Pain and injury in adolescents and young adults

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Supervisors' statement

As supervisors of Michael Steven Swain's doctoral work, we certify that we consider his thesis "Pain and injury in adolescents and young adults" is sufficiently well presented to be examined and does not exceed the prescribed word limit or any extended word limit for which prior approval has been granted.

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Candidate's statement

I, Michael Steven Swain, hereby declare that this submission is my own work and that it contains no material previously published or written by another person except where acknowledged in the text. Nor does it contain material which has been accepted for the award of another degree.

I, Michael Steven Swain, understand that if I am awarded a higher degree for my thesis entitled "Pain and injury in adolescents and young adults" being lodged herewith for examination, the thesis will be lodged in the University library and be available immediately for use. I agree that the University Librarian (or in the case of a department, the Head of the Department) may supply a photocopy or microform of the thesis to an individual for research or study or to a library.

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Publications and presentations

Parts of the work presented in this thesis have been published and presented at national and international conferences.

Published papers

- Swain MS, Henschke N, Kamper SJ, Downie A, Koes B, Maher CG. Accuracy of clinical tests in the diagnosis of anterior cruciate ligament injury: a systematic review. Chiropractic & Manual Therapies 2014;22(1):25 doi: 10.1186/s12998-014-0025-8
- Swain MS, Henschke N, Kamper SJ, Gobina I, Ottova-Jordan V, Maher CG. An international survey of pain in adolescents. BMC Public Health 2014;14(1):447 doi: 10.1186/1471-2458-14-447
- Swain MS, Henschke N, Kamper SJ, Gobina I, Ottova-Jordan V, Maher CG. Pain and moderate to vigorous physical activity in adolescence: An international population-based survey. Pain Medicine 2016;17(5):813-19 doi: 10.1111/pme.12923
- Swain MS, Kamper SJ, Maher CG, Latimer J, Broderick C, McKay D, Henschke N. Short-term clinical course of knee pain in children and adolescents: A feasibility study using electronic methods of data collection. Physiotherapy Research International 2017;22(4) doi: 10.1002/pri.1669
- Swain M, Kamper SJ, Maher CG, Broderick C, McKay D, Henschke N. Relationship between growth, maturation and musculoskeletal conditions in adolescents: A systematic review. The British Journal of Sports Medicine 2018;52(19):1246-52.

Presentations

- *Podium Oral Presentation.* An international survey of pain in adolescents. Swain MS, Henschke N, Kamper SJ, Gobina I, Ottová-Jordan V, Maher CG. The Chiropractic & Osteopathic College of Australasia's 10th Biennial National Conference, Melbourne, Australia, 12th October 2013.
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- *Poster Presentation.* Accuracy of clinical tests in the diagnosis of anterior cruciate ligament injury: A systematic review. The Chiropractic & Osteopathic College of Australasia's National Conference, Sydney, Australia, 10th October 2014. **Prize:** Best Poster.

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Author attribution statements

Chapter Two of this thesis is published as "Swain MS, Henschke N, Kamper SJ, Gobina I, Ottova-Jordan V, Maher CG. An international survey of pain in adolescents. BMC Public Health 2014;14(1):447". I co-designed the analyses with the co-authors, analysed the data and contributed to its interpretation, drafted the manuscript, and submitted the manuscript.

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In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

_____ Date: 28th September 2018

Michael Steven Swain

As supervisors for the candidature upon which this thesis is based, we can confirm that the authorship attribution statements above are correct.

_____ Date: 28th September 2018

Professor Christopher Maher

_____ Date: 28th September 2018

Associate Professor Steven Kamper

Preface

This thesis is arranged into seven chapters, written so that each chapter can be read independently. The chapters in this thesis comprise five individual studies on pains and injuries that are common in adolescents and young adults. The University of Sydney allows publications that arose from the candidature to be included in the thesis. Chapters Two, Three, Four, Five, and Six are PDF files of the published papers.

Chapter One is an introduction to the thesis and provides an overview of the concepts relevant to the study of pain and injury in adolescents and young adults. **Chapter Two** is a cross-sectional study that estimates the prevalence of backache, headache and stomach ache in adolescents from a representative sample of adolescents from 28 countries. The study is presented in the format required by *BMC Public Health* where it was accepted for publication. **Chapter Three** is a cross-sectional study that evaluates whether types of pain (backache, headache and stomach ache) or multiple pains, affect the odds of adolescents achieving the recommended 60 minutes of moderate to vigorous physical activity per day in a large representative sample. The study is presented in the format required by *Pain Medicine* where it was accepted for publication. **Chapter Four** is a systematic literature review that determines whether there is a relationship between physical growth, biological maturation, and musculoskeletal conditions in adolescents. The study is presented in the format required by *The British Journal of Sports Medicine* where it was accepted for publication. **Chapter Five** is a prospective cohort study that evaluates the feasibility of using electronic methods of data collection to assess the short-term clinical course of knee pain in children and adolescents. The study is

presented in the format required by *Physiotherapy Research International* where it was accepted for publication. **Chapter Six** consists of a systematic review of the literature that evaluates the accuracy of clinical tests in the diagnosis of anterior cruciate ligament injury. The study is presented in the format required by *Chiropractic and Manual Therapies* where it was commissioned, and peer reviewed for publication. Finally, **Chapter Seven** is an overview of the thesis, and discusses the public health and clinical implications of the findings and directions for future research.

Each chapter contains its own reference list. Appendices that were published as online supplementary material are included at the end of the relevant chapter. Additional appendices are included at the end of the thesis. Ethical approval was obtained for the studies reported in Chapter Two and Chapter Three from Human Ethics Institutional Review Boards for Health Behaviour of School-aged Children team members across Europe and North America prior to commencement. Ethical approval was obtained from the Human Research Ethics Committee of the University of Sydney for the study reported in Chapter Five prior to commencement (protocol number 14519). The remaining chapters did not require ethical approval.

Abstract

Pain and injury in adolescents and young adults pose a substantial burden to individuals, their families and the community, both during adolescence and later in life. Compared to adults, there is a paucity of research that investigates the epidemiology of pain and injury in young people, which is necessary to advance understanding in the field. This thesis aims to better the understanding of pain and injury in adolescents and young adults by investigating the prevalence, impact, risk factors, clinical course and diagnosis of common disorders.

Chapters 2 and 3 presents the results of studies which investigate prevalence of pain and relationship to physical activity in large international data sets. Chapter 2 presents the results of a study performed to investigate the prevalence and co-occurrence of pain in young people via analysis of data collected from 404,206 children in 28 countries across Europe and North America. The results showed that back pain, headache, and stomach ache were very common in adolescents, more often coexisting with each other than occurring in isolation. Girls had a higher prevalence of the three pain types than boys, and older adolescents more frequently experienced all types of pain than young adolescents. Despite some variation across countries, in no country were the three pains uncommon.

Back pain is thought to impact adolescents' participation in physical activity, however the impact of pain on adolescents meeting the World Health Organisations recommendations on levels of physical activity for health is currently unknown. In Chapter 3 analysis of data was conducted to investigate the association between pain (back pain, headache, stomach ache or multiple pains) and achieving the recommended 60 minutes of moderate to vigorous physical activity (MVPA) per day.

In a representative sample of 242,103 young people from 28 countries across Europe and North America, adolescents with pain generally had reduced odds of meeting physical activity recommendations. However, findings differed depending on age and gender; the association was most pronounced in 11- and 13-year old adolescents, and girls more so than boys.

Chapter 4 presents the results of a study performed to investigate whether physical growth and development (determined by markers of biological maturation) is a risk factor for musculoskeletal conditions in adolescents. A systematic review of the literature was conducted and found 56 studies, all at high risk of bias. There was a total of 208 estimates of association, which generally indicated no association or an unclear association between maturation, growth and musculoskeletal conditions in adolescents.

The clinical course of knee pain in adolescents is unclear because there are no short-term clinical-course studies. In Chapter 5, a feasibility study with 6-month follow-up was conducted to assess the recruitment, retention and response rates (feasibility) of weekly electronic follow-up (text messaging and an online questionnaire), in a clinical cohort of adolescents with knee pain. Study feasibility was threatened by slow recruitment, a high percentage of participants that stopped responding to text messaging prior to recovery, and high loss to follow-up at 6-months. Electronic data collection alone seems insufficient to track knee pain recovery in young people.

Traumatic anterior cruciate ligament injuries are common and impactful in young people and responsible for frequent presentations to clinical care. Peak incidence of anterior cruciate ligament injuries occurs during adolescence and young adulthood.

Chapter 6 reports a systematic review conducted to evaluate the diagnostic accuracy of clinical tests for diagnosis of anterior cruciate ligament injury. Fourteen diagnostic accuracy studies were included, the risk of bias was judged as low in the study conducted in primary care and moderate-to-high in studies conducted in secondary contact settings. The accuracy of clinical tests for anterior cruciate ligament injury was variable and imprecise in secondary contact settings, and only produced a small change in the probability of anterior cruciate ligament injury in primary care settings. Clinical tests in combination, but not individually, may assist the diagnosis of anterior cruciate ligament injury in clinical practice.

Collectively, this thesis provides an important contribution to the body of knowledge underpinning the epidemiology of pain and injury in adolescents and young adults. The new information provided aids development of public health and clinical management strategies in young people with pain and injury.

Chapter One

Introduction

“Every accomplishment starts with the decision to try”.

- John F. Kennedy

1.1 Preamble

This dissertation contains five linked research projects that address the central theme of the thesis, which is pain and injury in adolescents and young adults. The thesis includes a study investigating the prevalence of pain in adolescents, a study investigating the relationship between pain and physical activity in adolescents, a systematic review investigating the relationship between pubertal development and pain in adolescents, a feasibility study of the prognosis of knee pain in adolescents, and a systematic review of the diagnostic accuracy of tests for anterior cruciate ligament injury.

