americans, Hispanics, South Asians, whites, and East Asians) [37]. However, there appeared to be minimal difference between the trajectory groups in terms of ethnicity (Table 2). Medication use at the time of blood collection, such as anti-inflammatories, was not known. Blood samples were frozen for variable, short time frames before processing, but short term storage in this manner is unlikely to significantly affect the assay outcomes [38, 39] (in comparison to storage for many years which may have an effect [40]). Although data points with hs-CRP >10 mg/L were excluded, as this is likely to indicate acute inflammation and current infection rather than a chronic inflammation state, aligning with previous research methodology [16], there was still a possibility elevated CRP ≤10mg/L could still be secondary to acute illnesses.

Trajectory modelling is an increasingly popular method of analysing data over time. Debate continues around the use of different types of models [31, 41]. In interpretation of the results it is important to consider that; (1) individuals do not actually belong to a trajectory group, rather groups are used as a convenient approximating device to represent a more complex underlying reality, (2) the number of groups is not immutable, and (3) the trajectory is a summary device that describes the behaviour of individuals following approximately the same course (just the same way as an average will not exactly match each data component contributing to it; no individual trajectory will exactly match the group trajectory). The potential influence of other time-varying covariates on the form of the BMI and CRP trajectories and the association between them, such as physical activity, diet or allergies, was not considered in this study. These may be either confounders or on the mechanism pathway for the relationships. Further detailed analyses will be needed in future studies.

We opted to use BMI as the measure for adiposity in presenting the results of this study, given the high correlation between BMI and waist girth at all timepoints (between 0.867-0.900) and its use in other research. Given the complexity in involved in different measures of adiposity [42], there may be benefit in further research investigating the relationship between chronic, sub-clinical inflammation and other measures of adiposity.

Clinical relevance and future directions

The findings of this study support the presence of a chronic, sub-clinical, pro-inflammation state in individuals who are overweight/obese that persists from adolescence into early adulthood. Recognition of this as a mechanism in the negative effects of obesity at this stage of life appears warranted. Elevated sub-clinical levels of CRP inducing the presence of a pro-inflammatory state have been linked to health disorders affecting multiple body systems [9, 14] including cardiovascular disease, diabetes, mental health and musculoskeletal pain/arthritis. Trajectory based modelling of hs-CRP in adults [16] supports this in adults, and future research should assess possible links between the early-life trajectories identified here and specific health conditions as well as risk factors for future poor health. Further the emergence of this relationship may well start even earlier than adolescence [36], which would benefit from additional research using trajectory-based modelling. This is an important area of investigation as globally childhood obesity is increasing, including in developing countries [43]. This is projected to have a major impact on the global burden of non-communicable diseases [44].

It has been suggested that CRP levels during childhood and adolescence could be utilised in risk-profiling, monitoring disease states and to assess the effectiveness of treatment purposes [12, 13]. There is some suggestion it could increase the fidelity of risk profiling as part of a broad screening approach rather than just weight/adiposity screening [3, 13, 37]. Monitoring inflammatory status along with weight and body fat may be beneficial in providing additional insight into the potential complexity in interpreting clinical change [8]. Interestingly, it has been suggested monitoring CRP may be a useful motivational tool for patients in need of making lifestyle changes [12]. Overall though, the clinical utility of monitoring CRP from childhood to adolescence to early adulthood requires

further linking of longitudinal data, such as that in our study, with specific clinical outcomes.

Rather than considering prevention and management of health disorders and risk factors in silos, addressing obesity and chronic, sub-clinical pro-inflammation together as potential modifiable factors is warranted given the likely associated substantial disease burden [2, 45-49].

Conclusion

Overall, we found an associated between hs-CRP and BMI from adolescence to early adulthood. “Stable high” CRP trajectory membership was most likely in participants estimated to be in the “high-increasing” BMI trajectory group, and less likely in participants estimated to be in the “low” BMI trajectory group. Defining chronic, sub-clinical inflammatory trajectories from adolescence into early adulthood is an important step in understanding the significance of obesity in early life on health status at the time and into the future. The association of hs-CRP trajectories with BMI trajectories early in the life course indicate a longitudinal relationship between these measures, which is consistent with a biological link between sub-clinical inflammation and obesity. The information provided here should assist efforts to translate this knowledge into better clinical practice to prevent and manage inflammation and obesity related issues early in life.

Acknowledgments

The authors would like to thank Bobby Jones for his assistance in the data analysis through providing the necessary syntax. We would like to acknowledge the Raine Study participants and their families for their ongoing participation in the study and the Raine Study team for study co-ordination and data collection.

The core management of the Raine Study is funded by The University of Western Australia, Curtin University, Telethon Kids Institute, Women and Infants Research Foundation, Edith Cowan University, Murdoch University, The University of Notre Dame Australia and the Raine Medical Research Foundation. The Raine Study Gen2-14, 17, 20 and 22 year follow-ups were funded by the Australian National Health and Medical Research Council project grants (211912, 003209, 403981, 323200, 353514, 1021105, 1027449, 1044840 and 1021858), Safe Work Australia, and the WA Department of Health (G06302).

In relation to the biological essay data used in this study, we acknowledge the in-kind support provided by the following institutions for biosample storage and curation; The University of Western Australia, School of Women's and Infants' Health, King Edward Memorial Hospital; The University of Western Australia, Medical School, Royal Perth Hospital; Telethon Kids Institute.

AB was supported by a scholarship from Murdoch University, Western Australia and a scholarship provided by Chiropractic Australia Research Foundation.

Disclosures

Leon Straker and Anne Smith have been the Scientific Director of the Raine Study a various times, a role that supports high quality science through collection of new data from the cohort participants and analysis and reporting of existing data.

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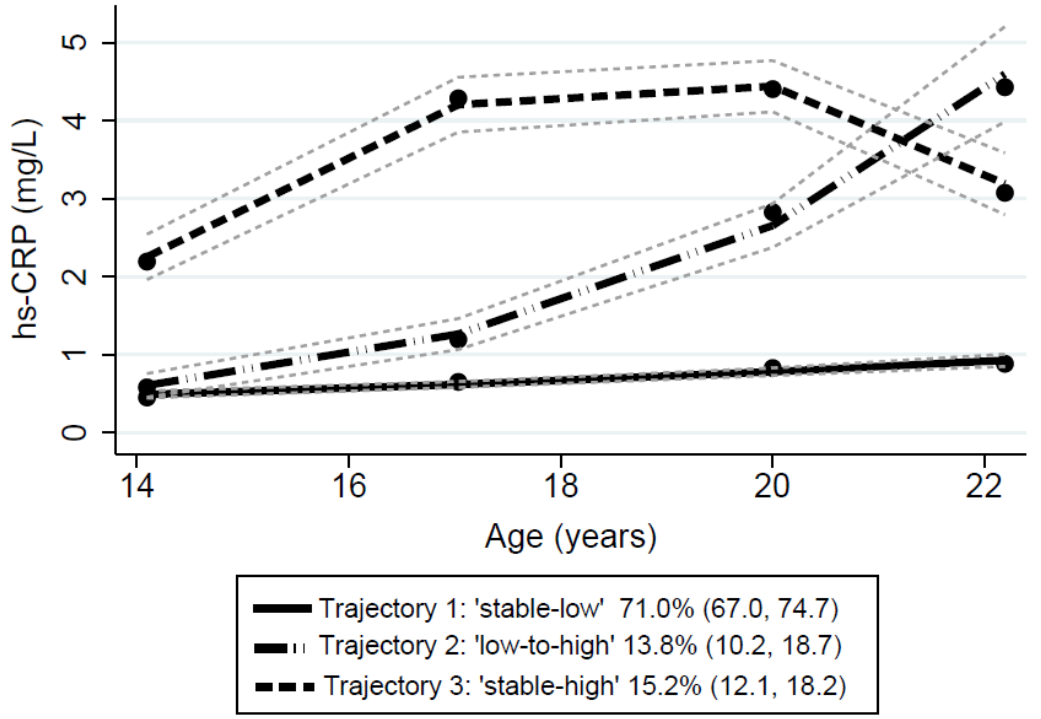

Figure 1: Trajectories of High Sensitivity C-Reactive Protein (hs-CRP) from 14 to 22 years with 95% confidence intervals.

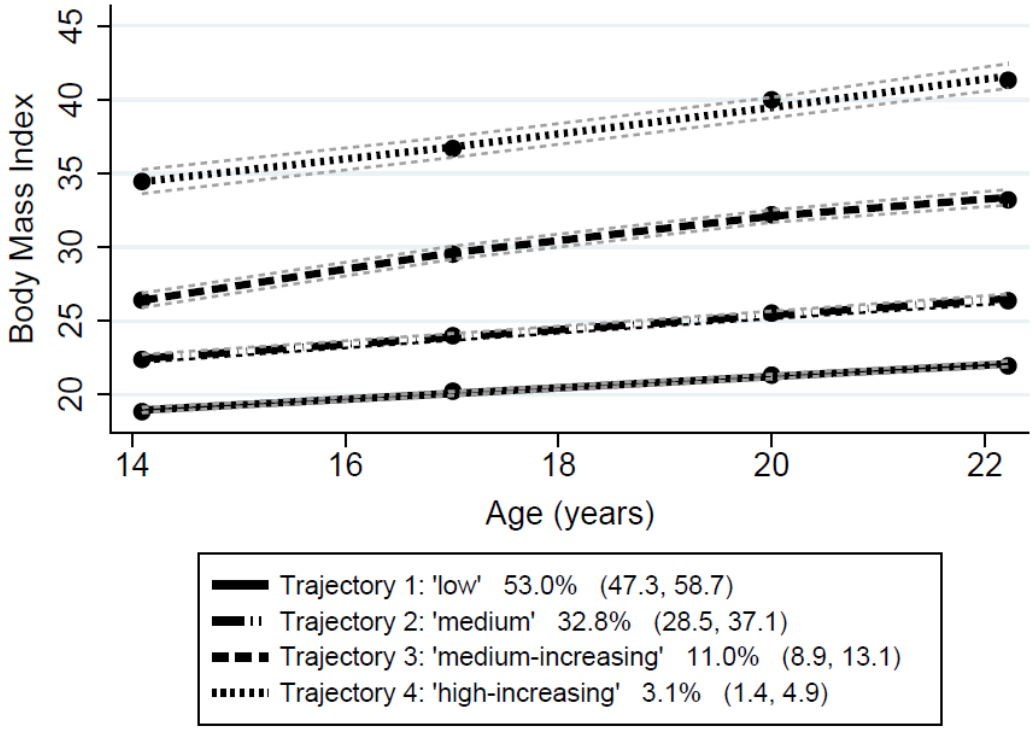

Figure 2: Trajectories of Body Mass Index from 14 to 22 years with 95% confidence intervals.

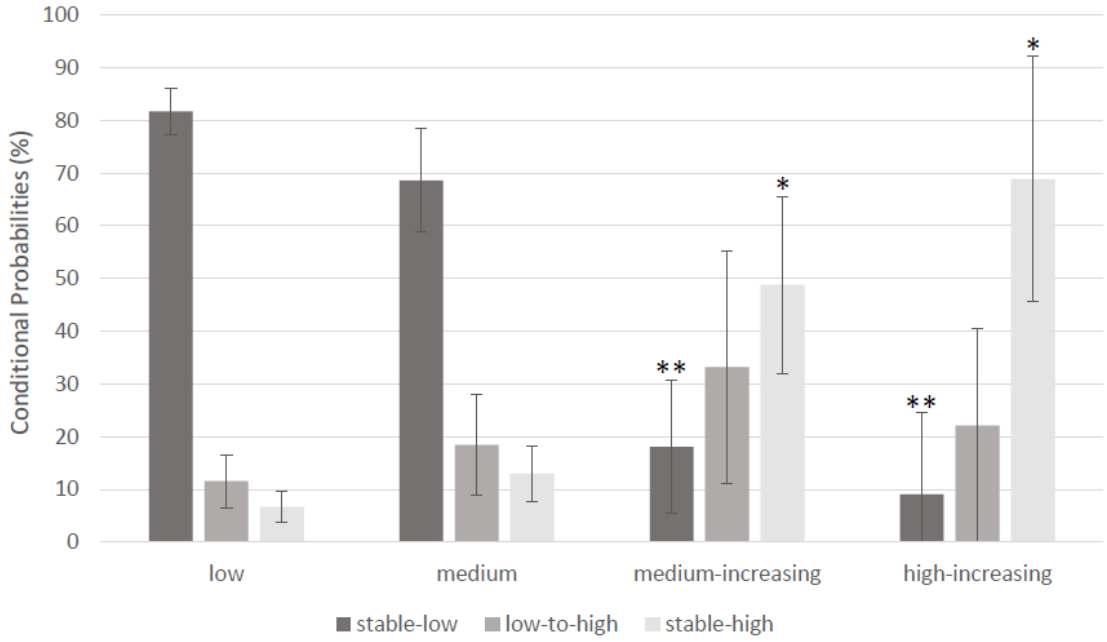

Figure 3: Conditional probability of C-Reactive Protein Trajectory Membership given Body Mass Index Trajectory with 95% confidence intervals. (Between Body Mass Index groups statistically significant difference: * 'stable-high' C-Reactive Protein: 'high-increasing' and 'medium-increasing' to other Body Mass Index groups; ** 'stable-low' C-Reactive Protein: 'high-increasing' and 'medium-increasing' to other Body Mass Index groups)

Table 1: Age, number and sex of participants at each follow-up, plus the number of participants with available data for each variable.