1.2 Musculoskeletal pain in young people

1.2.1 Musculoskeletal pain

Pain is a subjective experience defined by the International Association for the Study of Pain (ISAP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such tissue damage”.[1] Cognitive interpretation of pain develops through an individual’s experiences with pain early in life, and this serves as a reference for the interpretation and expression of future pain.[2] Musculoskeletal (MSK) pain is a common type of pain[3] that arises from conditions affecting muscles, joints, bones or related supporting tissues.[4]

1.2.2 Types of musculoskeletal pain (acute, chronic, and body regions)

MSK pain is typically separated into two forms, acute and chronic MSK pain. Acute pain is “the physiologic response and experience to noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviours to avoid actual or potential tissue damage.”[5] Chronic pain is pain that “persists beyond

normal tissue healing time"[6] following injury (or other condition), and may exist without a clear patho-anatomical reason. By convention,[7] the cut-point between acute and chronic MSK pain is 3-months.[5] For example, chronic MSK pain, such as chronic low back pain (LBP) has been operationally defined as "persistent or recurrent pain lasting longer than 3-months".[4 8]

Low back pain is the most common form of MSK pain in adults and is estimated to affect one-third of all people (1-month prevalence 30.8% ± 12.7%).[9] However, during adolescence the prevalence of knee pain is often reported to be higher than back pain. For example, a population-based study of 2,953 Danish adolescents (age 12-19 years) found knee pain in 32.3% (95% confidence interval (CI): 30.6% to 34.0%), which was more common than both back pain (24.1% [CI: 22.6% to 25.7%]) and shoulder pain (13.3% [CI: 12.1% to 14.5%]).[10] MSK pain is one of the most common types of pain experienced during adolescence.[11-13] A German study of adolescents reports the 3-month prevalence of back pain (38.6%), limb pain (46.4%), abdominal pain (47.7%), and headache (65.6%).[11] A large population level study in the Netherlands found chronic MSK pain (i.e. limb pain range 4.9% to 6.1% and back pain 2.7% to 2.9%) to be more common than chronic headache (3.5% to 4.6%) and chronic stomach-ache (2% to 2.3%), and much more common than chronic throat pain (0% to 0.3%), chronic ear pain (0.1% to 0.4%) or chronic pain at other sites (0.6% to 0.9%) during adolescence.[12]

1.2.3 Lifespan considerations

Historically, LBP was thought uncommon in adolescence; two influential publications in the 1980s suggested that the first episode of LBP most commonly occurred late in

the second and third decades of life.[14] Recent studies show that the first episode of LBP typically occurs much sooner, most frequently during early adolescence.[15-17] For example, the lifetime occurrence of LBP at seven years of age is estimated to be 1%, increasing to 12%-40% by 12 years, and 39%-71% by 12-15 years of age.[15] It is now well-established that the prevalence of LBP increases sharply during adolescence, with the prevalence in late adolescence approximating the prevalence in adults.[9 18 19] There is an association between MSK pain in adolescence (particularly persistent MSK pain and multiple pains) and MSK pain in adult life.[20-22] Hestbaek et al, followed approximately 10,000 adolescents (mean age 17.4 years) over 8-years and found adolescents with persistent LBP had higher odds of having persistent LBP in adulthood (odds ratio (OR) 4.3 [CI: 3.5 to 5.3]) than those without persistent LBP. Adolescents who experienced coexisting persistent LBP and persistent headache were at greater odds of experiencing LBP in adulthood (OR 4.6 [CI: 2.9 to 7.4]), compared to if they had experienced LBP alone.[20] Given this link, a life course epidemiological approach is increasingly being taken to the study of MSK pain. This approach aims to clarify the short and long-term risks of biological, behavioural, and psychosocial exposures on pain outcomes at various periods (such as childhood, adolescence, young adulthood) across the life course.[23 24]

1.2.4 Risk factors

Recent systematic reviews that evaluate risk factors for adolescent MSK pain show there is little robust evidence to support the association between most factors and a higher probability of MSK pain[25] or LBP in adolescents.[26 27] The literature is characterised by studies reporting inconsistent associations[16 19 25-31] and contradictory conclusions,[26] which draws doubt on whether any strong risk factors

have been conclusively identified to date. In a recent review, Huguet et al., identified a total of 65 potential risk factors associated with the onset of MSK pain in adolescents, across 36 (21 cohorts) studies. The reviewers reported high-quality evidence (4 cohorts, n=5,403) that low socioeconomic status (SES) (univariate OR 1.4, CI: 1.0 to 2.1), and moderate-quality evidence that negative emotional symptoms (7 cohorts, n=10,922; univariate OR 1.5, CI: 1.1 to 2.2) and regular smoking (4 cohorts, n=7,117, multivariate OR range 1.4 to 2.2) are risk factors for MSK pain.[25] Linked psychosocial factors (such as catastrophising, negative affect, and poor sleep hygiene) are proposed mechanisms underlying the associations between emotional symptoms, SES and MSK pain,[32] whereas exposure to cigarette smoke and nicotine may affect the brain circuitry linked to persistent pain.[33] Other potential risk factors in the review were based on low or very low quality evidence. There was moderate-quality evidence to suggest that some factors; higher body mass index, taller height, and joint hypermobility are not associated with increased risk of onset of MSK pain. Recent systematic reviews[34 35] have also evaluated commonly perceived risk factors, such as back packs and sleep problems. In both examples, authors draw doubt on a link between these factors and MSK pain in adolescents. Seldom are ‘activity and participation’ or ‘social and environmental’ factors[25] studied as risk factors for MSK pain in adolescents.[36]

1.2.5 Impacts of musculoskeletal pain

Pain in adolescence poses significant impacts on young people, their families and society. At the individual level, adolescents are negatively impacted by pain, particularly chronic pain through school absenteeism (missed school days),[13 37-40] impaired social functioning and peer relationships (social isolation and loneliness),[13]

[37 41] restriction of activities of daily living (participation in hobbies,[13 37] sleep problems,[13 37] eating problems[13 37]), reduced participation in recreational sport/physical activity,[39] increased care seeking[38 40] and medication use,[37 38 40] and reduced health-related quality of life.[38 40 42]

An Australian study quantified the impacts of LBP in a sample of 1,283 adolescents aged 17-years across five health domains: medication use, care seeking, missed school, interference with normal activities and recreational physical activities.[40] Adolescents reported LBP caused them to miss school/work (21.3%), take medication (34.3%), and seek health professional care (37.6%). LBP also interfered with normal activities (38.8%), and physical activities (43.6%). Adolescents with chronic LBP report greater impact than adolescents with acute LBP; 41% of adolescents with acute LBP report impact to one of the health domains versus 59% of adolescents with chronic LBP. The number of health domains impacted increased with the proportion of adolescents reporting chronic LBP; 12.5% of adolescents with acute LBP were impacted in 5 health domains versus 87.5% with chronic LBP.[40] The impact of chronic MSK pain is similar to other pain types in adolescents. A Spanish study[43] of 561 schoolchildren between the ages of 8 and 16 year measured the severity (intensity/disability, graded I-IV) of chronic lower extremity pain, headache, and abdominal pain (and combinations thereof). Using the Revised Faces Pain Scale[44] (range 0-10), the mean (± standard deviation) “usual” pain intensity was 3.4 ± 2.4, and the “highest” pain intensity was 5.4 ± 3.2, for all pain groups combined. Different pain types (MSK versus other) had similar grades of severity in adolescents.[38] Pain severity was positively associated with functional disability and

negatively associated with quality of life, physical and psychosocial functioning. The latter including aspects of school, social and emotional functioning.

Emotional problems such as psychological vulnerability,[41] distress, and anxiety[45 46] frequently accompany MSK pain in adolescents. For example, a representative sample of 2,360 Norwegian school children aged 12- to 15-years found adolescents with frequent MSK pain (back pain mean score 6.8/10, limb pain mean score 6.4/10) reported a higher mean anxiety/depression score than adolescents with infrequent back or limb pain (back pain mean score 4.9/10, limb pain mean score 4.9/10).[45] MSK pain in adolescents also negatively impacts family and parental functioning.[47] A systematic review by Lewandowski et al.,[48] showed families of children with chronic MSK pain generally have poorer family functioning than the families of children without chronic MSK pain. Furthermore, parents of adolescents with MSK pain report high levels of parenting stress[49] and feelings of helplessness and rumination which can reinforce pain behaviour (attentional avoidance) in adolescents.[50] Economic impacts on the families of children with MSK pain include loss of personal time, and costs due to missed work, care seeking, medication, and hospitalisation.[47]

1.2.5.1 The global economic and disability burden of MSK pain

The global economic cost of MSK pain is very large and appears to be growing.[51] In the United States (1995-2004) estimates of direct costs of LBP range from $12billion to $90billion and the estimates for indirect costs range from $14billion to $28billion. Australian estimates for 2001 were $9.2billion ($474 per capita) in total costs, comprising direct healthcare costs of $1billion and indirect productivity costs of $8.2billion.[52] The economic burden of LBP is seldom estimated in young people. A

cohort study of 149 adolescents aged 10-17 years provides insight, estimating the 2010 economic burden of chronic pain in the United States.[53] In this study, MSK pain was most common (42.3%), followed by multiple locations of pain (35.6%), abdominal pain (14.1%) and headache (8.1%). Extrapolating from this sample the total cost of moderate to severe chronic pain in adolescents in the United States, was estimated at $19.5billion per annum.[53] The estimated mean cost of interdisciplinary pain treatment was $11,787 per participant.

In the 2016 Global Burden of Disease Study, burden due to LBP was estimated in people aged 10-14 years at 1 million years lived with disability (YLD), 2 million YLD in those aged 15-19 years, and 3 million YLD in those aged 20-24 years.[54] A recent report attributes low back and neck pain as being responsible for 5% (CI:4.1% to 6.2%) of the total YLD in 10-14 year olds (ranked 5th), 10% (8.4% to 11.9%) of the YLD in 15-19 year olds (ranked 3rd) and 12.9% (11.1% to 15.0%) of the YLD in 20-24 year olds (rank 1).[55] Hence, MSK disorders in adolescence have a tremendous impact on the lives of adolescents and young adults globally. However, there remain several research challenges and knowledge gaps that need to be addressed to advance understanding in the field.

1.2.6 Research challenges and knowledge gaps

In general MSK pain is less frequently studied in young people than in adults.[56-59] Studies on the prevalence of MSK pain and other pains in adolescents have yielded inconsistent and wide ranging estimates of back pain from 7% to 70%,[27] limb pain from 4% to 40%, headache from 8% to 85% and stomach pain from 4% to 53%.[30] Part of the inconsistency is because most studies do not specify the type of pain

being studied, whether acute, recurrent, or chronic pain.[30 60] Further limitations include poorly defined criteria for intensity, severity, and duration; heterogeneous prevalence periods, and heterogeneous participant age-range within study samples.[19 27 30 60 61] Poor methodological quality of studies is also common.[27 30 60] Methodological quality influences estimates of LBP prevalence in adolescents, with studies of better methodology typically reporting higher prevalence than poor quality studies.[60]

Even for simple issues there is uncertainty in the field. For example, there is uncertainty as to whether females experience MSK pain more frequently than males during adolescence.[19 58] Studies to date report inconsistent findings; some report higher prevalence of LBP in females compared to males, some report the opposite, and some report no difference.[27 60] To illustrate this, Kovacs conducted a population based study of 16,394 schoolchildren aged 13 to 15 years on the island of Mallorca and found the lifetime prevalence of LBP was 69.3% for girls and 50.9% for boys.[62] Burton et al., studied the natural history of LBP in 216 adolescents in England and found the lifetime prevalence of LBP for girls was 40% and 60% for boys.[63] Silva et al., reports the 1-year prevalence of LBP as 57% among 343 schoolchildren aged 12 to 15 years in Brazil, and found no difference between sexes (OR 1.13 [CI: 0.93 to 1.37]).[64] Meta-analyses have attempted to determine whether there is a relationship between sex and MSK pain prevalence. Calvo-Muñoz et al., included 27 studies (sample size range: 88 to 34,423, publication years:1984 to 2010) in a meta-analysis to determine whether gender is related to lifetime prevalence of LBP in adolescents and found no relationship.[60] In this review, only 5 studies had a high methodological quality score. In a 2016 systematic review of risk factors for MSK pain in

adolescents, Huguet et al., performed meta-analysis on 7 cohort studies (n=10,579) and found females were not more likely than males to develop MSK pain OR 1.28 (CI: 0.86 to 1.91).[25] The authors noted serious limitations due to significant heterogeneity across studies and publication bias.

Regarding LBP in particular, lifetime prevalence estimates in adolescents vary widely across countries and regions from 27% to 49%.[60] For example, lifetime prevalence of LBP has been estimated across Europe as 39% (CI: 31.4% to 47.2%) (21 studies), North America as 45.5% (CI: 25.5% to 67.0%) (3 studies), Oceania as 40.3% (CI: 12.8% to 75.7%) (1 study), Africa as 27% (CI: 11.4% to 53.2%) (2 studies), and Asia as 49% (CI: 28.5% to 69.8%) (3 studies). Lifetime prevalence is the most frequently (30 studies, n=61,732) estimated prevalence period for LBP in adolescents, and ranges from 8.6% to 64.8% across studies.[60] Expert consensus to standardise back pain definitions in prevalence studies suggest a prevalence period within the past 4 weeks (1-month) is optimal.[8] A total of 14 studies (n=23,191) have reported the 1-month prevalence of LBP in adolescents, which ranges from 2.5% to 39.8% (mean 18.3%, CI:12.8% to 22.5%, I^2=99.2%).[60] Small sample sizes and very high inconsistency across studies limit precise estimates of adolescent LBP prevalence, despite several studies in the field.

Due to insufficient research, it is unclear the extent to which MSK conditions such as back pain coexist with other pain types in adolescents. In their systematic review, King et al found only 2 studies that estimated the prevalence of combined pain at yearly and monthly prevalence periods.[30] A school-based sample of 20,745 American adolescents aged 11 to 18 years found the yearly prevalence of MSK pain

was 27%, headache 29% and stomach pain 18%.[65] The prevalence of multiple symptoms was slightly higher than the annual prevalence estimates of single pain types, with 33% of respondents reporting multiple pain types. Conversely, a population-based prevalence study of 2,173 Icelandic adolescents aged 11-12 years and 15-16 years found the monthly prevalence of at least one of the three pains (back pain, headache, and stomach pain) to be much higher at 78.2%.[66] In both studies the multiple pains varied according to age and gender, however the reason for the magnitude of these differences is unclear. The impacts of pain in adolescents also seems to be proportional to the increasing number of pain sites,[67] for example, regarding ability to concentrate at school and frequency of medication use. The impact of multiple pains on health behaviours like physical activity remains unclear.

Chapter 2 addresses issues in the study of prevalence of pain in adolescents by drawing on a large representative sample of adolescents from countries in North America and Europe. The sample size in Chapter 2 is approximately twice as large as the number of participants in all previous prevalence studies on adolescent back pain, and more than 10 times larger than the next largest study. This enables precise estimates to clarify differences in pain prevalence in adolescents by gender, age, country and multiple pain types.

1.3 Pain and physical activity in young people

1.3.1 Physical activity behaviours in adolescents

Physical activity is broadly defined as ‘any bodily movement produced by skeletal muscles that requires energy expenditure’.[68] Among other things, it is a protective health behaviour that has profound health benefits across the lifespan. In young

people, physical activity is positively associated with cardiorespiratory, metabolic and psychological health, as well as bone strength and physical fitness.[69-71] A systematic review of the health benefits of physical activity and fitness in school-aged children and youth found that the least physically active young people had 6.8 (CI: 5.1 to 9.0) times the odds of having metabolic syndrome than those who were most physically active.[69] Given the health benefits of physical activity, public health agencies and non-governmental organisations have developed guidelines and implemented numerous initiatives to promote physical activity at national and international levels. The World Health Organisation (WHO), has established global recommendations on levels of physical activity for health.[70] To be healthy, WHO recommends 'children and young people aged 5–17 years old should accumulate at least 60 minutes of moderate- to vigorous-intensity physical activity daily'. Recent estimates of physical activity across 194 countries show between 70.5% (CI: 68% to 72.9%) and 94.8% (CI: 94.6% to 95.1%) of adolescents do not meet physical activity recommendations.[72]

Physical inactivity is known to increase the risk of many non-communicable diseases. Physical inactivity is responsible for an estimated 6% of the global burden in coronary heart disease, 7% of type 2 diabetes, 10% of breast cancer, 10% of colon cancer and 9% of premature mortality.[73] Participation in physical activity mitigates the risk of many health conditions[74] including diabetes, high blood pressure, heart disease, asthma, and arthritis, as well as self-reported fair or poor health along the life-course.[74 75] Physical inactivity and other unhealthy behaviours in adolescence track predictably into adulthood.[76] The Amsterdam Growth and Health Study, followed 181 participants for 15 years and found 13 year-olds in the lowest

quartile of daily physical activity had 3.6 times the odds (CI: 2.4 to 5.4) of remaining in the lowest quartile than those in the upper three quartile at 27 years of age.[77] Unhealthy behaviours including physical inactivity become more common during adolescence in response to numerous biological, psychological, sociocultural and environmental factors[78] and this increases the odds of chronic diseases later in life.[79] In adolescence, multidimensional factors are associated with physical activity; factors include male sex (biological), self-efficacy (psychological), family and general social support (sociocultural), and access or proximity to recreation facilities (environmental).[80]

1.3.2 Impact of pain on behaviour

Pain behaviours describe the interaction between an individual with pain and the surrounding world.[81] Thoughts, beliefs and emotional expressions surrounding pain, are thought to guide pain behaviours and coping mechanisms, which also provide a measure of the impact of pain in adolescents.[32] There can be a great deal of variability between individuals' behaviours despite apparent similarities in pathophysiological processes and pain symptoms. For example, some adolescents are not impacted by their pain experience, while for others pain can be physically and mentally disabling and linked to negative behaviours such as activity avoidance and functional impairments.[32 40] Unlike acute pain, chronic pain behaviours are more frequently maladaptive. Chronic pain can generate negative thoughts and emotional distress (like catastrophising, anxiety and fear), which can impact activity and function as seen with avoiding movement in fear of pain due to movement or re-injury.[82] O'Sullivan et al., found that acute LBP interfered with physical activity in 24% of adolescents with LBP, and chronic LBP interfered with physical activity in

76% of cases.[40] Similarly, Jones el al., found recurrent LBP prevented 31% of suffers from participating in sports or physical activity compared to 2% of acute LBP sufferers.[39] This evidence suggests that chronic MSK pain in adolescents commonly impacts physical activity behaviour, which raises additional concerns about the effect of MSK pain on chronic diseases across the lifespan.

1.3.3 Research challenges and knowledge gaps

Despite the apparent link between MSK pain and physical activity in adolescents, significant knowledge gaps remain. Studies that explore this relationship do so almost exclusively by conceptualising physical activity/inactivity as an aetiological factor for the onset of MSK pain in adolescents rather than an impact thereof. There is a paucity of research that explores the association and impact of LBP on physical activity levels in adolescents.

A moderate quality[27] systematic review found 5 cross-sectional and 2 cohort studies with conflicting and unclear evidence for an association between physical activity and LBP in school children.[83] Heterogeneity of physical activity measurements, which include type, intensity, and volume, likely explains the conflicting and unclear findings. For example, one study found high leisure physical activity was associated with an increase in LBP when activity was measured as metabolic equivalent and categorised as either low, moderate or high.[84] Another study found physical activity was associated with a decreased risk of LBP when physical activity type was measured as distance walking or bicycling.[85] A third study found no association between physical activity and LBP when activity was measured via metabolic rate hours.[86]

Regarding physical activity intensity, in adults there is thought to be a U-shaped relationship between back pain and physical activity intensity.[87] A recent cohort study found no association between objectively measured sedentary activity, moderate-vigorous physical activity and vigorous physical activity and the 2-year incidence of spinal pain in adolescents, with the exception of a very small association in the most active 10% of adolescents (OR 1.03 [CI: 1.01 to 1.05]).[88] A recent study evaluated the impact of LBP on physical activity in adolescents. Coenen et al., (n = 1,249) mapped trajectories of self-reported LBP and impact on daily life in adolescents and young adults.[89] They found the prevalence of back pain interfering with recreational physical activity at age 17 years was 14%, at 20 years was 18% and at 22 years was 25%. It is currently unclear if back pain in adolescents has an impact on adolescents achieving various levels of physical activity, particularly on the recommended levels of moderate-to-vigorous or vigorous physical activities advocated for health and wellbeing.

Chapter 3 draws on a large representative sample of adolescents from countries in North America and Europe to provide new insights into the association between back pain (as well as headache, stomach ache and combinations thereof) and physical activity in adolescents.

1.4 Pubertal growth and musculoskeletal disorders

1.4.1 Adolescence and puberty

Adolescence marks a critical transitional period for human development and health.[24] [90] It is a phase of life accompanied by a series of rapid and profound physical,

psychological, and emotional changes.[90] For more than 50 years the WHO has defined adolescence as the second decade of life, i.e. 10-19 years of age.[91] However, there are wide individual variations in the start and end points of pubertal and psychosocial changes in adolescents, which are not well anchored to chronological age.[90-92]

Activation of the neuroendocrine hypothalamic-pituitary-gonadal axis is considered the biological process that marks the start of adolescence and puberty.[91 93] In industrialised countries, the evolution of societies and changes in childhood health and nutrition has seen a downward shift in the age of major pubertal events such as menarche, which has reduced by approximately 4 years to 12–13 years in the past 150 years.[91 94 95] Puberty involves the overlapping and interlinked processes of adrenarche, gonadarche and growth spurts.[91] Adrenarche occurs first between the ages of 6 and 9 years and is the maturation of the adrenal glands that produce adrenal androgens.[91 93] At sufficient concentration adrenal androgens are primarily responsible for the production of axillary and pubic hair. In gonadarche, gonadotropins trigger the development of the primary sex organs leading to reproductive competence. Staging of the external signs of gonad and pubic hair development, whether by physical assessment or self-report, is the most common method of measuring puberty.[93] The rate of growth and the age at peak height velocity provides an indication of the intensity and timing of adolescent growth spurt, respectively.[96] Peak height velocity typically occurs during puberty around age 11 years in girls and 13 years in boys.[97] Pubertal development is usually measured in two ways: (1) pubertal status is the stage of physical maturation with no reference to

age, (2) pubertal timing is the stage of physical development at a given age, where an individual is either on or off time compared to same sex peers.[98]

The endpoint of adolescence has historically been defined by the adoption of social roles such as marriage and parenting.[90-92] However, as societies have changed, adolescents must now gain more education, financial and psycho-socio-cultural assets to successfully transition into adulthood in the modern workforce and economy.[91 92] From the biological onset of puberty to social transitions of completion, adolescence occupies a greater portion of the life course than ever before. Experts in the field have recently made a compelling argument to widen the definition of adolescence to chronological ages from 10 to 24 years (as WHO currently defines young people), to better fit the concept of adolescence to a contemporary world.[91 92] During adolescence, biological processes of puberty interact within the social environment to affect adolescent development and health.