Raine Study Follow-up Ages (mean (SD))	**Total Participants** (n (% female))	**Had hs-CRP data** (n)	**Had hs-CRP ≤10mg/L** (n)	**Mean hs-CRP** (mg/L)	**BMI data** (n)	**Waist girth data** (n)
14.1 (0.2)	1865 (49)	1370	1355	0.76	1606	1582
17.1 (0.3)	1693 (50)	1268	1239	1.33	1251	1205
20.0 (0.5)	1577 (50)	1173	1118	1.61	1325	1335
22.2 (0.8)	1235 (52)	980	938	1.65	1068	1067

SD = standard deviation, hs-CRP =high sensitivity C-reactive protein, BMI = body mass index

Table 2: Characteristics of the cohort included in this study and for each of the C-reactive protein trajectory groups.

	Cohort included in study	**C-reactive protein trajectory group**		
	(n=1312)	**stable-low (n= 987)**	**low-to-high (n=137)**	**stable-high (n= 188)**
Birth				
Birth Weight (g) (mean(SD))	3301.0 (620.9)	3296.5 (637.4)	3209.0 (626.2)	3391.9 (511.4)
Ethnicity (n (%))				
Caucasian	1142 (89.0)	859 (89.2)	118 (88.1)	165 (88.7)
Aboriginal	31 (2.4)	23 (2.4)	4 (3.0)	4 (2.2)
Polynesian	10 (0.8)	9 (0.9)	0 (0.0)	1 (0.5)
Vietnamese	3 (0.2)	3 (0.3)	0 (0.0)	0 (0.0)
Chinese	49 (3.8)	29 (3.0)	9 (6.7)	11 (5.9)
Indian	30 (2.3)	25 (2.6)	3 (2.2)	2 (1.1)
Other	18 (1.4)	15 (1.6)	0 (0.0)	3 (1.6)
Socioeconomic status (n (%))				
Economic Resources				
1st quartile	210 (23.8)	169 (25.4)	19 (20.9)	22 (17.7)
2nd quartile	226 (25.6)	165 (24.8)	25 (27.5)	36 (29.0)
3rd quartile	228 (25.9)	162 (24.3)	32 (35.2)	34 (27.4)
4th quartile	217 (24.6)	170 (25.5)	15 (16.5)	32 (25.8)

Education and occupation				
1st quartile	218 (24.7)	171 (25.7)	23 (25.3)	24 (19.4)
2nd quartile	215 (24.4)	157 (23.6)	28 (30.8)	30 (24.2)
3rd quartile	232 (26.3)	172 (25.8)	25 (27.5)	35 (28.2)
4th quartile	216 (24.5)	166 (24.9)	15 (16.5)	35 (28.2)
14 year follow-up				
Height (cm) (mean (SD))	164.5 (7.9)	164.5 (7.9)	164.3 (8.0)	164.2 (8.1)
Weight (kg) (mean (SD))	57.9 (13.1)	56.2 (11.1)	58.7 (13.6)	66.4 (18.2)
Waist Girth (cm) (mean(SD))	75.5 (10.6)	74.0 (9.0)	76.0 (11.2)	82.8 (14.3)
Diet Type (n (%))				
Healthy patterns				
Less (Low)	401 (55.2)	314 (56.3)	41 (57.8)	46 (47.4)
More (High)	325 (44.8)	244 (43.7)	30 (42.2)	51 (52.6)
Western patterns				
Less (Low)	380 (52.3)	280 (50.2)	44 (62.0)	56 (57.7)
More (High)	346 (47.7)	278 (49.8)	27 (38.0)	41 (42.3)
17 year follow-up				
Height (cm) (mean (SD))	172.4 (9.2)	173.0 (9.3)	170.1 (9.3)	170.8 (8.4)
Weight (kg) (mean (SD))	68.3 (14.5)	66.4 (12.4)	68.8 (15.3)	78.0 (19.6)
Waist Girth (cm) (mean(SD))	79.2 (11.0)	77.6 (9.2)	79.9 (11.5)	87.4 (15.4)
Diet Type (n (%))				
Healthy patterns				
Less (Low)	239 (57.0)	174 (56.7)	28 (59.6)	37 (57.9)

More (High)	180 (43.0)	133 (43.3)	19 (40.4)	28 (43.1)
Western patterns				
Less (Low)	232 (55.4)	171 (55.7)	28 (59.6)	33 (50.8)
More (High)	187 (44.6)	136 (44.3)	19 (40.4)	32 (49.2)
Total Metabolic Equivalent (mins/week (mean(SD))	5137.6 (6155.3)	5118.2 (6260.0)	5641.7 (6369.9)	4852.7 (5492.3)
20 year follow-up				
Height (cm) (mean (SD))	172.8 (9.5)	173.6 (9.6)	169.9 (9.0)	170.8 (8.5)
Weight (kg) (mean (SD))	73.1 (16.6)	71.0 (14.2)	73.5 (17.2)	84.0 (22.9)
Waist Girth (cm) (mean(SD))	80.0 (12.4)	78.2 (10.3)	80.6 (13.8)	89.2 (17.0)
22 year follow-up				
Height (cm) (mean (SD))	172.9 (9.5)	173.8 (9.7)	169.9 (8.5)	170.6 (8.3)
Weight (kg) (mean (SD))	75.4 (17.3)	73.0 (14.7)	78.3 (21.6)	85.5 (21.8)
Waist Girth (cm) (mean(SD))	83.3 (13.4)	80.9 (10.7)	86.6 (17.0)	92.9 (17.2)
Total Metabolic Equivalent (mins/week) (mean(SD))	3921.1 (3721.5)	3943.1 (3742.5)	3506.4 (2895.3)	4104.9 (4087.2)

Table 3: Model precision using bootstrap sampling: Conditional probabilities of CRP given BMI group

Body mass index	**C-reactive protein**	**Estimated Conditional probabilities (%)**	**95% CI**
Low	stable low	81.7	(77.2, 86.2)
	low-to-high	11.6	(6.5, 16.6)
	stable high	6.7	(3.7, 9.7)
Medium	stable low	68.6	(58.8, 78.5)
	low-to-high	18.4	(8.8, 28.1)
	stable high	12.9	(7.6, 18.3)
Medium-increasing	stable low	18.0	(5.4, 30.7)
	low-to-high	33.1	(11.1, 55.2)
	stable high	48.8	(31.9, 65.6)
High-increasing	stable low	9.1	(-6.4, 24.4)
	low-to-high	22.1	(-6.3, 40.4)
	stable high	68.9	(45.5, 92.2)

CI= confidence interval

Online Resource 1: Final List of Items of the Guidelines for Reporting on Latent Trajectory Studies (GRoLTS) Checklist: Guidelines for Reporting on Latent Trajectory Studies

	Checklist Item	Reported?	Notes/ Page(P)
1.	Is the metric of time used in the statistical model reported?	Yes	Data collection: P9. Table 1. Figures 1 and 2
2.	Is information presented about the mean and variance of time within a wave?	Yes	Table 1
3a.	Is the missing data mechanism reported?	Yes	Data Collection P9, Statistical analysis: starting P10, Table 1
3b.	Is a description provided of what variables are related to attrition/missing data?	Yes	Results: P13
3c.	Is a description provided of how missing data in the analyses were dealt with?	Yes	Statistical analysis: starting P10
4.	Is information about the distribution of the observed variables included?	Yes	Table 1 and 2
5.	Is the software mentioned?	Yes	Statistical analysis: starting P10
6a.	Are alternative specifications of within-class heterogeneity considered (e.g., LGCA vs. LGMM) and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration?	Yes	Statistical analysis: starting P10
6b.	Are alternative specifications of the between-class differences in variance−covariance matrix structure considered and clearly documented? If not, was sufficient justification provided as to eliminate certain specifications from consideration?	N/A	N/A for LCGA
7.	Are alternative shape/functional forms of the trajectories described?	Yes	Statistical analysis: starting P10
8.	If covariates have been used, can analyses still be replicated?	Yes	Statistical analysis: starting P10

9.	Is information reported about the number of random start values and final iterations included?	No	Not included. Not an option in utilised software. Understand that a local solution with low trajectories using LCGA is unlikely.
10.	Are the model comparison (and selection) tools described from a statistical perspective?	Yes	Statistical analysis: starting P10
11.	Are the total number of fitted models reported, including a one-class solution?	No	Online Resource 2. From 2-6 groups.
12.	Are the number of cases per class reported for each model (absolute sample size, or proportion)?	Yes	Online Resource 2
13.	If classification of cases in a trajectory is the goal, is entropy reported?	Yes	Entropy is not an output statistic; a number of other posterior probability fit measures are provided: Online Resource 2
14a.	Is a plot included with the estimated mean trajectories of the final solution?	Yes	Figures 1, 2 and 3
14b.	Are plots included with the estimated mean trajectories for each model?	No	Not included but can be provided from the authors at reasonable request
14c.	Is a plot included of the combination of estimated means of the final model and the observed individual trajectories split out for each latent class?	Yes	Online Resource 2
15.	Are characteristics of the final class solution numerically described (i.e., means, *SD/SE, n*, CI, etc.)?	Yes	Figures 1, 2 and 3, Table 2 Online Resource 2
16.	Are the syntax files available (either in the appendix, supplementary materials, or from the authors)?	Yes	Available from the authors at reasonable request and with approval given by the Raine Study committee.

Note. LGCA = latent class growth analysis; LGMM = latent growth mixture modeling.

Online Resource 2

TableS2.1: Model selection based on Bayesian Information Criterion (BIC)

C-REACTIVE PROTEIN			
Number of groups	**BIC[a]: Total number of observations**	**BIC[a]: Total number of participants**	**Smallest group size[b] n (%)**
2	-6099.58	-6095.56	286 (21.8%)
3	**-6037.45**	**-6032.29**	**137 (10.4%)**
4	-5998.10	-5991.22	29 (2.2%)
5	-5965.86	-5957.26	28 (2.1%)
6	-6019.76	-6009.44	1 (0.8%)
BODY MASS INDEX			
Number of groups	**BIC[a]: Total number of observations**	**BIC[a]: Total number of participants**	**Smallest group size[b] n (%)**
2	-11678.45	-11674.84	194 (15.2%)
3	-11243.86	-11238.44	112 (8.5%)
4	**-10944.62**	**-10937.39**	**42 (3.2%)**
5	-10807.04	-10798.01	16 (1.2%)
6	-10733.43	-10722.59	16 (1.2%)

[a]BIC: Bayesian Information Criterion (large BIC indicates better fit)
[b]Minimum group size of 30 participants

TableS2.2: Model fit diagnostic criteria for trajectories

C-REACTIVE PROTEIN				
Trajectory group	**Average posterior probability[a]: %**	**Odds of correct classification[b]**	**Estimated group proportions: % (95% CI)**	**Assigned membership: %**
1. “stable-low”	92.1	22.2	71.0 (67.0, 74.7)	75.2
2. “low-to-high”	75.3	60.8	13.8 (10.2, 18.7)	10.4
3. “stable-high”	88.0	104.8	15.2 (12.1, 18.2)	14.3
BODY MASS INDEX				
Trajectory group	**Average posterior probability[a]: %**	**Odds of correct classification[b]**	**Estimated group proportions: % (95% CI)**	**Assigned membership: %**
1. “low”	93.8	46.6	53.0 (47.3, 58.7)	53.7
2. “medium”	89.6	49.8	32.8 (28.5, 37.1)	32.3
3. “medium-increasing”	94.2	313.2	11.0 (8.9, 13.1)	10.8
4. “high-increasing”	95.3	1355.1	3.1 (1.4, 4.9)	3.2

[a]Lowest acceptable posterior probability 70%
[b]Lowest acceptable odds of correct classification 5.0
CI = confidence interval

Online Resource 3

Sensitivity Analyses for trajectories only including participants with all four timepoints

C-REACTIVE PROTEIN				
Trajectory group	**Average posterior probability[a]: %**	**Odds of correct classification[b]**	**Estimated group proportions: % (95% CI)**	**Assigned membership: %**
1. “stable-low”	95.4	135.9	73.4 (68.1, 78.4)	74.8
2. “low-to-high”	74.0	151.4	11.2 (6.1, 16.4	10.5
3. “stable-high”	85.3	220.0	15.4 (10.5, 20.3)	14.65
BODY MASS INDEX				
Trajectory group	**Average posterior probability[a]: %**	**Odds of correct classification[b]**	**Estimated group proportions: % (95% CI)**	**Assigned membership: %**
1. “low”	90.9	137.5	47.1 (34.8, 59.4)	47.7
2. “medium”	92.2	128.5	39.3 (29.5, 49.0)	38.4
3. “medium-increasing”	94.8	864.9	11.5 (7.3, 15.7)	11.7
4. “high-increasing”	99.9	240021.5	2.2 (0.6, 3.8)	2.2

[a]Lowest acceptable posterior probability 70%

[b]Lowest acceptable odds of correct classification 5.0

CI = confidence interval

Appendix Two- Ethics Approvals

Murdoch UNIVERSITY

Division of Research & Development
Research Ethics and Integrity

Chancellery Building
South Street
MURDOCH WA 6150
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Monday, 12 November 2018

Prof Bruce Walker
School of Health Professions
Murdoch University

Dear Bruce,

Project No. 2018/226
Project Title Early life illness factors as potential risk factors for back pain in adolescence and young adulthood. A secondary analysis of the Raine study

Your application in support of the above project was reviewed by the Murdoch University Human Research Ethics Committee and was:

APPROVED

Approval is granted on the understanding that research will be conducted according the standards of the ***National Statement on Ethical Conduct in Human Research*** **(2007), the *Australian Code for the Responsible Conduct of Research*** **(2007)** and **Murdoch University policies** at all times. You must also abide by the **Human Research Ethics Committee's standard conditions of approval (see attached).** All reporting forms are available on the Research Ethics and Integrity web-site.

I wish you every success for your research.

Please quote your ethics project number in all correspondence.

Kind Regards,

Dr. Yvonne Haigh
Chair
HREC Committee

Dr. Erich von Dietze
Manager
Research Ethics and Integrity

cc: Prof Jeffrey Hebert, Prof Charlotte Leboeuf-Yde, Ms Angela Jacques, Dr Darren Beales, Miss Amber Beynon

CRICOS Provider Code: 00125J
ABN 61 616 369 313

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Tuesday, 05 February 2019

Prof Bruce Walker
Chiropractic
Murdoch University

Dear Bruce,

Project No. 2019/012
Project Title Are children with cardiovascular risk factors at risk of future spinal pain? A secondary analysis of the CHAMPS Study-DK

Your application in support of the above project was reviewed by the Murdoch University Human Research Ethics Committee and was:

APPROVED

Approval is granted on the understanding that research will be conducted according the standards of the ***National Statement on Ethical Conduct in Human Research*** **(2007), the *Australian Code for the Responsible Conduct of Research*** **(2007)** and **Murdoch University policies** at all times. You must also abide by the **Human Research Ethics Committee's standard conditions of approval (see attached).** All reporting forms are available on the Research Ethics and Integrity web-site.

I wish you every success for your research.

Please quote your ethics project number in all correspondence.

Kind Regards,

Dr. Yvonne Haigh
Chair
HREC Committee

Dr. Erich von Dietze
Manager
Research Ethics and Integrity

cc: Prof Jeffrey Hebert, Prof Charlotte Leboeuf-Yde, Prof Niels Wedderkopp, Prof Jan Hartvigsen, Miss Amber Beynon

CRICOS Provider Code: 00125J
ABN 61 616 369 313

Appendix Three- Online Supporting Appendix for studies

Chapter Two: Scoping Review of potential risk factors and triggers for back pain in children and young adults. Part I

Additional file 1: Search strategy used for the literature search

Databases: PubMed, Cochrane Database. Database search from inception to September 2018, limited to English articles.

PubMed Search:

1. "young adult"
2. "adolescen*"
3. "teenager"
4. "juvenile"
5. "child*"
6. 1 OR 2 OR 3 OR 4 OR 5
7. "low back pain"
8. "back pain"
9. "mid back pain"
10. 7 OR 8 OR 9
11. "risk"
12. "risk factor"
13. "causality"
14. "epidemiological factor"
15. "indicators"
16. "prognostic"
17. "cause"
18. "comorbidities",
19. "prevalence"
20. "incidence".
21. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22. 6 AND 10 AND 21

Cochrane Search:

1. young adult OR adolescen* OR teenager OR juvenile OR child*
2. low back pain OR back pain OR mid back pain
3. risk OR risk factor OR causality OR epidemiological factor OR indicators OR prognostic OR cause OR comorbidities OR prevalence OR incidence
4. S1 AND S2 AND S3

Additional file 2: INCEPTION COHORT STUDIES reporting factors that are longitudinally associated with back pain.

Back pain, sample characteristics and associations between back pain and risk factors of back pain. Inception Cohorts

Reference	Back Pain					Characteristics of study sample			Significant positive (+) or negative (-) associations with back pain					
Reference (year of pub), country, pop size	MBP	LBP	Mix	?	Clear definition of BP (x/4) (Additional file 4)	Age range at baseline	Sex	No. of follow ups Follow-up period	Female	Male	Age	Height	Socioeconomic factors	Significant estimates (95% CI)
[23] Aartun, (2016), Denmark, 144	X	X	X		**4/4**	11-13	Both	1 2 years	(NT)	(NT)	(NT)	(NT)	(NT)	
[24] Barke, (2014), Germany, 2040				X	2/4	9-14	Both	1 1 year	+	(NT)	+	(NT)	(NT)	Female: OR 1.8 (1.1-3.1) Age: OR 1.2 (1.1-1.3)
[25] Burton, (1996), England, 216		X			3/4	11	Both	4 1 year		+	+	(NT)	(NT)	Males: prevalence percentage boys 60%, girls 40% (Female: OR 0.4 (0.3-0.8) (calculated)) Older age 11 yrs: 12% 15 yrs: 22% (Older age: OR 2.1 (1.2-3.7) (calculated))
[26] Mustard, (2005), Canada, 1043				X	3/4	4-16	Both	2 4 years, 14 years	0	0	0	(NT)	+	Lower parental education: OR 1.7 (1.1-2.8)
[27] Newcomer, (1996), USA 96		X			**4/4**	10-19	Both	1 4 years	0	0	+	(NT)	(NT)	Older age OR 3.4 (graph interpretation)
[28] Poussa, (2005), Finland, 430		X			3/4	10-11	Both	5 1 year (4x), 8 years (1)	0	0	(NT)	+	(NT)	Increased growth spurt of one SD (4.3cm) from 11-14 years: OR 1.3 (1.1-1.7)
[29] Triki, (2015), Tunisia, 5958		X			3/4	18-24	Both	7 1 year	+		(NT)	(NT)	(NT)	Female: Female 17%, male 13% (Female: OR 1.5 (1.3-1.7) (posthoc)) (the sex differences disappeared when looking at individual sports)

Pub: Publication, MBP: Mid-back pain, LBP: low back pain: BP: back pain, (NT): Not tested, + significant positive association, - significant negative association, 0: tested but non-significant estimate, CI: confidence interval, OR: odds ratio, SD: standard deviation, RR: relative risk, No.: number

Back pain, sample characteristics and associations between back pain and risk factors of back pain continued. Inception cohorts

Reference	Back Pain					Characteristics of study sample			Significant positive (+) or negative (-) associations with back pain						
Reference (year of pub), country, pop size	MBP	LBP	Mix	?	Clear definition of BP (x/4) (Additional file 4)	Age range at baseline	Sex	Follow-up period	BMI	Muscle strength	Psychosocial	Physical activity/ work	Smoking	Illness	Significant estimates (95% CI)
[23] Aartun, (2016), Denmark, 144	X	X	X		**4/4**	11-13	Both	1 2 years	(NT)	(NT)	(NT)	+	(NT)	(NT)	High level physical activity: RR 1.4 (1.1-1.9)
[24] Barke, (2014), Germany, 2040				X	2/4	9-14	Both	1 1 year	(NT)	(NT)	+	(NT)	(NT)	(NT)	Dysfunctional coping: OR 1.4 (1.1-2.0) (boys) Anxiety sensitivity: OR 1.5 (1.1-2.0) (boys) Somatosensory amplification: OR 1.8 (1.0-3.1) (girls) Pain catastrophizing: OR 0.5 (0.3-0.9) (girls)
[25] Burton, (1996), England, 216		X			3/4	11	Both	4 1 year	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	
[26] Mustard, (2005), Canada, 1928				X	3/4	4-16	Both	2 4 years, 14 years	0	(NT)	+	0	+	0	Heavy smoking: OR 1.9 (1.1-3.1) Psychological distress: OR 1.9 (1.1-3.0) (low), OR 1.9 (1.1-3.2) (mod/high) Emotional or behavioural disorders: OR 1.9 (1.0-3.4)
[27] Newcomer, (1996), USA 96		X			**4/4**	10-19	Both	1 4 years	(NT)	+	(NT)	+	(NT)	(NT)	Increased level of physical activity: OR 2.3 (graph interpretation) Stronger back flexors: OR 2.8 (graph interpretation)
[28] Poussa, (2005), Finland, 430		X			3/4	10-11	Both	5 1 year (4x), 8 years (1)	0	(NT)	(NT)	(NT)	(NT)	(NT)	
[29] Triki, (2015), Tunisia, 5958		X			3/4	18-24	Both	7 1 year	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	

Pub: Publication, MBP: Mid-back pain, LBP: low back pain: BP: back pain, (NT): Not tested, + significant positive association, - significant negative association, 0: tested but non-significant estimate, CI: confidence interval, OR: odds ratio, SD: standard deviation, RR: relative risk, No.: number

Additional file 3: COHORT STUDIES reporting factors that are longitudinally associated with back pain episodes.

Back pain, sample characteristics and associations between back pain and temporal precursor variables. Cohort Studies

Reference	Back pain					Characteristics of study sample			Significant positive (+) or negative (-) associations with back pain			
Ref, (year of pub), country, pop size	MBP	LBP	Mix	?	Clear definition of BP (x/4) (Additional file 5)	Age range at baseline	Sex	No. of follow ups Follow-up period	Female	Male	Age	Significant estimates (95% CI)
[30] van Gessel, (2011), Germany, 2025				X	2/4	9-14	Both	3 1 year	+		+	Females: OR 2.1 (1.9-2.5) Age: 9yr boy: OR 1 (index) 2.5 (1.5, 4.1) (13, boy), 3.2 (1.9, 5.3) (14, boy), 3.1 (1.8, 8.2) (15, boy), 3.0 (1.8, 5.2) (16, boy), 3.5 (1.9, 6.3) (17 boy), 2.4 (1.4, 4.1) (10 girl), 3.4 (2.1, 5.7) (11, girl), 4.6 (2.8, 7.5) (12, girl), 5.6 (3.4, 9.2) (13, girl), 5.4 (3.3, 8.9) (14, girl), 6.7 (4.1, 11.2) (15, girl), 6.7 (4.0, 11.3) (16, girl), 7.5 (4.2, 13.2) (17, girl).
Pub: Publication, MBP: Mid-back pain, LBP: low back pain: BP: back pain, + significant positive association, OR: odds ratio, No.: number												

Additional file 4: Clarity of definitions of Back pain: Inception Cohort studies

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[23] Aartun, (2016)	MB/LB*						X	-1st ever - - -	No	- - -	Diagram used, pilot study of the questionnaire	**4/4**
[24] Barke, (2014)	?			X (6 mth)	X		X	-1st ever - - -	No	- - -	NR	2/4
[25] Burton, (1996)	LB	X			X		X	-1st ever - - -	No	-Seek care - -Disability	NR	3/4
[26] Mustard, (2005)	?				X		X	-1st ever - - -	No	- - -Disability	Used a pre-validated questionnaire	3/4
[27] Newcomer, (1996)	LB				X		X	-1st ever - - -	No	-Seek care -Downtime -	Used a pre-validated questionnaire	**4/4**
[28] Poussa, (2005)	LB				X		X	-1st ever - - -	No	- - -	Diagram used	3/4
[29] Triki, (2015)	LB					X		-1st ever - - -	No	-Seek care - -	NR	3/4

BP: back pain, LB: low back, MB: mid back, NR: not reported, mth: months, MB/LB*: collected data from regions separately, however reported together as spinal pain

Additional file 5: Clarity of definitions of Back pain: Cohort studies

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[30] van Gessel, (2011)	?			X (6 mth)				- -Episodic - -	Yes	- - -	NR	2/4
BP: back pain, LB: low back, MB: mid back, NR: not reported, mth: months												

Chapter Two: Scoping Review of potential risk factors and triggers for back pain in children and young adults. Part II

Additional file 1: Search strategy used for the literature search

Databases: PubMed, Cochrane Database. Database search from inception to September 2018, limited to English articles.

PubMed Search:

1. "young adult"
2. "adolescen*"
3. "teenager"
4. "juvenile"
5. "child*"
6. 1 OR 2 OR 3 OR 4 OR 5
7. "low back pain"
8. "back pain"
9. "mid back pain"
10. 7 OR 8 OR 9
11. "risk"
12. "risk factor"
13. "causality"
14. "epidemiological factor"
15. "indicators"
16. "prognostic"
17. "cause"
18. "comorbidities",
19. "prevalence"
20. "incidence".
21. 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20
22. 6 AND 10 AND 21

Cochrane Search:

1. young adult OR adolescen* OR teenager OR juvenile OR child*
2. low back pain OR back pain OR mid back pain
3. risk OR risk factor OR causality OR epidemiological factor OR indicators OR prognostic OR cause OR comorbidities OR prevalence OR incidence
4. S1 AND S2 AND S3

Additional file 2: PROSPECTIVE STUDIES reporting factors that are longitudinally associated with back pain.