1.4.2 Puberty and health

Pubertal changes typically propel adolescents to peaks in strength, speed, and fitness analogous with good physical health. However, puberty and the timing of adrenarche also marks a transition period for increased health risks and the emergence of many physical, mental, and behavioural disorders.[92 99] For example, the global burden rate of depressive disorders increases approximately 10-fold from 28 YLD per 100,000 at age 5-9 years to 238 YLD per 100,000 at age 10-14 years, it more than doubles again to 527 YLD per 100,00 at age 15-19 years, and increases to 615 YLD per 100,000 at age 20-24 years.[100] Since 1990, the number of YLD

attributed to major depression disorders has increased by 10.8% in people aged 10-24 years.[100]

The increasing prevalence of psychosocial health disorders in adolescents is thought to relate to the growing mismatch between biological and social maturation.[90] Adolescents are now later in adopting mature social roles and responsibilities such as marriage, parenthood, and employment, at the same time earlier in initiation of sexual activity and substance use, as two examples. Substance abuse is but one adverse health behaviour associated with rising mental health disorders[55 101 102] in young people. For example, in early adolescence developmental mismatch between insufficient cognitive capacities (i.e. a physically immature brain pre-frontal cortex, which regulates self-control and mature judgement) and emotional reactions to powerful social forces (such as global connectedness through social media) may undermine health behaviours and lifestyle choices and create behavioural problems.[90 91 99] Puberty has traditionally been considered the trigger of biological processes that initiate psychological and social development.[92 99] It is now apparent that social and cultural norms and lifestyles are important drivers of development and health.

Risky health behaviours, specifically drug and alcohol abuse are the leading causes of mental health disorders in young people aged 10-24 years, explaining 14% of the global burden of mental health disorders.[100] The above example illustrates how the integration of biopsychosocial factors determine health and health behaviours in adolescents. Whether or not adolescents experience health problems may have either protective or adverse effects on disease risk in the short or long term (i.e.

establish susceptibility or resilience).[24] The timing of biological events and overly rapid change in particular are thought to adversely affect some individuals, rendering them vulnerable to certain health conditions including MSK disorders.

1.4.3 Pubertal development as a risk factor for MSK pain

Rapid or early pubertal changes and adolescent development are thought to be associated with an increased risk of MSK pain and injuries.[90] The global burden of MSK disorders, increases 6 fold from 39 YLD per 100,000 at age 5-9 years to 236 YLD per 100,000 at age 10-14 years, nearly triples to 649 per 100,00 at age 15-19 years, and increases again to 1,037 YLD per 100,000 at age 20-24 years.[100] Hence, common MSK pain conditions begin and worsen across adolescence. The increasing rate of LBP (and other pains like headache and stomach pain) during adolescence is thought to be associated with pubertal status in both boys and girls.[98 103 104] Potential mechanisms include: (1) rapid growth spurts increasing susceptibility to mechanical injuries or vulnerability to mechanical loading, and (2) gonadal hormone induced changes which may alter pain thresholds, attitudes and perceptions.[105] In addition to LBP, specific MSK disorders such as idiopathic scoliosis and slipped femoral epiphysis are thought to be linked to peak growth velocity during adolescence, as are Osteochondroses such as Scheuermann's disease, Osgood-Schlatter's disease, and osteochondritis dissecans.[106 107] Growing pains are thought to be a MSK condition linked to low bone mass during rapid bone growth.[108 109] Despite the supposed association between puberty and MSK disorders in adolescents, the field is limited by scant epidemiological evidence and knowledge gaps.

1.4.4 Research challenges and knowledge gaps

There is no comprehensive synthesis of evidence regarding the association between pubertal development and MSK pain. Only one systematic review evaluates whether puberty is a risk factor for back pain in youth, but it did not include key indicators of growth rate and timing of growth spurts which have previously been linked to MSK pains.[110] This review included only four studies (one longitudinal, three cross-sectional) in a narrative synthesis. A logistical challenge to researchers in the field is the measurement of growth rate and growth spurts. This requires longitudinal research with brief and regular follow-up intervals to estimate the timing of biological events such as peak height velocity. Another challenge is the variations to pubertal staging (4 or 5 stage categories), and the reliability of different staging measurement methods (for example staging questionnaire, telephone interviews or physical examination) across geographically diverse samples. To test aetiological mechanisms, it is also necessary to account for all important potential confounders such as demographic, biomechanical, psychosocial or lifestyle behavioural factors. There remains much uncertainty as to whether pubertal development is a risk factor for MSK pain in adolescence.

Chapter 4 evaluates the relationship between growth, maturation (as determined by markers of biological maturation) and MSK conditions in adolescents by systematically reviewing and synthesising the available literature.

1.5 Knee pain in adolescents and young people

1.5.1 Frequency, consequences and risk factors

Knee pain is the second most prevalent MSK disorder across the lifespan,[111] and the most common MSK disorder in adolescents.[10 112] At the population level, monthly or more frequent knee pain affects 32.3% (CI: 30.6% to 34.0%) of adolescents aged 12-19 years.[10] A 3-year cohort study of 1,465 schoolchildren aged 8-14 years found the annual prevalence of lower extremity pain was 50%, and of those with lower extremity pain 15% had knee pain diagnosed on clinical examination.[113] In adolescents, non-traumatic episodes of knee pain were 6 times more likely than traumatic episodes.[113] Patellofemoral pain (PFP) is the most common type of non-traumatic knee pain, typically affecting adolescents and active young adults. A recent systematic review and meta-analysis reports the pooled point prevalence of PFP in adolescent boys and girls to be 7.2%, with higher estimates in adolescent female athletes.[114] Proposed mechanisms include increased physical activity and short periods of unaccustomed repetitive or excessive loading in activities like squatting, running, climbing, and descending stairs.[114] Adolescents with knee pain report poorer knee function, lower health-related quality of life and lower self-reported health than adolescents without knee pain.[115 116] Importantly, adolescents with persistent PFP are more likely to reduce or stop sports participation.[116]

Lower extremity pain,[117] specifically knee pain,[118 119] is the most common type of pain for which adolescents and young adults seek healthcare. The high consultation rate has been attributed mostly to sprains of the knee, acquired during exercise or sports.[120] Almost 60% of adolescents who report monthly or more frequent knee pain seek medical care for their knee pain.[121] Adolescents with traumatic onset knee pain

typically experienced pain of higher severity and are more likely to seek medical care than those with non-traumatic knee pain, such as PFP.[121] While PFP leads to less medical care seeking, it more frequently persists and disables over time, compared to traumatic knee pain.[116 122]

Risk factors for adolescent knee pain are unclear due to the small number of studies focusing on non-specific knee pain, and inconsistent associations. Despite this, proposed factors include female sex, sport participation, obesity and older age.[123-126] Regarding chronic knee pain, high pain severity, female sex, leisure time sports participation and low health related quality of life are thought to be risk factors for persistent knee pain in adolescence.[116 122 124] However, there are few reliable data that describe the progression of knee pain outcomes in adolescents over time.

1.5.2 Course and prognosis

The body of evidence that underpins knowledge on the natural history, clinical course, and prognostic factors for MSK pain in adolescents is comprised of a small number of studies.[25 27-29] For other types of pain such as headache and stomach ache the evidence base is sparse or non-existent.[28 29]

A 3-year cohort of Danish school children found that adolescents who experience lower extremity pain reported on average 2.5 episodes of pain per year that lasts on average 3-weeks. Although 50% of adolescents with lower extremity pain recovered within 1-week, 20% experienced lower extremity pain for 12 or more weeks.[113] Another prospective school-based cohort study found approximately half of all adolescents with knee pain reported ongoing pain at 1-year[124] and 2-year[116] follow-

ups. Adolescents with knee pain were 4.5 (CI: 3.2 to 6.5) times more likely to have knee pain at 2-year follow-up compared to those without knee pain at baseline.[116] Adolescents diagnosed with PFP were at higher risk of developing knee pain 2-years later compared to adolescents with other types of knee pain (relative risk (RR) 1.3 [CI: 1.1 to 1.5]).

Huguet et al., recently conducted a high quality[27] systematic review on prognostic factors for persistent MSK pain in adolescents.[25] While 38 prognostic factors were identified, only 5 (negative emotional states, high functional limitations, high body mass index, female sex, and older age) have been evaluated in 3 or more cohorts, so the overall quality of evidence for each factor was rated as low or very low.[25] It is currently unclear which factors, if any, predict the clinical course of MSK pain in adolescents. Only one study has attempted to determine the prognosis of non-traumatic knee pain in adolescence, albeit in a sample consisting of both adolescents and adults aged 12-35 (n=172).[127] This study provides estimates for unspecified knee pain persisting at 1-year and 6-years of 41% and 19%, respectively. Prognostic factors identified with knee pain at 1-year follow-up were BMI>25 (OR 3.7 [CI: 1.3 to 10.4]), low/middle education level (OR 6.0 [CI: 2.0 to 18.1]), bilateral symptoms (OR 2.6 [CI: 0.9 to 7.4]) and self-reported absence of crepitus in the knee (OR 0.3 [CI: 0.1 to 1.2]).[127] However, caution is required when interpreting these findings due to high risk of bias associated with the study design and analyses. It was limited by common methodological issues of small sample size, long follow-up intervals and high loss to follow-up (42.4% of participants). No data is currently available on the short-term recovery of knee pain in clinical cohorts of young people. There is a need to track recovery with short follow-up intervals to

understand factors that contribute to initial recovery and transitions to persistent knee pain in adolescents.

1.5.3 Research challenges and knowledge gaps

To accurately and reliably measure the course and prognosis of adolescent MSK pain requires large prospective studies that are expensive and logistically challenging. For example, in a 3-year study on trajectories of adolescent pain, Dunn et al. initially contacted 4,073 adolescents and enrolled 1,996 via a 30-minute telephone survey (recruitment rate 49%).[128] Follow-ups occurred every three months via prepaid-return postal questionnaire (a total of 10 follow-ups). At each follow-up, non-responders were contacted by telephone and repeat envelopes were sent if needed. The final follow-up telephone survey (a replicate of baseline) was completed by 1,336 adolescents (follow-up rate 67%). Participants were compensated $5 (voucher) at baseline and after each postal questionnaire, and compensated $10 for completion of the final follow-up[128] This example illustrates several challenges facing longitudinal studies that track the course of pain over time: (1) they are burdensome on the researcher's and participant's time, (2) they are logistically complex with many participants being tracked across multiple time-points for a long period, (3) rates of participant attrition are high and (4) they are expensive in terms of participant remunerations and research staff costs.