Back pain, sample characteristics and associations between back pain and temporal precursor variables. Prospective Studies

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain								
Ref, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 4)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**History of back pain**	**Significant estimates (95% CI)**
[8] Auvinen, (2010), Finland, 1773		X			2/4	15-16	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	Female: OR 1.7 (1.4-2.0) (age 16), OR 1.9 (1.6-2.3) (age 18) (calculated)
[9] Balague´, (2010), Switzerland, 95		X			2/4	13-14 (14.0)	Male	(NT)	(NT)	(NT)	(NT)	+	(NT)	(NT)	(NT)	Family history: OR 3.6 (1.3-10.2)
[12] Feldman, (2001), Canada, 502		X			2/4	13-14 (13.8)	Both	0	0	0	(NT)	(NT)	(NT)	+	(NT)	High growth spurt: OR 3.1 (1.5-6.0)
[15] Franz, (2016), Denmark, 1240	X	X	X		**4/4**	6-12	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	Incidence rate (per 1000): Girls: 0.3 (0.2-0.3), Boys: 0.1 (0.1-0.2) (OR 1.9 (1.4-2.4) (calculated))
[16] Gill, (2014), Australia, 1291	X	X	X		2/4	(14)	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	Females: (X2 = 33.1, p < .001) (OR 2.4 (1.9-3.1) (calculated LBP)) (OR 2.2 (1.6-2.9) (calculated MBP))
[17] Hebert, (2019), Denmark, 1021			X		**4/4**	(9.4)	Both	(NT)	(NT)	(NT)	+	(NT)	(NT)	+	(NT)	Spinal pain (wks), later pubertal status: Tanner stage 2: IRR 1.5 (1.2-2.0) Tanner stage 3: IRR 2.1 (1.5-3.1) Tanner stage 4/5: IRR 3.3 (2.1-5.0) Spinal pain (episodes), pubertal status: Tanner stage 3: 1.4 (1.0-1.8) Tanner stage 4/5: 2.1 (1.4-3.0) Spinal pain (wks): linear growth: IRR 1.2 (1.2-1.2) Spinal pain (episodes), linear growth: IRR 1.1 (1.1-1.2)

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain								
Ref, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 4)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**History of back pain**	**Significant estimates (95% CI)**
[20] Hestbaek, (2006), Denmark, 9600		X			**4/4**	12-22 (17.3)	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	BP in adolescence for BP in adulthood: OR 4.3 (3.5-5.4)
[21] Janssens, (2011), USA/ Denmark 4226				X	1/4	11-15 (11.6) /(13.7)	Both	(NT)	(NT)	(NT)	+	(NT)	(NT)	0	(NT)	Later pubertal status: OR 1.6 (1.3-2.0) (USA) OR 1.3 (1.1-1.6) (Dutch)
[22] Jones, (2009), England, 178		X			2/4	11-14	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	(NT)	Shorter than median height (158cm): RR 2.1 (1.2-3.8)
[23] Jones, (2003), England, 1046		X			2/4	11-14	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	0	(NT)	
[25] Kroner-Herwig, (2017), Germany, 1522				X	1/4	7-14 (13.4)	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	Female: OR 1.6 (1.2-2.0)
[26] Mattila, (2008), Finland, 57408		X			2/4	14-18 (16.6)	Both		+	(NT)	-	(NT)	(NT)	(NT)	(NT)	Males: HR 3.2 (2.7-3.7) Later pubertal status: HR 0.6 (0.5-0.8) (males)
[27] Mikkonen, (2016), Finland, 1625		X			2/4	15-16	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	Female: Girls 44%, boys 31% (OR 1.7 (1.4-2.1) (calculated))
[28] Mikkonen, (2013), Finland, 1660		X			2/4	15-16	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	Female: prevalence percentage girls 61%, boys 49% (OR 1.6 (1.4-2.0) (calculated)

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain								
Ref, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 4)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**History of back pain**	**Significant estimates (95% CI)**
[30] Nissinen, (1994), Finland, 859		X			2/4	10-11 (10.8)	Both	0	0	(NT)	(NT)	(NT)	(NT)	+	(NT)	Height: OR 1.2 (1.0-1.5)
[31] Sano, (2015), Japan, 4597		X			2/4	9-10	Both	0	0	+	(NT)	(NT)	(NT)	(NT)	(NT)	Age: 9 yr 10%, 14 yr 25% (OR 2.9 (2.6-3.3) (calculated)
[32] Sjolie, (2004), Norway, 85		X			2/4	14-16 (14.7)	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	History of BP: OR 2.7 (1.1-7.1) (ever) OR 9.1 (3.0-27.2) (>7days)
[33] Smith, (2017), Australia, 1088		X			3/4	(14)	Both	+		(NT)	(NT)	(NT)	+	(NT)	+	Females: OR: 2.0 (1.2- 3.0) (no previous BP) OR 7.7 (4.7, 12.6) (previous BP) Higher socioeconomic index: OR 0.8 (0.7-1.0) History of BP: OR 7.7 (4.7-12.6)(girl)
[34] Szita, (2018), Hungary, 952	X	X	X		3/4	7-16 (11.0)	Both	0	0	+	(NT)	+	(NT)	(NT)	(NT)	Older age: OR 1.5 (1.1-2.3) Family history: OR 2.1 (1.4-3.1)
[35] Szpalski, (2002), Belgium, 287		X			1/4	9-12	Both	(NT)	(NT)	(NT)	(NT)	+	(NT)	(NT)	(NT)	Family history: OR 2.0 (1.1-4.0)

Pub: Publication, (NT): Not tested, (NR): Included in study but not reported, + significant positive association, - significant negative association, 0: tested but non-significant estimate, OR: odds ratio, PR: prevalence ratio, RR: relative risk

Back pain, sample characteristics and associations between back pain and some bidirectional variables. Prospective Studies

Reference	Back Pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain									
Reference (year of pub), country, pop size	MBP	LBP	Mix	?	Clear definition of BP (x/4) (Additional file 4)	Age range (mean)	Sex	BMI	Muscle strength	Flexibility Tightness	Posture	Physical activity/ work	Screen time	Poor Sleep	Carry Bags	Smoke	Illness/ Psychos ocial	Significant estimates (95% CI)
[7] Aartun, (2016), Denmark, 625	X	X	X		3/4	11-13	Both	(NT)	(NT)	(NT)	(NT)	0	(NT)	(NT)	(NT)	(NT)	(NT)	
[8] Auvinen, (2010), Finland, 1773		X			2/4	15-16	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	(NT)	(NT)	(NT)	Insufficient Sleep: OR 2.9 (1.7-5.2) (girls) OR 2.4 (1.3-4.5) (boys)
[9] Balague´, (2010), Switzerland, 95		X			2/4	13-14 (14.0)	Male	+	(NT)	(NT)	(NT)	+	(NT)	(NT)	(NT)	(NT)	(NT)	Higher BMI: OR 1.3 (1.0-1.5) Playing sport: OR 9.5 (1.9-48.2)
[10] Deere, (2012), England, 3378	X	X			2/4	17 (17.8)	Both	0	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	
[11] Feldman, (2002), Canada, 502		X			2/4	13-14 (13.8)	Both	(NT)	(NT)	(NT)	(NT)	+	(NT)	(NT)	(NT)	(NT)	(NT) 0	White collar work: OR 4.9 (1.7-14.2)
[12] Feldman, (2001), Canada, 502		X			2/4	13-14 (13.8)	Both	(NT)	(NT)	+	(NT)	0	(NT)	(NT)	(NT)	+	(NT)	Tight hamstrings: OR 1.1 (1.0-1.1) Smoking: OR 2.2 (1.4-3.5)
[13] Feldman, (1999), Canada, 502		X			2/4	13-14 (13.8)	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	(NT)	Smoking: OR 2.4 (1.3-6.0)
[14] Franz, (2017), Denmark, 1205	X	X	X		**4/4**	6-12	Both	(NT)	(NT)	(NT)	(NT)	+	(NT)	(NT)	(NT)	(NT)	(NT)	Vigorous intensity physical activity: OR 1.2 (1.0-1.4) (diagnostic spinal pain) OR 1.3 (1.0-1.5) (traumatic)

Reference	Back Pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain										
Reference (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 4)**	**Age range (mean)**	**Sex**	**BMI**	**Muscle strength**	**Flexibility Tightness**	**Posture**	**Physical activity/ work**	**Screen time**	**Poor Sleep**	**Carry Bags**	**Smoke**	**Illness/ Psychos ocial**	**Significant estimates (95% CI)**
[15] Franz, (2016), Denmark, 1240	X	X	X		**4/4**	6-12	Both	(NT)	(NT)	(NT)	(NT)	0	(NT)	(NT)	(NT)	(NT)	(NT)	
[16] Gill, (2014), Australia, 1291	X	X	X		2/4	(14)	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	(NT) 0	Smoking: OR 3.1 (1.1-9.2) (MB) OR: 1.8 (1.2-2.8) (BP)
[18] Hestbaek, (2006), Denmark, 9600		X			**4/4**	12-22 (17.3)	Both	0	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	(NT)	Smoking: OR 1.7 (1.4-2.1)
[19] Hestbaek, (2006), Denmark, 9600		X			**4/4**	12-22 (17.3)	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	Asthma: OR 1.4 (1.1-1.7) (female) Headache: OR 1.6 (1.1-2.1) (female) OR 2.4 (1.2-4.7) (male)
[22] Jones, (2009), England, 178		X			2/4	11-14	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	0 +	High level of peer problems: RR 2.3 (1.3-4.2)
[23] Jones, (2003), England, 1046		X			2/4	11-14	Both	0	(NT)	(NT)	(NT)	+	0	(NT)	0	(NT)	+ +	High level of sports activity (>18hr/wk): RR 1.6 (1.1-2.3) Part-time work: RR 1.5 (1.1-2.1) Abdominal pain: RR 1.8 (1.1-3.0) High level of psychological factors: RR 1.6 (1.1-2.3)
[24] Kanchanomai, (2015), Thailand, 524		X			2/4	18-25 (19.4)	Both	(NT)	(NT)	+	+	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	Tight quad muscle: OR 1.7 (1.1-2.8) No LB support: OR 1.7 (1.2-2.6) OR 2.9 (1.1-3.5) (persistent LBP)

Reference	Back Pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain										
Reference (year of pub), country, pop size	MBP	LBP	Mix	?	Clear definition of BP (x/4) (Additional file 4)	Age range (mean)	Sex	BMI	Muscle strength	Flexibility Tightness	Posture	Physical activity/ work	Screen time	Poor Sleep	Carry Bags	Smoke	Illness/ Psychos ocial	Significant estimates (95% CI)
[25] Kroner-Herwig, (2017), Germany, 1522				X	1/4	7-14 (13.4)	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+ 0	Headache: OR 2.4 (1.8-3.1)
[26] Mattila, (2008), Finland, 57408		X			2/4	14-18 (16.6)	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	(NT)	Daily smoking: HR 1.6 (1.4-1.9)
[27] Mikkonen, (2016), Finland, 1625		X			2/4	15-16	Both	0	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT) +	Externalising behaviour: RR: 1.5 (1.3-1.7) (boys) RR: 1.4 (1.3-1.5) (girls) RR: 3.6 (1.5-8.5) (girls 18)
[28] Mikkonen, (2013), Finland, 1660		X			2/4	15-16	Both	+	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	BMI: RR 1.1 (1.0-1.2) (girls) RR: 1.1 (1.0-1.3) (boys)
[29] Mikkonen, (2008), Finland, 1987		X			2/4	15-16	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	(NT)	Smoking: OR 2.5 (1.4-4.5) (females)
[30] Nissinen, (1994), Finland, 859		X			2/4	10-11 (10.8)	Both	0	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	
[31] Sano, (2015), Japan, 4597		X			2/4	9-10	Both	+	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	High BMI range: OR 2.9 (1.7-5.1) (9 yr) OR 2.2 (1.4-3.5) (10 yr) OR 1.6 (1.2-2.1) (13 yr)
[32] Sjolie, (2004), Norway, 85		X			2/4	14-16 (14.7)	Both	(NT)	(NT)	(NT)	+	+	0	(NT)	(NT)	(NT)	(NT)	Provoked by sitting: OR 3.8 (1.3-11.3) Provoked by manual work: OR 9.2 (2.9-28.8)

Reference	Back Pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain										
Reference (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 4)**	**Age range (mean)**	**Sex**	**BMI**	**Muscle strength**	**Flexibility Tightness**	**Posture**	**Physical activity/ work**	**Screen time**	**Poor Sleep**	**Carry Bags**	**Smoke**	**Illness/ Psychos ocial**	**Significant estimates (95% CI)**
[33] Smith, (2017), Australia, 1088		X			3/4	(14)	Both	(NT)	+	(NT)	+	+	(NT)	(NT)	(NT)	(NT)	(NT) +	Poor back muscle endurance: OR 1.9 (1.2-3.0) Non-neutral standing posture: OR 2.2 (1.3-3.6) Increased physical activity: OR 1.9 (1.2-2.8) High levels of aggressive behaviour: OR 1.4 (1.2-1.6) High levels of somatic complaints: OR 1.3 (1.1-1.5)
[34] Szita, (2018), Hungary, 952	X	X	X		3/4	7-16 (11.0)	Both	(NT)	(NT)	(NT)	+	0	+	+	0	(NT)	(NT)	Increased TV time: OR 2 (1.4-2.9) Uncomfortable school desk: OR 6.0 (3.7-9.7) Frequent sleeping problems: 2.2 (1.7-3.8)
[35] Szpalski, (2002), Belgium, 287		X			1/4	9-12	Both	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	+	+	(NT)	(NT)	Quality of sleep: OR 1.2 (1.1-1.4) Heavy school satchel: OR 2.2 (1.0-4.8)
[36] Tobias, (2013), UK, 2901	X	X			3/4	13 (13.8)	Both	(NT)	(NT)	0	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	(NT)	

Pub: Publication, (NT): Not tested, (NR): Included in study but not reported, + significant positive association, - significant negative association, 0: tested but non-significant estimate, OR: odds ratio, PR: prevalence ratio, RR: relative risk

Additional file 3: CROSS-SECTIONAL STUDIES reporting factors that are associated with back pain.

Back pain, sample characteristics and associations between back pain and temporal precursor variables. Cross-sectional studies

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain							
Reference, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4)** (Additional file 5)	**Age range** (mean)	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**Significant estimates (95% CI)**
[37] Aggarwal, (2013) India, 160		X			3/4	17-25	Both	(NT)	(NT)	(NT)	(NT)	+	(NT)	(NT)	Family history: OR 2.6 (1.4-5.9)
[38] Andersen, (2006), Denmark, 9413			X		2/4	(17)	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	Female: OR 1.7 (1.5-2.0)
[39] Balague´, (1994), Switzerland, 1755		X			1/4	8-16	Both	(NT)	(NT)	(NT)	(NT)	+	(NT)	(NT)	Family history: OR 2.1
[40], Bejia, (2005), Tunisia, 622		X			**4/4**	11-19	Both	0	0	0	(NT)	+	(NT)	0	Family history: OR 3.8 (2.9-5.9)
[41], Cakmak, (2004), Turkey, 1527		X			3/4	17-26	Both	+		+	(NT)	(NT)	(NT)	(NT)	Female OR: 1.3 (1.4-3.3) Age: 17 yr: OR 1 (index) 21 yr OR: 2.2 (1.2-4.2) 23 yr OR: 3.2 (1.7-6.2) 24 yr OR: 2.8 (1.5-5.3) 25+ yr OR: 3.1 (1.4-6.7)
[42] Dianat, (2017), Iran, 1611		X			3/4	11-14	Both	+		0	(NT)	+	(NT)	(NT)	Female: OR 1.5 (1.2–1.8) Family History: OR 1.8 (1.4–2.4)
[43] Dianat, (2014), Iran, 586		X			3/4	12-14	Both	+		0	(NT)	(NT)	(NT)	(NT)	Female: OR 2.2 (1.4-3.3)

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain							
Reference, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 5)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**Significant estimates (95% CI)**
[44] Diepenmaat, (2006), Netherlands, 3485		X			2/4	12-16	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	Female: OR 1.5 (1.1-1.9)
[45] Erne, (2011), Switzerland, 189		X			2/4	10-13	Both	0	0	+	(NT)	0	(NT)	(NT)	Younger age: OR 0.2 (0.1-0.6)
[46] Fernandes, (2015), Brazil, 1461		X			3/4	10-14	Both	+		+	(NT)	(NT)	(NT)	(NT)	Female: OR 1.5 (1.1-1.9) Age: 10-11 yr: OR 1 (index) 12-14 yr: OR 1.1 (1.1-1.3)
[47] Ganesan, (2017), India, 1355		X			1/4	20-29	Both	0	0	0	(NT)	+	(NT)	(NT)	Family history: Standard error 0.2 (1.4, 2.7) (OR 1.5 (1.1-1.9) calculated)
[48] Ghandour, (2004), USA, 8350				X	2/4	11-19	Both	NR	NR	NR	(NT)	(NT)	0	(NT)	
[49] Gilkey, (2010), USA, 963				X	1/4	18-22	Both	-		0	(NT)	(NT)	0	0	Female: OR 0.6 (0.4-0.8)
[50] Graup, (2014), Brazil, 1455		X			2/4	10-17	Both	+		+	(NT)	(NT)	0	(NT)	Female: OR 2.4 (1.7-3.3) Older age: OR 1.1 (1.1-1.2)
[51] Gunzburg, (1999), Belgium, 392		X			2/4	8-11	Both	0	0	(NT)	(NT)	(NT)	(NT)	(NT)	

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain							
Reference, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 5)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**Significant estimates (95% CI)**
[52] Haag, (2016), New Zealand, 1110			X		3/4	15-19	Both	+		+	(NT)	(NT)	(NT)	(NT)	Female: OR 1.5 (1.0-2.1) Age 15 yr: OR 1 (index) 16/17 yr OR 1.7 (1.2-2.3) 18/19 yr: OR 1..8 (1.2-2.8)
[53] Harreby, (1999), Denmark, 1389		X			**4/4**	13-16	Both	+		+	(NT)	(NT)	(NT)	(NT)	Female: OR 2.1 (1.6-2.9) Older age 14 to 15 yr: 6.4%
[54] Hestbaek, (2008), Denmark, 4771		X			3/4	12-18	Both	(NT)	(NT)	(NT)	(NT)	(NT)	+	(NT)	Higher social class: OR 0.9 (0.8-0.9)
[55] Hulsegge, (2011), Netherlands, 2638				X	1/4	10-12	Both	(NT)	(NT)	(NT)	0	(NT)	0	0	
[56] Jones, (2004), England, 1326		X			2/4	12-15	Both	(NT)	(NT)	(NT)	(NT)	0	(NT)	(NT)	
[57] Kaspiris, (2010), Greece, 153		X			3/4	7-14	Both	+		+	(NT)	+	(NT)	+	Female: OR 1.4 (1.0-2.1) (calculated) Older age: OR 1.2 Family history: OR 1.7
[58] Kovacs, (2003), Spain, 7048		X			3/4	13-15	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	Female: OR 1.1 (1.1-1.2)
[59] Kristensen, (2001), Norway, 190		X			3/4	(15)	Both	(NT)	(NT)	(NT)	(NT)	0	(NT)	(NT)	

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain							
Reference, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 5)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**Significant estimates (95% CI)**
[60] Kristjansdottir, (2002), Iceland, 2173				X	0/4	11-16	Both	0	0	+	(NT)	(NT)	0	(NT)	Older age: r 0.2
[61] Leboeuf-Yde, (2002), Denmark, 806			X		3/4	8-16	Both	(NT)	(NT)	(NT)	(NT)	(NT)	+ 0	(NT)	Children parental low level of education: OR 1.8 (1.1-2.0) (no significant association in adolescence)
[62] LeResche, (2005), USA, 3101				X	1/4	11-17	Both	0	0	(NT)	+	(NT)	(NT)	(NT)	Later pubertal status: OR 2.0 (girls) OR 1.9 (boys)
[63] Masiero, (2008), Italy, 7542		X			3/4	13-16	Both	+		(NT)	(NT)	+	(NT)	(NT)	Female: OR 1.9 (1.7-2.2) Family history: OR 1.8 (1.5-2.0)
[64] Mattila, (2008), Finland, 7040		X			2/4	18-29	Males	(NT)	(NT)	+	(NT)	(NT)	(NT)	(NT)	Age 17/18 yr: OR: 1 (index) 21+ yr: OR 1.6 (1.2-2.1)
[65] Minghelli, (2014), Portugal, 966		X			3/4	10-16	Both	+		+	(NT)	(NT)	(NT)	(NT)	Females: OR 2.1 (1.6-2.7) Age 10-12 yr: OR 1 (index) 13-16 yr: 1.5 (1.2-2.0)
[66] Mohseni-Bandpei, (2007), Iran, 4813		X			2/4	11-14	Both	0	0	-	(NT)	(NT)	(NT)	(NT)	Age: OR 0.5 (0.4-0.6)
[67] Ng, (2014), Australia, 265		X			2/4	14-16	Both		+	(NT)	(NT)	(NT)	(NT)	(NT)	Prevalence percentage Male: Lifetime 94%, point 65% Female: Lifetime 78%, point 53% (Females: Lifetime: OR 0.2 (0.1-0.5), point: OR 0.3 (0.2-0.5) calculated)

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain							
Reference, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 5)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**Significant estimates (95% CI)**
[68] Noll, (2016), Brazil, 1597				X	2/4	11-16	Both	+		0	(NT)	+	0	(NT)	Female: PR 1.1 (1.1-1.2) Family history: PR 1.2 (1.2-1.3)
[69] Noll, (2016), Brazil, 361				X	2/4	14-20	Both	+		0	(NT)	+	+	(NT)	Female: PR 1.2 (1.1-1.3) Family history: PR 1.2 (1.1-1.3) Ethnicity: White: PR: 1 Asian: PR 1.2 (1.1-1.4) Indigenous: PR 1.4 (1.3-1.5)
[70] Onofrio, (2012), Brazil, 1233		X			3/4	13-19	Both	0	0	0	(NT)	(NT)	+	(NT)	Non-white: PR 1.4 (1.0-1.9)
[71] Pasanen, (2016), Finland, 401		X			3/4	13-17	Both	0	0	+	(NT)	+	(NT)	(NT)	Age (per year): OR 1.2 (1.1-1.4) Family history: OR 2.0 (1.2-3.3)
[72] Prista, (2004), Mozambique, 204		X			3/4	11-16	Both	0	0	0	(NT)	(NT)	+	(NT)	Living in peripheral centre: OR 1 Living in wealthier urban centre OR: 3.1
[73] Rodrigues-Oviedo, (2012), Spain, 1403				X	1/4	12-17	Both	+		+	(NT)	(NT)	(NT)	(NT)	Female: OR 1.6 (1.3-2.1) Older age: OR 1.2 (1.1-1.3)
[74] Scarabottolo, (2017), Brazil, 1011		X			3/4	10-17	Both	0	0	+	(NT)	(NT)	0	(NT)	Older age: older 25.1%, younger adolescents 12.4%
[75] Shehab, (2004), Kuwait, 400		X			2/4	10-18	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	Female: prevalence percentage 64.7% males: prevalence percentage 50.8% (Females: OR: 1.8 (1.2-2.7) calculated)

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain							
Reference, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 5)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**Significant estimates (95% CI)**
[76] Sheir-Neiss (2003), USA, 1126				X	2/4	12-18	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	Female: OR 2.2 (1.6-2.9)
[77] Shipp, (2007), USA, 2536				X	3/4	14-18	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	Female: OR 4.6 (1.8-11.7)
[78] Silva, (2016), Brazil, 961			X		3/4	14-19	Both	+		0	(NT)	(NT)	(NT)	(NT)	Female: OR 2.4 (1.9-3.2)
[79] Silva, (2014), Brazil, 343		X			3/4	12-15	Both	0	0	+	(NT)	(NT)	0	(NT)	Age 12 yr: OR 1 (index) 14 yr: OR 1.3 (1.1-1.7)
[80] Skaggs, (2006), USA, 1540				x	1/4	10-15	Both	+		-	(NT)	(NT)	(NT)	(NT)	Female: 43%, Male: 32% (Female: OR: 1.6 (1.3-2.0) calculated) Younger age: OR 1.5(male), OR 1.4(female)
[81] Turk, (2011), Slovenia, 190		X			2/4	11-15	Both	(NT)	(NT)	0	(NT)	(NT)	(NT)	0	
[82] Van Gent, (2003), Netherlands, 745				X		12-14	Both	+		0	(NT)	(NT)	+	(NT)	Female: 54%, Males 39% (females: OR: 1.8 (1.3-2.4) calculated) Residence: 52% (city), 43% (village)
[83] Viry, (1999), France 123				X	2/4	13-15	Both	+		(NT)	(NT)	(NT)	(NT)	(NT)	Female: OR 2.7 (1.2-6.1)

Reference	Back pain					Characteristics of study sample		Significant positive (+) or negative (-) associations with back pain							
Reference, (year of pub), country, pop size	**MBP**	**LBP**	**Mix**	**?**	**Clear definition of BP (x/4) (Additional file 5)**	**Age range (mean)**	**Sex**	**Female**	**Male**	**Age**	**Pubertal status**	**Family history BP**	**Socioeconomic factors**	**Height**	**Significant estimates (95% CI)**
[84] Watson, (2003), Great Britain, 1446		X			3/4	11-14	Both	+		+	(NT)	(NT)	(NT)	(NT)	Female: 28%, Males 19% Girls 11 yr: 18%, 14 yr: 34% Boys 11 yr: 14%, 14 yr: 25%
[85] Wedderkopp, (2005), Denmark, 254	X	X	X		3/4	8-16	Both	(NT)	(NT)	(NT)	+	(NT)	(NT)	(NT)	Later pubertal status: Stage 1: OR 1 (index) Stage 4: OR 2.0 (1.3-3.5) Stage 5: OR 2.1 (1.1-4.1)
[86] Wedderkopp, (2001), Denmark, 806	X	X	X		3/4	8-16	Both	0	0	(NT)	(NT)	(NT)	(NT)	(NT)	
[87] Wirth, (2015), Switzerland, 412	X	X	X		3/4	10-16	Both	0	0	+	(NT)	0	(NT)	(NT)	Older age: OR 1.3 (1.1-1.7)
[88] Wirth, (2013), Switzerland, 434	X	X	X		3/4	6-16	Both	+		+	(NT)	+	(NT)	(NT)	Female: OR 1.9 (1.3-3.0) Older age: OR 1.3 (1.2-1.4) Family history: 2.3 (1.2-4.7)
[89] Yao, (2012), China, 1214		X			3/4	13-17	Both	(NT)	(NT)	0	(NT)	+	(NT)	0	Family history: 2.6 (1.9-3.6)

(NT): Not tested, (NR): Included in study but not reported, *+ significant positive association, *- significant negative association, 0: tested but non-significant estimate, OR: odds ratio, SE: standard error, PR: prevalence ratio, RR: relative risk

Additional file 4: Clarity of definitions of Back pain: Prospective studies

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[7] Aatun, (2016)	MB/LB						X	- - - -?	No	- - -	Diagram used, pilot study of the questionnaire	3/4
[8] Auvinen, (2010)	LB			X (6 mth)				- - - -?	No	-Seek care - -	Diagram used	2/4
[9] Balague´, (2010)	LB		X	X	X			- - - -?	No	-Seek care - -Disability	Used diagram	2/4
[10] Deere, (2012)	MB/LB	X		X (6 mth)				- - - -?	Yes	- - -	Used a pre-validated questionnaire. Diagram used.	3/4
[11] Feldman, (2002)	LB			X (6 mth)				- - - -?	No	- - -	NR	2/4
[12] Feldman, (2001)	LB			X (6 mth)				- - - -?	No	-Seek care - -Disability	NR	2/4
[13] Feldman, (1999)	LB			X (6 mth)				- - - -?	No	- - -	NR	2/4
[14] Franz, (2017)	MB/LB		X					- -Episodic -Ongoing -	No	- - -	Weekly SMS tracking	**4/4**