Measurement of adolescent MSK pain is typically based on self-reported episode frequency, without measurement of intensity or impact. For example, at 3-months follow-up Dunn et al. asked participants whether pain was present ''almost every day," ''more than half the days" or ''fewer than half the days" in the past 3 months.[128]

Participants were then grouped into two categories for analysis: (1) pain on more than half the days in the last 3 months (including almost every day), (2) pain on less than half the days in the last 3 months or no pain in last 3 months, at each follow-up time point. Hence, the severity of pain conditions (i.e. pain intensity or interference with ADLs) was not recorded.

Follow-up measurements of MSK pain have traditionally been taken too infrequently to track the initial rapid improvement that commonly occurs in adolescent MSK pain cases. Fuglkjær et al., have recently overcome this problem by collecting measures at weekly time intervals.[113] Communication technology, specifically mobile telephone text message questions (SMS questions), were used to monitor MSK pain in 1,465 adolescents over 3-years. The SMS questions were sent to parents every Sunday evening: (1) about presence or absence of MSK pain in their child and, (2) about the child's sports participation. If a parent reported pain in their child, they were contacted by telephone and interviewed about the nature of their child's pain. While this study uses technology to overcome the logistical burden of shorter duration follow-up points it also has some limitations as it directs SMS questions to parents rather than children. It is well established that parents tend to poorly interpret and underrate the impact of pain and injury in their children.[37 129-131] In this study there was poor concordance of parent versus child pain measures, children commonly experienced pain that was not reported by their parents.[132] Finally, this study was not conducted in a clinical sample of adolescents, and no published research exists that reports on the clinical course (i.e. recruited from a clinical sample) of low back or knee pain in adolescents over time.[25 27] There is a need to devise research studies

that are logistically feasible to capture the necessary information to better inform clinical decision making.

Chapter 5 addresses this need by conducting a feasibility study that uses electronic methods of data collection to follow the short-term clinical course of knee pain in adolescents.

1.6 Anterior cruciate ligament injuries in young people

1.6.1 Epidemiology

The anterior cruciate ligament (ACL) is an important stabilising structure inside the knee, protecting the joint against excessive translational and rotational movements. Disruption of the ACL is of concern as it renders the knee vulnerable to pathological movements, particularly during dynamic physical activities. In adolescents, the knee is the most common site of traumatic injury causing pain.[133] While knee injuries are typically from minor trauma, a tear to the ACL typically follows major trauma. Most commonly (60%), ACL injuries follow non-contact trauma[134] at the knee via side-stepping, pivoting or decelerating during sporting activities. The remaining injuries follow traumatic contact[134] (40%) either directly at the knee or at another body site such as the hip while the foot is in contact with the ground. Surgical reconstruction data provides a method to estimate the annual incidence of ACL injuries.[135 136] Albeit, national registries of hospital administration and surgery are known to underestimate the true population incidence of injury occurrence.[137] The National Hospital Morbidity Database of the Australian Institute of Health and Welfare shows the overall incidence of ACL injury is greatest among 15 to 24-year olds.[136] The peak incidence of ACL injuries for males was 20 to 24-year olds (283 per 100,000 population); and

for females, 15 to 19-years olds (164 per 100,000 population).[136] In countries where females participate more frequently in high risk sports, they have a higher national incidence rate of ACL injury than males.[138] Australian data are consistent with recent studies from elsewhere;[139 140] recent trends over the past two decades show the greatest annual growth in the incidence of ACL surgeries was in people aged 5 to 14-years (boys, 7.7%; girls, 8.8%).[136] The recent growth in ACL reconstruction rates in young people has been attributed to several factors,[140-142] including: (1) improved methods of diagnosis,[135] (2) higher/more intense participation rates in organised sports at a younger age, and (3) increased participation at a higher level, particularly in high risk sports with pivoting, jumping and rapid deceleration, such as soccer, basketball and Australian rules football.[134 143 144] However, low quality evidence underpins knowledge pertaining to risk factors for ACL injury.[145] In addition to sport participation, other proposed risk factors for ACL injury include female sex, and anatomic, hormonal, neuromuscular, and biomechanical factors.[146] Females have a higher rate of ACL injury than males when exposed to the same sport.[138] Girls also appear to be more severely affected by ACL injury, more often requiring surgery and not returning to sports participation.[147 148]

1.6.2 Impact of anterior cruciate ligament injury

ACL injuries in young people have important short and long-term impacts. The short-term impacts of ACL injuries include acute knee pain and disability, time lost from school and sport affecting academic performance and mental health,[149] as well as healthcare use, surgery and associated costs. Trentacosta et al., measured the school impacts of ACL injury on adolescent athletes that underwent ACL reconstruction and found on average they missed 9.5 ± 17.4 days of school, with all

cases reporting negative impacts on their grades.[150] In a one-season prospective study of 1,263 high school girls, Hewett et al., found that every case of ACL injury was season ending for soccer and basketball participation.[151] Traumatic knee pain[118] [119] is the most common pain condition for which adolescents and young adults seek medical care.[106] [109] The high consultation rate has been attributed mostly to sprains of the knee acquired during exercise or sports.[120] In Australia, hospital-admissions data shows the rate of adolescent ACL injury has increased from 2.7 to 6.8 injuries per 100,000 population between 2005 and 2015.[152] Of those adolescents admitted with ACL injury, 98.4% were managed by surgical intervention, 77.2% of patients required 2 days in hospital (the other 22.8% spent 2-7 days).[135] The remaining 1.6% of ACL injury cases were managed non-surgically via allied health (physiotherapy) interventions. Trentacosta et al., found American adolescent athletes that underwent ACL reconstruction attended physical therapy on average 2.9 ± 0.5 times per week for 4.8 ± 2.3 months.[150] Gianotti et al., conducted a population level study in New Zealand 2000-2005 and reported the average costs and number of treatment/rehabilitation visits for ACL injuries as an indicator of severity.[134] On average, ACL injuries required 14.3 ± 0.2 pre-surgery visits, 12.5 ± 0.1 post-surgery visits, at a total mean cost of $11,157 ± $110 per ACL injury.[134] In the long term, athletes with ACL injuries are more likely to develop knee osteoarthritis and subsequent pain, disability and reduction in sport participation. A systematic review of long-term follow-up studies found a 50% probability of knee osteoarthritis 20 years post ACL injury.[153] The increasing trend of ACL injuries in adolescents has long term consequences, with more people at risk of developing osteoarthritis and associated health problems.[154] ACL injuries in children and adolescents translate to earlier cases of degenerative knee pain and functional limitations, starting in the twenties

and thirties.[149] Given the potential impacts of ACL injury, consensus of expert opinion recommends timely diagnosis and effective management to protect vulnerable knee structures like the meniscus and hyaline cartilage from further damage (secondary injury).[155]

1.6.3 Diagnosis

Diagnosis is currently thought to provide the basis of clinical decision-making, the primary guide of treatment choice, and the core function of primary care.[156] [157] In current models of practice, a clinician must first identify the presence, or absence, of clinical features of ACL injuries. In this approach a thorough clinical history, physical examination and imaging as indicated enables a clinician to construct a clinical picture to make an accurate diagnosis. Various expert commentators have described indicative clinical characteristics of ACL injury.[149] History findings include pain, knee effusion, reduced range of motion, difficulty weight bearing, a pop at the time of the injury, and giving way or difficulty with cutting, twisting or jumping sports. Physical examination findings include acute effusion, and a positive Lachman, anterior drawer and/or pivot shift test. Imaging is commonly sought, first X-ray to rule out fracture, followed by magnetic resonance imaging (MRI) to confirm the diagnosis.

Recently, the International Olympic Committee (IOC) published a consensus statement on prevention, diagnosis and management of paediatric ACL injuries.[155] An expert group of physiotherapists and orthopaedic surgeons aimed to provide a comprehensive evidence-informed summary to support clinicians. They advocate for timely and accurate diagnosis and contend that a thorough history and clinical examination will enable the clinician to make an accurate diagnosis. The consensus

statement offers three clinical pearls: (1) haemarthrosis is an important clue for paediatric ACL injury; (2) diagnosis in children can be more challenging because of poor recall, greater pre-injury laxity, and difficulty with MRI interpretation; (3) there is an increased likelihood of different knee injuries associated with an immature skeleton (e.g. epiphysiolysis). The IOC statement does not specifically mention the accuracy of clinical tests. Instead, it suggests there is limited performance of clinical tests (broadly) as well as MRI, citing a single study by Kocher et al.[158] This study consecutively enrolled participants in the paediatric age range (mean 11.9 years, range 3-16 years) and assessed clinical diagnosis as an index test, on the basis of composite history, physical examination, and standard radiographs. Therefore, the discrete elements of clinical diagnosis (namely, history and physical examination) were not evaluated. There is some discrepancy between traditional expert opinion and the more recent expert consensus statement. There remains uncertainty surrounding the accuracy of clinical tests for the diagnosis of ACL injuries, which may explain high rates of missed initial and delayed diagnoses.[159 160] Diagnostic uncertainty, defined as “the subjective inability of a clinician to provide a clear pathological cause and label that explains symptoms and leads to a selection of an intervention to cure a problem,” has important implications for people seeking care as it is thought to negatively impact the course of pain.[161]

1.6.4 Diagnostic research, challenges and knowledge gaps

Diagnostic accuracy research aims to assess a test’s ability to rule in (confirm) or rule out (exclude) a disease. It does this by comparing the performance of an index test (such as a clinical test for ACL injury) against a reference test (i.e. a ‘gold standard’) that is thought to be the best way to diagnose a target condition (e.g.

arthroscopic visualisation of the ACL). The participants in a primary diagnostic accuracy study are categorised according to the outcome of both the index test and reference test as either truly positive, falsely positive, truly negative, or falsely negative, from which summary statistics such as sensitivity and specificity can be calculated.

Five systematic reviews have been conducted to summarise and synthesise research on the accuracy of clinical tests for the diagnosis of ACL injury.[162-166] These reviews generally provide positive accounts of evidence in favour of the diagnostic accuracy of clinical examination methods. Reviewers frequently qualify the accuracy of physical tests according to the experience or type of healthcare provider. For example Solomon et al., state the accuracy of tests when "performed by orthopaedic physician are highly predictive."[165] Jackson et al, share this sentiment about the accuracy of physical tests, which "is remarkably good in the hands of a trained examiner."[163] Scholten et al., explain the rationale for this, "because primary care physicians will be less experienced in performing these tests, the tests will presumably be less accurate in a primary care setting."[164] However, systematic reviews to date have not differentiated primary care from other care settings to test this hypothesis.

The reviews to date provide inconsistent recommendations about the accuracy of specific physical tests used to diagnose ACL injuries. For example, Benjaminse et al., state "based on this meta-analysis, our study clearly indicates that the Lachman test has a high diagnostic accuracy in terms of sensitivity and specificity,"[162] which differs from Scholten et al., who also performed meta-analysis where "the pivot shift

test seems to have favourable positive predictive value, and the Lachman's test good negative predictive value".[164] Scholten et al., also state that the anterior drawer test is of unproven value. Hence, there is much uncertainty around the use of specific clinical tests, particularly when applied to young populations (considering differences in young and adult joints) and in primary care settings where most people with knee injuries initially present.