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[15] Franz, (2016)	MB/LB		X					- -Episodic -Ongoing -	No	- - -	Weekly SMS tracking	**4/4**
[16] Gill, (2014)	MB/LB			X				- - - -?	No	- - -	NR	2/4
[17] Hebert, (2019)	MB/LB		X					- -Episodic -Ongoing -	No	- - -	SMS tracking	**4/4**
[18] Hestbaek, (2006)	LBP				X			- -Episodic -Ongoing -	No	- - -	Used pre-validated questionnaire. Diagram used.	**4/4**
[19] Hestbaek, (2006)	LBP				X			- -Episodic -Ongoing -	No	- - -	Used pre-validated questionnaire. Diagram used.	**4/4**
[20] Hestbaek, (2006)	LBP				X			- -Episodic -Ongoing -	No	- - -	Used pre-validated questionnaire. Diagram used.	**4/4**
[21] Janssens, (2011)	?			X (3 mth)				- - - -?	No	- - -	NR	1/4
[22] Jones, (2009)	LB			X				- - - -?	No	- - -	Diagram used	2/4
[23] Jones, (2003)	LB			X				- - - -?	No	- - -	Diagram used	2/4

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[24] Kanchanomai, (2015)	LB			X (3mth)				- - - -?	No	- - -	Diagram used	2/4
[25] Kroner-Herwig (2017)	?			X (6 mth)				- - - -?	No	- - -	NR	1/4
[26] Mattila, (2008)	LB				X			- - - -?	No	-Seek care - -	Used ICD-10 diagnosis codes	2/4
[27] Mikkonen, (2016)	LB			X (6 mth)				- - - -?	No	-Seek care - -	NR	2/4
[28] Mikkonen, (2013)	LB			X (6 mth)				- - - -?	No	-Seek care - -	Diagram used	2/4
[29] Mikkonen, (2008)	LB			X (6 mth)				- - - -?	No	-Seek care - -	Diagram used	2/4
[30] Nissinen, (1994)	LB	X	X	X	X		X	- - - -?	No	-Seek care - -	Diagram used	2/4
[31] Sano, (2015)	LB	X					X	- - - -?	No	- - -	Diagram used	2/4
[32] Sjolie, (2004)	LB				X		X	- - - -?	No	-Seek care - -Disability	Diagram used	2/4

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[33] Smith, (2017)	LB			X				- - - -?	No	-Seek care -Downtime -Disability	Used pre-validated questionnaire	3/4
[34] Szita, (2018)	LB/MB			X				- - - -?	No	-Seek care -Downtime -	Pilot study of questionnaire.	3/4
[35] Szpalski, (2002)	LB	?	?	?	?	?	?	- - - -?	Yes	- - -	NR	1/4
[36] Tobias, (2013)	MB/LB			X				- - - -?	Yes	- - -Disability	Used pre-validated questionnaire	3/4
BP: back pain, LB: low back, MB: mid back, NR: not reported, mth: months												

Additional file 5: Clarity of definitions of Back pain: Cross-sectional studies

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[37] Aggarwal, (2013)	LB		X	X	X			- - - -?	Yes	- - Downtime - Disability	Questionnaire based on previous guidelines, pretested in pilot study.	3/4
[38] Andersen, (2006)	LB, MB,	X		X			X	- - - -?	No	- Seek care - Downtime -	NR	2/4
[39] Balague´, (1994)	LB	?	?	?	?	?	?	- - - -?	No	- - -	NR	1/4
[40] Bejia, (2005)	LB		X	X	X			- -Episodic -Ongoing -	No	-Seek care -Downtime -Disability	Used pre-validated questionnaire (kappa: 0.7-1.0) Used diagrams	**4/4**
[41] Cakmak, (2004)	LB			X			X	- - - -?	Yes	- - - Disability	Pilot study of questionnaire: ICC +1 (perfect agreement)	3/4
[42] Dianat, (2017)	LB			X				- - - -?	Yes	- Seek care - Downtime - Disability	Pilot study on questionnaire prior. Test-retest stability kappa: 0.72-0.96) Used diagrams	3/4
[43] Dianat, (2014)	LB			X				- - - -?	No	- - -	Modified pre-validated questionnaire. Pilot study on questionnaire. Test-retest: phi coefficients: 0.72-0.91) Used diagrams	3/4
[44] Diepenmaat, (2006)	LB			X				- - - -?	No	- - -	Used diagram	2/4

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[45] Erne, (2011)	LB			X				- - - -?	No	- - -	Used diagram	2/4
[46] Fernandes, (2015)	LB				X			- - - - ?	No	- - -	Adapted a pre-validated questionnaire Used diagram	3/4
[47] Ganesan, (2017)	LB	?	?	?	?	?	?	- - - -?	Yes	- - - Disability	NR	1/4
[48] Ghandour, (2004)	?		X	X				- -Episodic -Ongoing -	No	- - -	NR	2/4
[49] Gilkey, (2010)	?				X			- - - - ?	No	- Seek care - -	NR	1/4
[50] Graup, (2014)	LB						X	- - - - ?	No	- - -	Diagrams used	2/4
[51] Gunzburg, (1999),	LB						X	- - - - ?	Yes	- Seek care -Downtime -	NR	2/4
[52] Haag, (2016)	Mix				X			- - - - ?	Yes	- - -	Stated used a validated questionnaire, diagram used	3/4
[53] Harreby, (1999)	LB	X	X	X	X		X	- -Episodic -Ongoing -	Yes	-Seek care -Downtime -Disability	Pilot study on questionnaire. Diagram used	4/4

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[54] Hestbaek, (2008)	LB				X			- - - -?	No	- - -	Used a pre-validated questionnaire	3/4
[55] Hulsegge, (2011)	?				X			- - - - ?	No	-Seek care - -	NR	1/4
[56] Jones, (2004)	LB			X				- - - - ?	No	- - -	Diagrams used	2/4
[57] Kaspiris, (2010)	LB				X			- - - -?	Yes	- - -Disability	Used a pre-validated questionnaire, diagrams used	3/4
[58] Kovacs, (2003)	LB		X				X	- - - -?	No	-Seek care -Downtime -Disability	Use a pre-validated questionnaire	3/4
[59] Kristensen, (2001)	LB				X		X	- - - -?	No	-Seek care -Downtime -Disability	Use pre-validated questionnaire, piloted the questionnaire, used diagram	3/4
[60] Kristjansdottir, (2002)	?	?	?	?	?	?	?	- - - -?	No	- - -	NR	0/4
[61] Leboeuf-Yde, (2002),	Mix	X	X	X				- - - -?	No	-Seek care -Downtime -Disability	NR	3/4
[62] LeResche, (2005)	?			X (3 mth)				- - - -?	Yes	- - -	NR	1/4

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[63] Masiero, (2008)	LB				X			- - - -?	Yes	-Seek care - -	Assessed for comprehensibility in a pilot study	3/4
[64] Mattila, (2008)	LB						X	- - - -?	No	-Seek care - -	NR	2/4
[65] Minghelli, (2014)	LB	X			X		X	- - - -?	No	- - -	Used a pre-validated questionnaire	3/4
[66] Mohseni-Bandpei, (2007),	LB	X		X	X			- - - -?	No	- - -	NR	2/4
[67] Ng, (2014)	LB	X	X				X	- - - -?	Yes	- - -	Diagram used	2/4
[68] Noll, (2016)	?			X (3 mth)				- - - -?	No	- - -	Used a pre-validated questionnaire	2/4
[69] Noll, (2016)	?			X (3 mth)				- - - -?	No	- - -	Used a pre-validated questionnaire	2/4
[70] Onofrio, (2012)	LB			X				- - - -?	No	- - -	Pilot study of questionnaire, diagram used	3/4
[71] Pasanen, (2016)	LB		X		X			- - - -?	No	-Seek care -Downtime -Disability	Used pre-validated questionnaire	3/4

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[72] Prista, (2004)	LB			X	X		X	- -Episodic - -	No	-Seek care - -	NR	3/4
[73] Rodrigues-Oviedo, (2012)	?				X			- - - -?	No	- - -	NR	1/4
[74] Scarabottolo, (2017)	LB		X					- - - -?	No	- - -	Used a pre-validated questionnaire, (kappa: 0.57-1.00)	3/4
[75] Shehab, (2004)	LB	?	?	?	?	?	?	- - -?	Yes	- - -Disability	Questionnaire was pre-tested. Diagrams used.	2/4
[76] Sheir-Neiss (2003)	?			X				- - - -?	Yes	-Seek care -Downtime -Disability	Adapted a pre-validated questionnaire. Diagrams used.	2/4
[77] Shipp, (2007)	?			X (9 mth)				- - -?	No	-Seek care -Downtime -Disability	Pre-validated questionnaire used. Diagram used.	3/4
[78] Silva, (2016)	MB/LB			X (6 mth)				- - - -?	No	-Seek care - -	Diagrams used. Use a pre-validated questionnaire.	3/4
[79] Silva, (2014)	LBP				X			- - - -?	No	- - -	Use a pre-validated questionnaire. Diagrams used.	3/4
[80] Skaggs, (2006)	?	?	?	?	?	?	?	- - - -?	Yes	-Seek care - -Disability	Use a pre-validated questionnaire	1/4

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[81] Turk, (2011)	LB			X (3 mth)				- - - -?	Yes	-Seek care - -Disability	NR	2/4
[82] Van Gent, (2003)	?	?	?	?	?	?	?	- - - -?	No	-Seek care - -Disability	NR	0/4
[83] Viry, (1999)	?	X					X	- -Episodic -Ongoing -	No	-Seek care -Downtime -	NR	2/4
[84] Watson, (2003)	LB			X				- - - -?	No	- - -	Piloted questionnaire. Used diagram	3/4
[85] Wedderkopp, (2005)	MB/LB	X	X	X				- - - -?	No	-Seek care -Downtime -	Pilot study used for questionnaire, diagrams used.	3/4
[86] Wedderkopp, (2001)	MB/LB	x	x	x				- - - -?	No	-Seek care -Downtime -	Pilot study used for questionnaire, diagrams used.	3/4
[87] Wirth, (2015)	MB/LB			X			X	- -Episodic -Ongoing -	yes	-Seek care -Downtime -Disability	Diagram used	3/4
[88] Wirth, (2013)	MB/LB			X			X	- -Episodic -Ongoing -	Yes	-Seek care -Downtime -Disability	NR	3/4

	Area of BP (1 point)	Recall period (1 point)						Type (1 point)	Severity described	Consequences reported	Attempted to collect valid data (1 point)	Conclusion
Ref (year of pub)	**Location**	**Now**	**Past week**	**Past month**	**Past year**	**> 1 year**	**pain ever**	**-1st ever -Episodic -Ongoing -?**		**-Seek care -Downtime -Disability**		**Clear definition of BP (x/4)**
[89] Yao, (2012)	LB			X (3 mth)				- - - -?	No	- - -	Pilot study used for questionnaire, test=retest coefficient 0.5-0.8)	3/4
BP: back pain, LB: low back, MB: mid back, NR: not reported,												

Chapter Three: Systematic Review: Chronic physical illnesses, mental health disorders, and psychological features as potential risk factors for back pain from childhood to young adulthood

Online Resource 1: Full Search Strategies

MEDLINE

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

1	exp Back Pain/
2	exp Sciatic Neuropathy/
3	back ache.ti,ab.
4	back disorder*.ti,ab.
5	back injur*.ti,ab.
6	back pain.ti,ab.
7	backache.ti,ab.
8	coccydynia.ti,ab.
9	coccyx.ti,ab.
10	dorsalgia.ti,ab.
11	lumbago.ti,ab.
12	lumbar pain.ti,ab.
13	sciatic neuropathy.ti,ab.
14	sciatica.ti,ab.
15	spondylosis.ti,ab.
16	or/1-15
17	risk.mp.
18	mortality.mp.
19	cohort.tw.
20	or/17-19
21	Pediatrics/
22	(infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or underage* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).mp.
23	school*.ti,ab.
24	or/21-23
25	Epidemiologic studies/
26	Exp case control studies/
27	Exp cohort studies/
28	Case control.tw.
29	(cohort adj (study or studies)).tw.
30	Cohort analy$.tw.

31	(Follow up adj (study or studies)).tw.
32	(observational adj (study or studies)).tw.
33	Longitudinal.tw.
34	Retrospective.tw.
35	or/25-34
36	16 and 20 and 24 and 35

Embase

1	'backache'/exp
2	'sciatic neuropathy'/exp
3	'back ache':ti,ab
4	'back disorder*':ti,ab
5	'back injur*':ti,ab
6	'back pain':ti,ab
7	backache:ti,ab
8	coccydynia:ti,ab
9	coccyx:ti,ab
10	dorsalgia:ti,ab
11	lumbago:ti,ab
12	'lumb* pain':ti,ab
13	'sciatic neuropathy':ti,ab
14	sciatica:ti,ab
15	spondylosis:ti,ab
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	risk
18	mortalit*
19	cohort
20	#17 OR #18 OR #19
21	'pediatrics'/de
22	infan* OR newborn* OR 'new-born*' OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm*
23	school*:ti,ab
24	#21 OR #22 OR #23
25	'clinical study'/de
26	'case control study'/de
27	'family study'/de
28	'longitudinal study'/de
29	'retrospective study'/de
30	'prospective study'/de
31	'randomized controlled trial'/de
32	#30 NOT #31

33	'cohort analysis'/de
34	cohort NEAR/1 (study OR studies)
35	'case control' NEAR/1 (study OR studies)
36	'follow up' NEAR/1 (study OR studies)
37	observational NEAR/1 (study OR studies)
38	epidemiologic* NEAR/1 (study OR studies)
39	#25 OR #26 OR #27 OR #28 OR #29 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
40	#16 AND #20 AND #24 AND #39

CINAHL with Full Text

1	(MH "Back Pain+")
2	(MH "Sciatica")
3	TI "back ache" OR AB "back ache"
4	TI "back disorder*" OR AB "back disorder*"
5	TI "back injur*" OR AB "back injur*"
6	TI "back pain" OR AB "back pain"
7	TI backache OR AB backache
8	TI coccydynia OR AB coccydynia
9	TI coccyx OR AB coccyx
10	TI dorsalgia OR AB dorsalgia
11	TI lumbago OR AB lumbago
12	TI "lumbar pain" OR AB "lumbar pain"
13	TI "sciatic neuropathy" OR AB "sciatic neuropathy"
14	TI sciatica OR AB sciatica
15	TI spondylosis OR AB spondylosis
16	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
17	risk
18	mortalit*
19	cohort
20	S17 OR S18 OR S19
21	(MH "Pediatrics")
22	infan* OR newborn* OR 'new-born*' OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm*
23	TI school* OR AB school*
24	S21 OR S22 OR S23
25	(MH "Prospective Studies")
26	(MH "Case Control Studies+")
27	(MH "Correlational Studies")
28	(MH "Nonconcurrent Prospective Studies")

29	cohort N1 (study OR studies)
30	observational N1 (study OR studies)
31	S25 OR S26 OR S27 OR S28 OR S29 OR S30
32	S16 AND S20 AND S24 AND S31

Scopus

(TITLE-ABS-KEY ("back ache" OR "back disorder*" OR "back injur*" OR "back pain" OR backache OR coccydynia OR coccyx OR dorsalgia OR lumbago OR "lumbar pain" OR "sciatic neuropathy" OR sciatica OR spondylosis)) AND (TITLE-ABS-KEY (risk OR mortality OR cohort)) AND (TITLE-ABS-KEY (infan* OR newborn* OR "new-born*" OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR school* OR schoolchild* OR schoolchild OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm*)) AND ((TITLE-ABS-KEY ((prospective OR epidemiologic* OR "case control" OR cohort OR "follow up" OR observational) W/1 (study OR studies))) OR (TITLE-ABS-KEY ("cohort analy*" OR longitudinal OR retrospective))) AND NOT INDEX (medline) AND NOT INDEX (embase)

Online Resource 2: Modified QUIPS: Risk of bias for Etiological studies

Domains	Issues to consider for judging overall rating of "Risk of bias"	Ratings
Study Participation	a) The source population or population of interest is adequately described for key characteristics b) Similar identification of non-diseased populations at baseline c) The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care) d) Period of recruitment is adequately described. e) Place of recruitment (setting and geographic location) are adequately described. f) Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria description). g) There is adequate participation in the study by eligible individuals. h) The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.	**High bias**: The relationship between the RF and outcome is very likely to be different for participants and eligible nonparticipants **Moderate bias:** The relationship between the RF and outcome may be different for participants and eligible nonparticipants **Low bias:** The relationship between the RF and outcome is unlikely to be different for participants and eligible nonparticipants
Study Attrition	a) Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate. b) Attempts to collect information on participants who dropped out of the study are described c) Reasons for loss to follow-up are provided. d) Participants lost to follow-up are adequately described for key characteristics (LIST). e) There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	**High bias:** The relationship between the RF and outcome is very likely to be different for completing and non-completing participants **Moderate bias:** The relationship between the RF and outcome may be different for completing and non-completing participants **Low bias:** The relationship between the RF and outcome is unlikely to be different for completing and non-completing participants
Risk Factor Measurement	a) A clear definition or description of 'RF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement). b) Method of RF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). c) The method and setting of measurement of RF is the same for all study participants. d) Adequate proportion of the study sample has complete data for RF variable. e) Appropriate methods of imputation are used for missing 'RF' data.	**High bias:** The measurement of the RF is very likely to be different for different levels of the outcome of interest **Moderate bias:** The measurement of the RF may be different for different levels of the outcome of interest **Low bias:** The measurement of the RF is unlikely to be different for different levels of the outcome of interest

Outcome Measurement	a) A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct. b) The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test). c) The method and setting of outcome measurement is the same for all study participants.	**High bias:** The measurement of the outcome is very likely to be different related to the baseline level of the RF **Moderate bias**: The measurement of the outcome may be different related to the baseline level of the RF **Low bias:** The measurement of the outcome is unlikely to be different related to the baseline level of the RF
Study Confounding	a) All important confounders, including treatments (key variables in conceptual model), are measured. b) Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures). c) Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall). d) The method and setting of confounding measurement are the same for all study participants. e) Appropriate methods are used if imputation is used for missing confounder data. f) Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups). g) Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	**High bias:** The observed effect of the RF on the outcome is very likely to be distorted by another factor related to RF and outcome **Moderate bias:** The observed effect of the RF on outcome may be distorted by another factor related to RF and outcome **Low bias**: The observed effect of the RF on outcome is unlikely to be distorted by another factor related to RF and outcome
Statistical Analysis and Reporting	a) There is sufficient presentation of data to assess the adequacy of the analysis. b) The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model. c) There is no selective reporting of results.	**High bias:** The reported results are very likely to be spurious or biased related to analysis or reporting **Moderate bias:** The reported results may be spurious or biased related to analysis or reporting **Low bias:** The reported results are unlikely to be spurious or biased related to analysis or
Modified from: Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Annals of Internal Medicine. 2006; 144:427-437.		

Chapter Five: Multi-trajectory analysis of C-reactive protein and low back pain from adolescence to early adulthood

Online Resource 1 Model selection and Model fit diagnostic criteria for trajectories

Model selection based on Bayesian Information Criterion (BIC) and smallest group size

Number of groups	BIC[a]: Total number of observations	BIC[a]: Total number of participants	Smallest group size[b] (n)
LBP with impact			
2	-2771.76	-2768.89	746
3	**-2759.84**	**-2754.68**	**151**
4	-2769.20	-2762.32	132
5	-2782.22	-2773.04	123
Multi-trajectory LBP with impact and hs-CRP			
2	-3925.35	-3910.86	446
3	**-3772.43**	**-3752.76**	**50**
4	-3753.61	-3726.69	22
5	-3768.84	-3735.71	21
[a]BIC: Bayesian Information Criterion (large BIC indicates better fit) **[b]Minimum group size of 30 participants**			

Model fit diagnostic criteria for trajectories

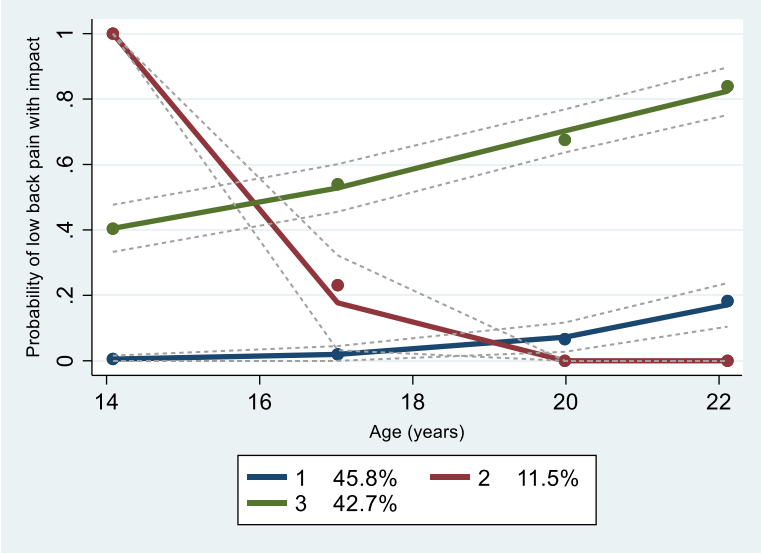
Trajectory group	Average posterior probability[a]: %	Odds of correct classification[b]	Estimated group proportions: % (95% CI)	Assigned membership: %
LBP with impact				
1 "consistently low"	85.6	17.1	46.1 (41.2, 50.9)	49.3
2 "decreasing"	78.3	65.0	10.4 (8.3, 12.5)	10.1
3 "increasing"	87.9	26.6	43.5 (38.3, 48.6)	40.7
Multi-trajectory LBP with impact and hs-CRP				
1 "low CRP, low LBP"	82.9	21.6	52.4 (40.1, 64.7)	54.4
2 "low CRP, increasing LBP"	82.7	31.2	39.9 (27.6, 52.2)	40.3
3 "increasing CRP, moderate LBP"	93.4	1060.5	7.7 (5.0, 10.3)	5.3
[a]Lowest acceptable posterior probability 70% **[b]Lowest acceptable odds of correct classification 5.0**				

Online Resource 2 Sensitivity analyses of trajectory models

Model fit diagnostic criteria for sensitivity analyses of trajectory models

Trajectory group	Average posterior probability	Odds of correct classification	Estimated group proportions: % (95% CI)	Assigned membership: %
Low back pain with impact: Males				
1. "consistently low"	85.4	38.1	45.8 (39.3, 52.2)	49.5
2. "decreasing"	79.2	120.2	11.5 (8.6, 14.5)	11.4
3. "increasing"	89.0	69.22	42.7 (35.9, 49.5)	39.0
Low back pain with impact: Females				
1. "consistently low"	84.2	36.8	45.0 (34.9, 55.2)	48.8
2. "decreasing"	79.5	181.9	10.7 (2.8, 18.5)	8.1
3. "increasing"	86.7	51.5	44.3 (36.4, 52.2)	43.1
Low back pain with impact: without 14-year timepoint				
1. "consistently low"	71.7	5.1	51.2 (29.5, 72.9)	59.8
2. "decreasing"	70.0	527.29	11.5 (1.4, 34.3)	5.6
3. "increasing"	86.1	27.9	37.4 (30.2, 44.5)	34.6
Low back pain with impact: participants with all four timepoints				
1. "consistently low"	80.1	43.0	37.8 (27.5, 48.0)	42.5
2. "decreasing"	81.3	153.9	16.6 (5.8, 27.4)	13.7
3. "increasing"	90.9	103.6	45.6 (38.3, 52.9)	43.8
Multi-trajectory hs-CRP and LBP with impact: Males				
1. "low CRP, low LBP"	83.2	44.7	58.9 (48.6, 69.1)	64.5
2. "low CRP, increasing LBP"	82.1	95.2	28.4 (18.4, 38.3)	29.6
3. "increasing CRP, moderate LBP"	92.6	1368.0	12.8 (7.3, 18.2)	5.8
Multi-trajectory hs-CRP and LBP with impact: Females				
4. "low CRP, low LBP"	85.5	69.7	46.4 (28.6, 64.2)	45.1
5. "low CRP, increasing LBP"	83.8	51.0	50.3 (32.4, 68.0)	53.1
6. "increasing CRP, moderate LBP"	99.5	67361.0	3.4 (1.2, 5.5)	1.8
Multi-trajectory hs-CRP and LBP with impact: without 14-year timepoint				
1. "low CRP, low LBP"	81.2	18.8	51.7 (38.5, 64.9)	56.7
2. "low CRP, increasing LBP"	84.7	37.2	50.8 (27.6, 53.9)	39.5
3. "increasing CRP, moderate LBP"	91.9	894.7	7.5 (4.8, 10.2)	3.8
Multi-trajectory hs-CRP and LBP with impact: participants with all four timepoints				
1. "low CRP, low LBP"	84.6	40.9	54.9 (44.2, 65.7)	58.6
2. "low CRP, increasing LBP"	83.9	68.4	32.8 (22.3, 43.3)	35.3
3. "increasing CRP, moderate LBP"	93.3	1120.3	12.2 (7.8, 16.6)	6.1

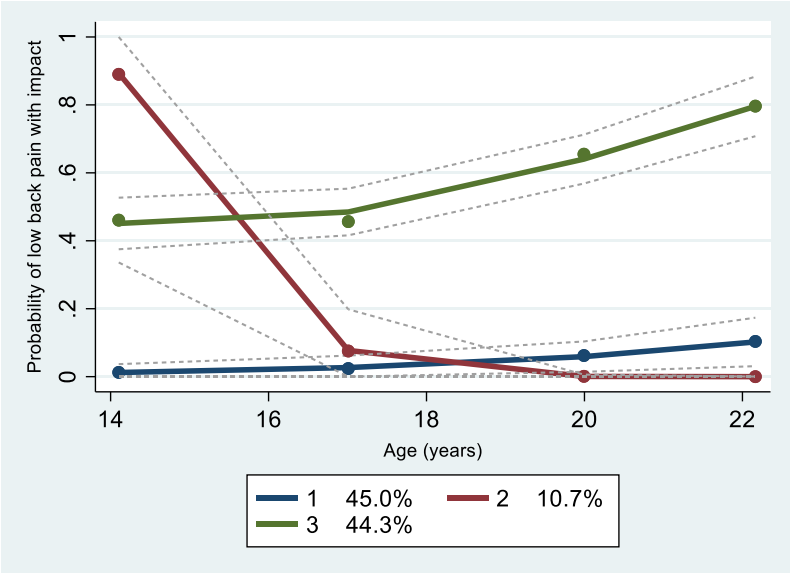
Only males



Crosstab of low back pain trajectory and low back trajectory with just males

LBP trajectories	**LBP males trajectories**			
GROUP	1	2	3	Total
1	370	0	1	371
2	0	76	0	76
3	11	12	299	322
TOTAL	381	88	300	769