Two of the most important challenges to the field are the problems of verification bias[167] and selection bias.[168] Verification bias occurs when a study includes only participants that have been 'verified' by a reference test. In practice, this means that only a subset of patients gets the reference test, usually because it is expensive, invasive or risky. Verification bias generally results in overestimation of the accuracy of an index test.[167] Selection bias occurs when a diagnostic test is evaluated in a less representative sample, which results in inaccurate findings.[168] While this has been identified as a problem in systematic reviews[162 164 166] there has been no attempt to control for this in the selection of included studies. Three of the five reviews to date performed appraisal of methodological quality of included studies,[162 164 166] however, none report the accuracy of clinical tests alongside the risk of bias (RoB) within a given study. This is important as biased studies report inflated accuracy estimates, for example the sensitivity of a test will be higher when practitioners conducting the clinical test are not blind the to the results of the reference standard.[166] Recent advances in tools that appraise quality in diagnostic accuracy studies, such as the QUADAS-2 enable researchers to more transparently rate RoB and applicability concerns in studies that evaluate the diagnostic accuracy of clinical tests.[169]

Chapter 6 is a systematic review that evaluates the accuracy of clinical tests in the diagnosis of ACL injury and appraises the quality of research evaluating these tests.

1.7 Thesis aims

This thesis aims to examine issues surrounding pain and injury in adolescents and young adults.

Specifically, the thesis aims to:

1. Estimate the prevalence of back pain, headache and stomach pain in adolescents and explore the extent to which these pain conditions coexist.
2. Evaluate whether back pain, headache and stomach pain, or combinations thereof affect the likelihood of achieving guideline recommendations for moderate-vigorous physical activity.
3. Determine whether there is a relationship between physical growth rate and/or stage of pubertal development, and musculoskeletal pain in adolescents.
4. Determine the feasibility of recruiting, retaining, and following up a prospective cohort of young people with knee pain presenting to primary care, using electronic data collection methods (SMS and online questionnaire).
5. Evaluate the diagnostic accuracy of clinical tests for the diagnosis of ACL injury and describe the quality of research evaluating these tests.

1.8 References

1. Merskey H, Albe-Fessard DG, Bonica JJ, et al. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain* 1979;6:249.
2. Jaaniste T, Noel M, von Baeyer CL. Young children's ability to report on past, future, and hypothetical pain states: a cognitive-developmental perspective. *Pain* 2016;157:2399-409.
3. Harkness EF, Macfarlane GJ, Silman AJ, et al. Is musculoskeletal pain more common now than 40 years ago?: two population-based cross-sectional studies. *Rheumatology (Oxford)* 2005;44:890-95.
4. Treede R-D, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain* 2015;156:1003-07.
5. Tighe P, Buckenmaier IIICC, Boezaart AP, et al. Acute Pain Medicine in the United States: A Status Report. *Pain Med* 2015;16:1806-26.
6. Merskey H, Bogduk N. Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. Seatle, USA: IASP Press 1994.
7. Von Korff M, Dworkin SF, Le Resche L. Graded chronic pain status: an epidemiologic evaluation. *Pain* 1990;40:279-91.
8. Dionne CE, Dunn KM, Croft PR, et al. A consensus approach toward the standardization of back pain definitions for use in prevalence studies. *Spine (Phila Pa 1976)* 2008;33:95-103.
9. Hoy D, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012;64:2028-37.

10. Rathleff MS, Roos EM, Olesen JL, et al. High prevalence of daily and multi-site pain – a cross-sectional population-based study among 3000 Danish adolescents. *BMC Pediatr* 2013;13:191.
11. Roth-Isigkeit A, Thyen U, Raspe H, et al. Reports of pain among German children and adolescents: an epidemiological study. *Acta Paediatr* 2004;93:258-63.
12. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, et al. Pain in children and adolescents: a common experience. *Pain* 2000;87:51-8.
13. Roth-Isigkeit A, Thyen U, Stoven H, et al. Pain among children and adolescents: restrictions in daily living and triggering factors. *Pediatrics* 2005;115:e152-62.
14. Kelsey JL, Hochberg MC. Epidemiology of chronic musculoskeletal disorders. *Annu Rev Public Health* 1988;9:379-401.
15. Hill JJ, Keating JL. A systematic review of the incidence and prevalence of low back pain in children. *Phys Ther Rev* 2009;14:272-84.
16. Hill JJ, Keating JL. Risk factors for the first episode of low back pain in children are infrequently validated across samples and conditions: a systematic review. *J Physiother* 2010;56:237-44.
17. Kjaer P, Wedderkopp N, Korsholm L, et al. Prevalence and tracking of back pain from childhood to adolescence. *BMC Musculoskelet Disord* 2011;12:98.
18. Leboeuf-Yde C, Kyvik KO. At what age does low back pain become a common problem? A study of 29,424 individuals aged 12-41 years. *Spine (Phila Pa 1976)* 1998;23:228-34.
19. Jeffries LJ, Milanese SF, Grimmer-Somers KA. Epidemiology of adolescent spinal pain: a systematic overview of the research literature. *Spine (Phila Pa 1976)* 2007;32:2630-7.

20. Hestbaek L, Leboeuf-Yde C, Kyvik KO. Is comorbidity in adolescence a predictor for adult low back pain? A prospective study of a young population. *BMC Musculoskelet Disord* 2006;7:29.

21. Hestbaek L, Leboeuf-Yde C, Kyvik KO, et al. The course of low back pain from adolescence to adulthood: eight-year follow-up of 9600 twins. *Spine (Phila Pa 1976)* 2006;31:468-72.

22. Jones GT, Silman AJ, Power C, et al. Are common symptoms in childhood associated with chronic widespread body pain in adulthood?: Results from the 1958 british birth cohort study. *Arthritis Rheum* 2007;56:1669-75.

23. Dunn KM. Extending conceptual frameworks: life course epidemiology for the study of back pain. *BMC Musculoskelet Disord* 2010;11:23.

24. Kuh D, Ben-Shlomo Y, Lynch J, et al. Life course epidemiology. *J Epidemiol Community Health* 2003;57:778-83.

25. Huguet A, Tougas ME, Hayden J, et al. Systematic review with meta-analysis of childhood and adolescent risk and prognostic factors for musculoskeletal pain. *Pain* 2016;157:2640-56.

26. Calvo-Munoz I, Kovacs FM, Roque M, et al. Risk Factors for Low Back Pain in Childhood and Adolescence: A Systematic Review. *Clin J Pain* 2018;34:468-84.

27. Kamper SJ, Yamato TP, Williams CM. The prevalence, risk factors, prognosis and treatment for back pain in children and adolescents: An overview of systematic reviews. *Best Pract Res Clin Rheumatol* 2016;30:1021-36.

28. Huguet A, Olthuis J, McGrath PJ, et al. Systematic review of childhood and adolescent risk and prognostic factors for persistent abdominal pain. *Acta Paediatr* 2017;106:545-53.

29. Huguet A, Tougas ME, Hayden J, et al. Systematic Review of Childhood and Adolescent Risk and Prognostic Factors for Recurrent Headaches. *J Pain* 2016;17:855-73.e8.

30. King S, Chambers CT, Huguet A, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. *Pain* 2011;152:2729-38.

31. Onate JA, Everhart JS, Clifton DR, et al. Physical Exam Risk Factors for Lower Extremity Injury in High School Athletes: A Systematic Review. *Clin J Sport Med* 2016;26:435-44.

32. O'Sullivan P, Smith A, Beales D, et al. Understanding Adolescent Low Back Pain From a Multidimensional Perspective: Implications for Management. *J Orthop Sports Phys Ther* 2017;47:741-51.

33. Petre B, Torbey S, Griffith JW, et al. Smoking increases risk of pain chronification through shared corticostriatal circuitry. *Hum Brain Mapp* 2015;36:683-94.

34. Andreucci MA, Campbell P, Dunn KM. Are Sleep Problems a Risk Factor for the Onset of Musculoskeletal Pain in Children and Adolescents? A Systematic Review. *Sleep* 2017;40

35. Yamato TP, Maher CG, Traeger AC, et al. Do schoolbags cause back pain in children and adolescents? A systematic review. *Br J Sports Med* 2018;52:1241-45.

36. McGrath PJ, Walco GA, Turk DC, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J Pain* 2008;9:771-83.

37. Haraldstad K, Sorum R, Eide H, et al. Pain in children and adolescents: prevalence, impact on daily life, and parents' perception, a school survey. *Scand J Caring Sci* 2011;25:27-36.

38. Huguet A, Miro J. The severity of chronic pediatric pain: an epidemiological study. *J Pain* 2008;9:226-36.

39. Jones MA, Stratton G, Reilly T, et al. A school-based survey of recurrent non-specific low-back pain prevalence and consequences in children. *Health Educ Res* 2004;19:284-89.

40. O'Sullivan PB, Beales DJ, Smith AJ, et al. Low back pain in 17 year olds has substantial impact and represents an important public health disorder: a cross-sectional study. *BMC Public Health* 2012;12:100.

41. Forgeron PA, King S, Stinson JN, et al. Social functioning and peer relationships in children and adolescents with chronic pain: A systematic review. *Pain Res Manag* 2010;15:27-41.

42. Pellisé F, Balagué F, Rajmil L, et al. Prevalence of low back pain and its effect on health-related quality of life in adolescents. *Arch Pediatr Adolesc Med* 2009;163:65-71.

43. Huguet A, Stinson JN, McGrath PJ. Measurement of self-reported pain intensity in children and adolescents. *J Psychosom Res* 2010;68:329-36.

44. Hicks CL, von Baeyer CL, Spafford PA, et al. The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain* 2001;93:173-83.

45. Larsson B, Sund AM. Emotional/behavioural, social correlates and one-year predictors of frequent pains among early adolescents: influences of pain characteristics. *Eur J Pain* 2007;11:57-65.

46. Merlijn VP, Hunfeld JA, van der Wouden JC, et al. Psychosocial factors associated with chronic pain in adolescents. *Pain* 2003;101:33-43.

47. Palermo TM. Impact of recurrent and chronic pain on child and family daily functioning: a critical review of the literature. *J Dev Behav Pediatr* 2000;21:58-69.

48. Lewandowski AS, Palermo TM, Stinson J, et al. Systematic Review of Family Functioning in Families of Children and Adolescents With Chronic Pain. *J Pain* 2010;11:1027-38.

49. Eccleston C, Crombez G, Scotford A, et al. Adolescent chronic pain: patterns and predictors of emotional distress in adolescents with chronic pain and their parents. *Pain* 2004;108:221-29.

50. Vervoort T, Trost Z, Van Ryckeghem DML. Children's selective attention to pain and avoidance behaviour: The role of child and parental catastrophizing about pain. *Pain* 2013;154:1979-88.

51. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008;8:8-20.

52. Walker BF, Muller R, Grant WD. Low back pain in Australian adults: the economic burden. *Asia Pac J Public Health* 2003;15:79-87.

53. Groenewald CB, Essner BS, Wright D, et al. The Economic Costs of Chronic Pain Among a Cohort of Treatment-Seeking Adolescents in the United States. *J Pain* 2014;15:925-33.

54. Vos T, Abajobir AA, Abbafati C, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390:1211-59.

55. Mokdad AH, Forouzanfar MH, Daoud F, et al. Global burden of diseases, injuries, and risk factors for young people's health during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2016;387:2383-401.

56. Cohen E, Uleryk E, Jasuja M, et al. An absence of pediatric randomized controlled trials in general medical journals, 1985–2004. *J Clin Epidemiol* 2007;60:118-23.

57. Eccleston C, Malleson P. Managing chronic pain in children and adolescents. *BMJ* 2003;326:1408.

58. McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol* 2007;21:403-25.

59. Michaleff ZA, Kamper SJ, Maher CG, et al. Low back pain in children and adolescents: a systematic review and meta-analysis evaluating the effectiveness of conservative interventions. *Eur Spine J* 2014;23:2046-58.

60. Calvo-Munoz I, Gomez-Conesa A, Sanchez-Meca J. Prevalence of low back pain in children and adolescents: a meta-analysis. *BMC Pediatr* 2013;13:14.

61. Briggs AM, Smith AJ, Straker LM, et al. Thoracic spine pain in the general population: prevalence, incidence and associated factors in children, adolescents and adults. A systematic review. *BMC Musculoskelet Disord* 2009;10:77.

62. Kovacs FM, Gestoso M, Gil del Real MT, et al. Risk factors for non-specific low back pain in schoolchildren and their parents: a population based study. *Pain* 2003;103:259-68.

63. Burton AK, Clarke RD, McClune TD, et al. The natural history of low back pain in adolescents. *Spine (Phila Pa 1976)* 1996;21:2323-8.

64. Silva MROGCM, Badaró AFV, Dall'Agnol MM. Low back pain in adolescent and associated factors: A cross sectional study with schoolchildren. *Braz J Phys Ther* 2014;18:402-09.

65. Rhee H, Miles MS, Halpern CT, et al. Prevalence of recurrent physical symptoms in U.S. adolescents. *Pediatr Nurs* 2005;31:314-9, 50.

66. Kristjánsdóttir G. Prevalence of pain combinations and overall pain:A study of headache, stomach pain and back pain among school-children. *Scand J Soc Med* 1997;25:58-63.

67. Smedbråten BK, Natvig B, Rutle O, et al. Self-reported bodily pain in schoolchildren. *Scand J Rheumatol* 1998;27:273-76.

68. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985;100:126-31.

69. Janssen I, LeBlanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. *Int J Behav Nutr Phys Act* 2010;7:40.

70. World Health Organization. Global Recommendations on Physical Activity for Health. 2010 https://www.ncbi.nlm.nih.gov/books/NBK305057/ (Accessed 3 Aug 2018).

71. Ekelund U, Luan J, Sherar LB, et al. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. *JAMA* 2012;307:704-12.

72. World Health Organization. Prevalence of insufficient physical activity among school going adolescents. 2015

http://apps.who.int/gho/data/node.main.A893ADO?lang=en (Accessed 3 Aug 2018).

73. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 2012;380:219-29.

74. Humphreys BR, McLeod L, Ruseski JE. Physical activity and health outcomes: evidence from Canada. *Health Econ* 2014;23:33-54.

75. Granger E, Di Nardo F, Harrison A, et al. A systematic review of the relationship of physical activity and health status in adolescents. *Eur J Public Health* 2017;27:100-06.

76. Hirvensalo M, Lintunen T. Life-course perspective for physical activity and sports participation. *Eur Rev Aging Phys Act* 2011;8:13-22.

77. Twisk JW, Kemper HC, van Mechelen W. Tracking of activity and fitness and the relationship with cardiovascular disease risk factors. *Med Sci Sports Exerc* 2000;32:1455-61.

78. Sterdta E, Lierscha S, Walter U. Correlates of physical activity of children and adolescents: A systematic review of reviews. *Health Educ J* 2014;73:72-89.

79. Spring B, Moller AC, Coons MJ. Multiple health behaviours: overview and implications. *J Public Health* 2012;34:i3-i10.

80. Bauman AE, Reis RS, Sallis JF, et al. Correlates of physical activity: why are some people physically active and others not? *Lancet* 2012;380:258-71.

81. Vlaeyen JWS, Van Eek H, Groenman NH, et al. Dimensions and components of observed chronic pain behavior. *Pain* 1987;31:65-75.

82. Asmundson GJG, Noel M, Petter M, et al. Pediatric fear-avoidance model of chronic pain: Foundation, application and future directions. *Pain Res Manag* 2012;17:397-405.

83. Sitthipornvorakul E, Janwantanakul P, Purepong N, et al. The association between physical activity and neck and low back pain: a systematic review. *Eur Spine J* 2011;20:677-89.

84. Kujala UM, Taimela S, Viljanen T. Leisure physical activity and various pain symptoms among adolescents. *Br J Sports Med* 1999;33:325-8.

85. Sjolie AN. Associations between activities and low back pain in adolescents. *Scand J Med Sci Sports* 2004;14:352-9.

86. Diepenmaat AC, van der Wal MF, de Vet HC, et al. Neck/shoulder, low back, and arm pain in relation to computer use, physical activity, stress, and depression among Dutch adolescents. *Pediatrics* 2006;117:412-6.

87. Heneweer H, Vanhees L, Picavet HSJ. Physical activity and low back pain: A U-shaped relation? *Pain* 2009;143:21-25.

88. Aartun E, Boyle E, Hartvigsen J, et al. The most physically active Danish adolescents are at increased risk for developing spinal pain: a two-year prospective cohort study. *BMJ Open Sport Exerc Med* 2016;2

89. Coenen P, Smith A, Paananen M, et al. Trajectories of Low Back Pain From Adolescence to Young Adulthood. *Arthritis Care Res* 2017;69:403-12.

90. Patton GC, Viner R. Pubertal transitions in health. *Lancet* 2007;369:1130-39.

91. Sawyer SM, Azzopardi PS, Wickremarathne D, et al. The age of adolescence. *Lancet Child Adolesc Health* 2018;2:223-28.

92. Patton GC, Sawyer SM, Santelli JS, et al. Our future: a Lancet commission on adolescent health and wellbeing. *Lancet* 2016;387:2423-78.

93. Dorn LD, Biro FM. Puberty and Its Measurement: A Decade in Review. *J Res Adolesc* 2011;21:180-95.

94. Juul A, Teilmann G, Scheike T, et al. Pubertal development in Danish children: comparison of recent European and US data. *Int J Androl* 2006;29:247-55; discussion 86-90.

95. Parent AS, Teilmann G, Juul A, et al. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. *Endocr Rev* 2003;24:668-93.

96. Malina RM, Bouchard C, Bar-Or O. Growth, Maturation, and Physical Activity: Human Kinetics 2004.

97. Tanner JM, Whitehouse RH, Marubini E, et al. The adolescent growth spurt of boys and girls of the Harpenden Growth Study. *Ann Hum Biol* 1976;3:109-26.

98. Rhee H. Relationships between physical symptoms and pubertal development. *J Pediatr Health Care* 2005;19:95-103.

99. Patton GC, Olsson CA, Skirbekk V, et al. Adolescence and the next generation. *Nature* 2018;554:458.

100. Institute for Health Metrics and Evaluation (IHME). GBD Compare. 2016 http://vizhub.healthdata.org/gbd-compare (Accessed 3 Aug 2018).

101. National Institute on Drug Abuse. Common Comorbidities with Substance Use Disorders. 2018 https://www.drugabuse.gov/publications/research-reports/common-comorbidities-substance-use-disorders (Accessed 4 July 2018).

102. Kamper SJ, Michaleff ZA, Campbell P, et al. Back pain, mental health and substance use are associated in adolescents. *J Public Health (Oxf)* 2018

103. LeResche L, Mancl LA, Drangsholt MT, et al. Relationship of pain and symptoms to pubertal development in adolescents. *Pain* 2005;118:201-9.

104. Wedderkopp N, Bo Andersen L, Froberg K, et al. Back pain reporting in young girls appears to be puberty-related. *BMC Musculoskelet Disord* 2005;6:52.

105. Riley JL, 3rd, Robinson ME, Wise EA, et al. A meta-analytic review of pain perception across the menstrual cycle. *Pain* 1999;81:225-35.

106. Burwell RG. Aetiology of idiopathic scoliosis: current concepts. *Pediatr Rehabil* 2003;6:137-70.

107. Puylaert D, Dimeglio A, Bentahar T. Staging puberty in slipped capital femoral epiphysis: importance of the triradiate cartilage. *J Pediatr Orthop* 2004;24:144-7.

108. Friedland O, Hashkes PJ, Jaber L, et al. Decreased bone speed of sound in children with growing pains measured by quantitative ultrasound. *J Rheumatol* 2005;32:1354-7.

109. Harreby M, Neergaard K, Hesselsoe G, et al. Are radiologic changes in the thoracic and lumbar spine of adolescents risk factors for low back pain in adults? A 25-year prospective cohort study of 640 school children. *Spine (Phila Pa 1976)* 1995;20:2298-302.

110. Lardon A, Leboeuf-Yde C, Le Scanff C, et al. Is puberty a risk factor for back pain in the young? a systematic critical literature review. *Chiropr Man Therap* 2014;22:27.

111. Urwin M, Symmons D, Allison T, et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. *Ann Rheum Dis* 1998;57:649-55.

112. Rathleff MS. Patellofemoral pain during adolescence: much more prevalent than appreciated. *Br J Sports Med* 2016;50:831-32.

113. Fuglkjær S, Hartvigsen J, Wedderkopp N, et al. Musculoskeletal extremity pain in Danish school children – how often and for how long? The CHAMPS study-DK. *BMC Musculoskelet Disord* 2017;18:492.

114. Smith BE, Selfe J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: A systematic review and meta-analysis. *PLoS One* 2018;13:e0190892.

115. Rathleff CR, Baird WN, Olesen JL, et al. Hip and knee strength is not affected in 12-16 year old adolescents with patellofemoral pain--a cross-sectional population-based study. *PLoS One* 2013;8:e79153.

116. Rathleff MS, Rathleff CR, Olesen JL, et al. Is Knee Pain During Adolescence a Self-limiting Condition? Prognosis of Patellofemoral Pain and Other Types of Knee Pain. *Am J Sports Med* 2016;44:1165-71.

117. Henschke N, Harrison C, McKay D, et al. Musculoskeletal conditions in children and adolescents managed in Australian primary care. *BMC Musculoskelet Disord* 2014;15:164.