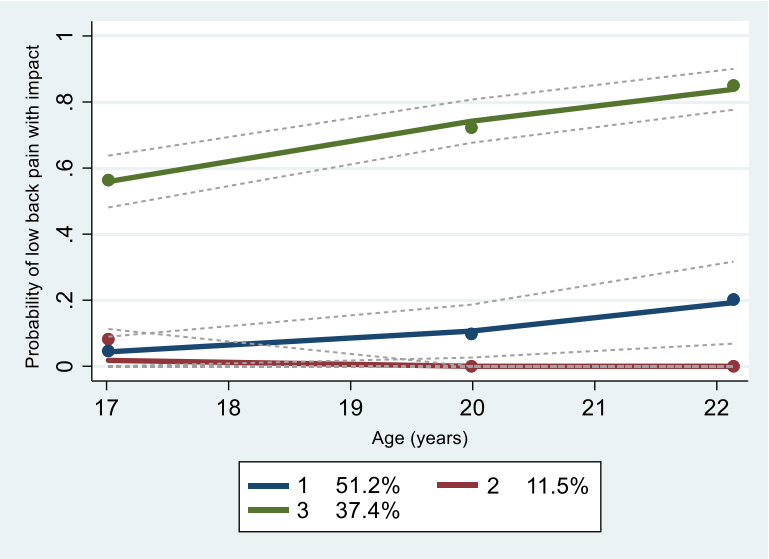
Only females



Crosstab of low back pain trajectory and low back trajectory with just females

LBP trajectories	**LBP females trajectories**			
GROUP	1	2	3	Total
1	363	0	12	375
2	0	60	15	75
3	0	0	294	294
TOTAL	364	60	321	744

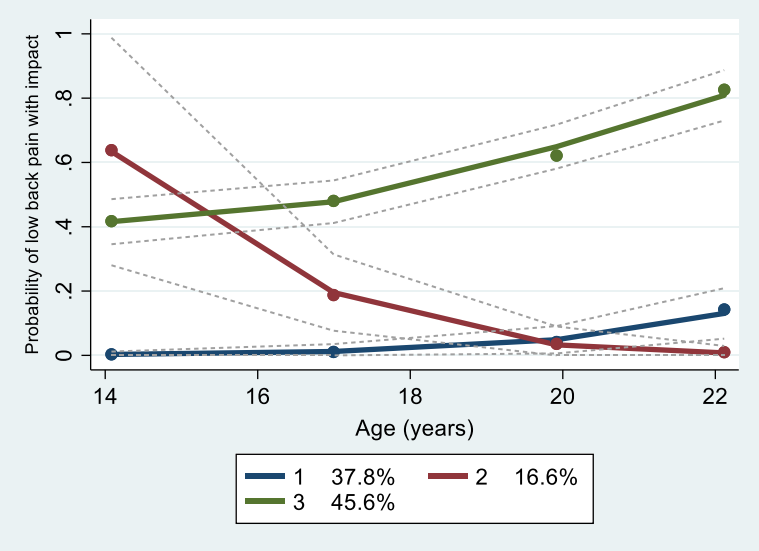
Without 14 years (17-22only)



Crosstab of low back pain trajectory and low back trajectory with just 17-22 years timepoints

LBP trajectories	**LBP 17-22 years**			
GROUP	1	2	3	Total
1	735	11	0	746
2	80	71	0	151
3	92	1	523	616
TOTAL	907	83	523	1513

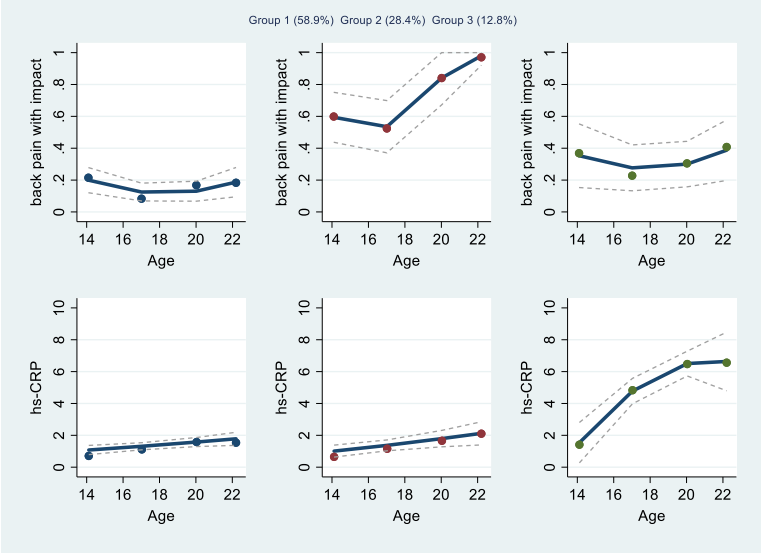
Participants with all four timepoints



Crosstab of low back pain trajectory and low back trajectory with participants with all four timepoints

LBP trajectories	**LBP Participants with 4 timepoints**			
GROUP	1	2	3	Total
1	246	8	26	280
2	0	65	0	65
3	0	6	227	233
TOTAL	246	79	253	578

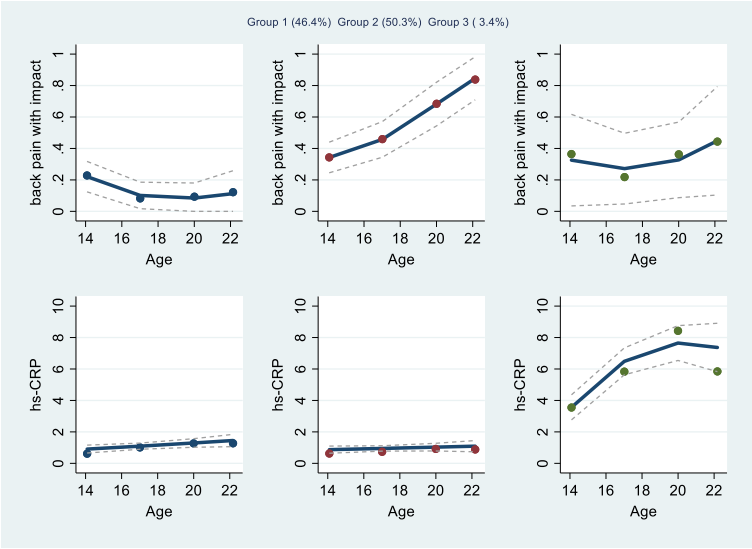
Only males



Crosstab of multi-trajectories with just males

LBP/CRP trajectories	LBP/CRP male trajectories			Total
GROUP	1	2	3	
1	249	1	1	251
2	36	131	0	167
3	2	0	25	27
TOTAL	287	132	26	445

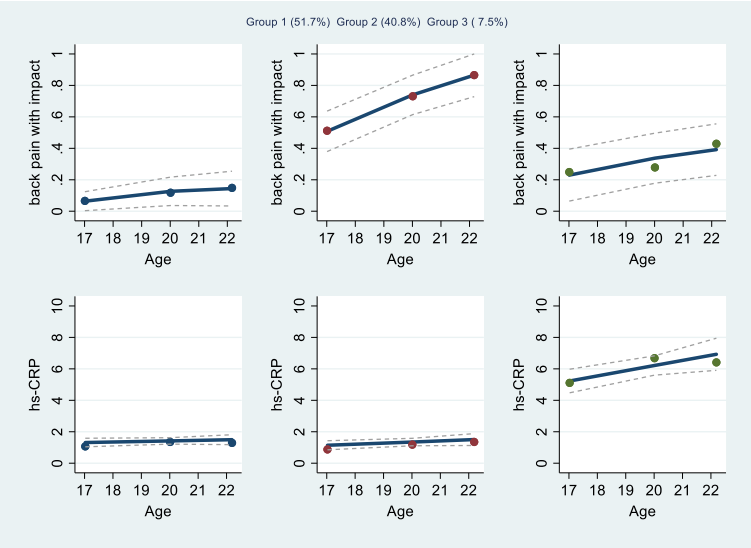
Only females



Crosstab of multi-trajectories with just females

LBP/CRP trajectories	LBP/CRP females trajectories			
GROUP	1	2	3	Total
1	219	52	0	271
2	3	212	0	215
3	2	0	9	11
TOTAL	224	264	9	497

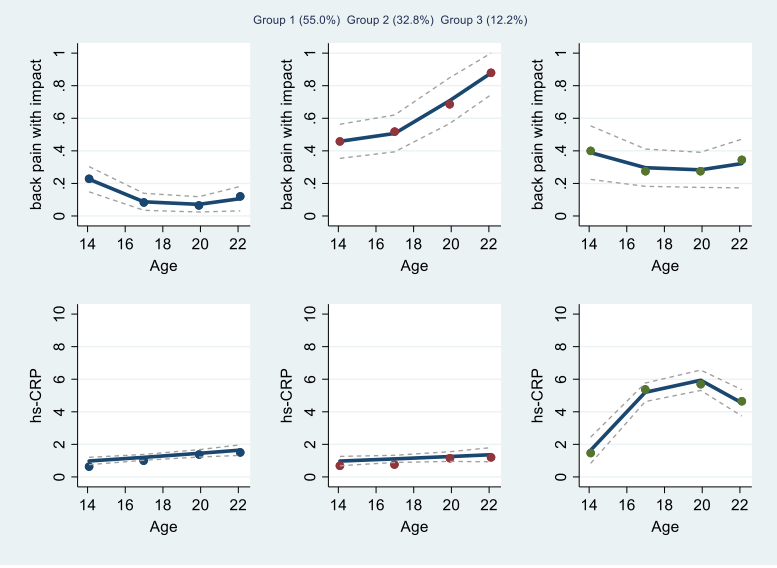
Without 14 years (17-22only)



Crosstab of multi-trajectories without 14 year timepoint

LBP/CRP trajectories	LBP/CRP 17-22 years trajectories			
GROUP	1	2	3	Total
1	509	12	1	522
2	21	360	1	382
3	4	0	34	38
TOTAL	534	372	36	942

Participants with all four timepoints



Crosstab of multi-trajectories with participants with all four timepoints

LBP/CRP trajectories	LBP/CRP Participants with 4 timepoints			
GROUP	1	2	3	Total
1	239	4	3	246
2	2	195	4	201
3	1	0	20	21
TOTAL	242	199	27	468

Chapter Six: Association between cardiovascular disease risk factors and future spinal pain with the potential moderating role of health-related physical activity (CHAMPS Study-DK)

APPENDIX A:

Associations between HOMA-IR and Clustered cardiovascular disease risk score and spinal pain

Cardiovascular disease risk factors 2008	**N**	**Weeks with spinal pain Nov 2008-Nov 2010 Tertile 2 *beta coefficients (95% CI)**	**Weeks with spinal pain Nov 2008-Nov 2010 Tertile 3 *beta coefficients (95% CI)**
Log HOMA-IR	Girls=440	**-0.83 (-1.57, -0.08)**	-0.80 (-1.65, 0.05)
	Boys=406	0.04 (-0.74, 0.83)	0.25 (-0.68, 1.17)
Clustered CV risk score	Girls=433	-0.62 (-1.29, 0.05)	-0.00 (-0.83, 0.83)
	Boys=397	0.30 (-0.29, 0.89)	0.60 (-0.36, 1.57)
Cardiovascular disease risk factors 2010	**N**	**Weeks with spinal pain Nov 2010-Nov 2012 Tertile 2 *beta coefficients (95% CI)**	**Weeks with spinal pain Nov 2010-Nov 2012 Tertile 3 *beta coefficients (95% CI)**
Log HOMA-IR	Girls=370	-0.38 (-1.21, 0.45)	**-1.57 (-2.63, -0.51)**
	Boys=367	0.42 (-0.37, 1.21)	0.28 (-0.87, 1.43)
Clustered CV risk score	Girls=370	0.39 (-1.08, 1.86)	-0.47 (-2.02, 1.07)
	Boys=366	-0.11 (-1.13, 0.91)	0.22 (-1.06, 1.50)

Tertile 1: reference group

HOMA-IR: homeostasis assessment model-estimated insulin resistance, CV: cardiovascular

*All models adjusted for age

Bolded results indicate statistically significant results.

Chapter Seven: No association between sub-clinical elevation of C-reactive protein levels and spinal pain trajectories in children (CHAMPS Study-DK)

Appendix A Model selection and Model fit diagnostic criteria for trajectories

Model selection based on Bayesian Information Criterion (BIC)

Number of groups	BIC[a]: Total number of observations	BIC[a]: Total number of participants
2	-61843.81	-61837.58
3	-54867.53	-54856.12
4	-53700.79	-53684.19
5	**-52554.81**	**-52531.99**
6	-52228.38	-52198.30
7	-51905.85	-51872.66
8	-51789.11	-51789.11
[a]BIC: Bayesian Information Criterion (large BIC indicates better fit)		

Trajectory model diagnostics of Non-traumatic spinal pain trajectories

Trajectory group	Average posterior probability[a]: %	Odds of correct classification[b]	Estimated group proportions: % (95% CI)	Assigned membership: %
1 “No pain”	86.8	5.3	55.3 (51.9, 58.6)	61.6
2 “Rare”	80.0	16.2	23.7 (20.1, 27.4)	20.3
3 “Rare, increasing”	85.6	50.3	13.6 (11.9, 15.3)	10.9
4. **“**Moderate, increasing”	90.4	154.1	6.1 (5.3, 6.9)	6.0
5. Early onset, decreasing	97.9	3667.1	1.3 (1.0, 1.5)	1.3
[a]Lowest acceptable posterior probability 70% [b]Lowest acceptable odds of correct classification 5.0				