118. Jordan KP, Kadam UT, Hayward R, et al. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. *BMC Musculoskelet Disord* 2010;11:144-44.

119. Tan A, Strauss VY, Protheroe J, et al. Epidemiology of paediatric presentations with musculoskeletal problems in primary care. *BMC Musculoskelet Disord* 2018;19:40.

120. van der Waal JM, Bot SDM, Terwee CB, et al. The incidences of and consultation rate for lower extremity complaints in general practice. *Ann Rheum Dis* 2006;65:809-15.

121. Rathleff MS, Skuldbol SK, Rasch MN, et al. Care-seeking behaviour of adolescents with knee pain: a population-based study among 504 adolescents. *BMC Musculoskelet Disord* 2013;14:225.

122. El-Metwally A, Salminen JJ, Auvinen A, et al. Lower limb pain in a preadolescent population: prognosis and risk factors for chronicity--a prospective 1- and 4-year follow-up study. *Pediatrics* 2005;116:673-81.

123. Pereira DS, Castro SS, Bertoncello D, et al. Relationship of musculoskeletal pain with physical and functional variables and with postural changes in school children from 6 to 12 years of age. *Braz J Phys Ther* 2013;17:392-400.

124. Rathleff CR, Olesen JL, Roos EM, et al. Half of 12-15-year-olds with knee pain still have pain after one year. *Dan Med J* 2013;60:A4725.

125. Saes MO, Soares MCF. Knee pain in adolescents: prevalence, risk factors, and functional impairment. *Braz J Phys Ther* 2017;21:7-14.

126. Vahasarja V. Prevalence of chronic knee pain in children and adolescents in northern Finland. *Acta Paediatr* 1995;84:803-5.

127. Kastelein M, Luijsterburg PAJ, Heintjes EM, et al. The 6-year trajectory of non-traumatic knee symptoms (including patellofemoral pain) in adolescents and young adults in general practice: a study of clinical predictors. *Br J Sports Med* 2015;49:400-05.

128. Dunn KM, Jordan KP, Mancl L, et al. Trajectories of pain in adolescents: A prospective cohort study. *Pain* 2011;152:66-73.

129. Goubert L, Vervoort T, Cano A, et al. Catastrophizing about their children's pain is related to higher parent-child congruency in pain ratings: an experimental investigation. *Eur J Pain* 2009;13:196-201.

130. Sundblad GM, Saartok T, Engstrom LM. Child-parent agreement on reports of disease, injury and pain. *BMC Public Health* 2006;6:276.

131. Waters E, Stewart-Brown S, Fitzpatrick R. Agreement between adolescent self-report and parent reports of health and well-being: results of an epidemiological study. *Child Care Health Dev* 2003;29:501-9.

132. Kamper SJ, Dissing KB, Hestbaek L. Whose pain is it anyway? Comparability of pain reports from children and their parents. *Chiropr Man Therap* 2016;24:24.

133. Kraus T, Švehlík M, Singer G, et al. The epidemiology of knee injuries in children and adolescents. *Arch Orthop Trauma Surg* 2012;132:773-79.

134. Gianotti SM, Marshall SW, Hume PA, et al. Incidence of anterior cruciate ligament injury and other knee ligament injuries: a national population-based study. *J Sci Med Sport* 2009;12:622-7.

135. Shaw L, Finch CF. Trends in Pediatric and Adolescent Anterior Cruciate Ligament Injuries in Victoria, Australia 2005–2015. *Int J Environ Res Public Health* 2017;14:599.

136. Zbrojkiewicz D, Vertullo C, Grayson JE. Increasing rates of anterior cruciate ligament reconstruction in young Australians, 2000-2015. *Med J Aust* 2018;208:354-58.

137. Mitchell R, Finch C, Boufous S. Counting organised sport injury cases: evidence of incomplete capture from routine hospital collections. *J Sci Med Sport* 2010;13:304-8.

138. Moses B, Orchard J, Orchard J. Systematic review: Annual incidence of ACL injury and surgery in various populations. *Res Sports Med* 2012;20:157-79.

139. Beck NA, Lawrence JTR, Nordin JD, et al. ACL Tears in School-Aged Children and Adolescents Over 20 Years. *Pediatrics* 2017;139

140. Dodwell ER, Lamont LE, Green DW, et al. 20 years of pediatric anterior cruciate ligament reconstruction in New York State. *Am J Sports Med* 2014;42:675-80.

141. Shea KG, Grimm NL, Ewing CK, et al. Youth sports anterior cruciate ligament and knee injury epidemiology: who is getting injured? In what sports? When? *Clin Sports Med* 2011;30:691-706.

142. Werner BC, Yang S, Looney AM, et al. Trends in Pediatric and Adolescent Anterior Cruciate Ligament Injury and Reconstruction. *J Pediatr Orthop* 2016;36:447-52.

143. Arendt E, Dick R. Knee injury patterns among men and women in collegiate basketball and soccer. NCAA data and review of literature. *Am J Sports Med* 1995;23:694-701.

144. Janssen KW, Orchard JW, Driscoll TR, et al. High incidence and costs for anterior cruciate ligament reconstructions performed in Australia from 2003-2004 to 2007-2008: time for an anterior cruciate ligament register by Scandinavian model? *Scand J Med Sci Sports* 2012;22:495-501.

145. Volpi P, Bisciotti GN, Chamari K, et al. Risk factors of anterior cruciate ligament injury in football players: a systematic review of the literature. *Muscles Ligaments Tendons J* 2016;6:480-85.

146. Hewett TE, Myer GD, Ford KR, et al. The 2012 ABJS Nicolas Andry Award: The sequence of prevention: a systematic approach to prevent anterior cruciate ligament injury. *Clin Orthop Relat Res* 2012;470:2930-40.

147. Bjordal JM, Arnly F, Hannestad B, et al. Epidemiology of anterior cruciate ligament injuries in soccer. *Am J Sports Med* 1997;25:341-5.

148. Powell JW, Barber-Foss KD. Sex-related injury patterns among selected high school sports. *Am J Sports Med* 2000;28:385-91.

149. LaBella CR, Hennrikus W, Hewett TE. Anterior cruciate ligament injuries: diagnosis, treatment, and prevention. *Pediatrics* 2014;133:e1437-50.

150. Trentacosta NE, Vitale MA, Ahmad CS. The Effects of Timing of Pediatric Knee Ligament Surgery on Short-term Academic Performance in School-Aged Athletes. *Am J Sports Med* 2009;37:1684-91.

151. Hewett TE, Lindenfeld TN, Riccobene JV, et al. The effect of neuromuscular training on the incidence of knee injury in female athletes. A prospective study. *Am J Sports Med* 1999;27:699-706.

152. Shaw L, Finch CF, Bekker S. Infographic: Trends in paediatric and adolescent ACL injuries. *Br J Sports Med* 2018

153. Lohmander LS, Englund PM, Dahl LL, et al. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med* 2007;35:1756-69.

154. Finch CF, Kemp JL, Clapperton AJ. The incidence and burden of hospital-treated sports-related injury in people aged 15+ years in Victoria, Australia, 2004-2010: a future epidemic of osteoarthritis? *Osteoarthritis Cartilage* 2015;23:1138-43.

155. Ardern CL, Ekås G, Grindem H, et al. 2018 International Olympic Committee consensus statement on prevention, diagnosis and management of paediatric anterior cruciate ligament (ACL) injuries. *Knee Surg Sports Traumatol Arthrosc* 2018;26:989-1010.

156. Clinch J, Eccleston C. Chronic musculoskeletal pain in children: assessment and management. *Rheumatology (Oxford)* 2009;48:466-74.

157. Junnila JL, Cartwright VW. Chronic musculoskeletal pain in children: part I. Initial evaluation. *Am Fam Physician* 2006;74:115-22.

158. Kocher MS, DiCanzio J, Zurakowski D, et al. Diagnostic performance of clinical examination and selective magnetic resonance imaging in the evaluation of intraarticular knee disorders in children and adolescents. *Am J Sports Med* 2001;29:292-6.

159. Arastu MH, Grange S, Twyman R. Prevalence and consequences of delayed diagnosis of anterior cruciate ligament ruptures. *Knee Surg Sports Traumatol Arthrosc* 2015;23:1201-5.

160. Perera NS, Joel J, Bunola JA. Anterior cruciate ligament rupture: Delay to diagnosis. *Injury* 2013;44:1862-5.

161. Pincus T, Noel M, Jordan A, et al. Perceived diagnostic uncertainty in pediatric chronic pain. *Pain* 2018;159:1198-201.

162. Benjaminse A, Gokeler A, van der Schans CP. Clinical diagnosis of an anterior cruciate ligament rupture: a meta-analysis. *J Orthop Sports Phys Ther* 2006;36:267-88.

163. Jackson JL, O'Malley PG, Kroenke K. Evaluation of acute knee pain in primary care. *Ann Intern Med* 2003;139:575-88.

164. Scholten RJ, Opstelten W, van der Plas CG, et al. Accuracy of physical diagnostic tests for assessing ruptures of the anterior cruciate ligament: a meta-analysis. *J Fam Pract* 2003;52:689-94.

165. Solomon DH, Simel DL, Bates DW, et al. The rational clinical examination. Does this patient have a torn meniscus or ligament of the knee? Value of the physical examination. *JAMA* 2001;286:1610-20.

166. van Eck CF, van den Bekerom MP, Fu FH, et al. Methods to diagnose acute anterior cruciate ligament rupture: a meta-analysis of physical examinations

with and without anaesthesia. *Knee Surg Sports Traumatol Arthrosc* 2013;21:1895-903.

167. O'Sullivan JW, Banerjee A, Heneghan C, et al. Verification bias. *BMJ Evid Based Med* 2018;23:54-55.

168. Hegedus EJ, Moody J. Clinimetrics corner: the many faces of selection bias. *J Man Manip Ther* 2010;18:69-73.

169. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529-36.

Chapter Two

An international survey of pain in adolescents

“It you’re trying to achieve, there will be roadblocks. But obstacles don’t have to stop you. If you run into a wall, don’t turn around and give up. Figure out how to climb it, go through it, or work around it.”

- Michael Jordan

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An international survey of pain in adolescents

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Abstract

Background: A common belief is that pain is uncommon and short lived in adolescents. However, the burden of pain in adolescents is unclear because of limitations in previous research. The aim of this study is to estimate the prevalence of headache, stomach-ache and backache in adolescents and to explore the extent to which these three forms of pain coexist based upon a representative sample of adolescents from 28 countries.

Methods: Data were analysed from three consecutive waves (1997/98, 2001/02 and 2005/06) of the Health Behavior in School-aged Children: WHO Collaborative Cross-National survey (HBSC). Prevalence estimates are based upon adolescents who reported experiencing headache, stomach-ache or backache at least monthly for the last 6 months.

Results: There were a total of 404,206 participants with a mean (±SD) age of 13.6 (±1.7) years (range 9.8 to 17.3 years). The prevalence of headache was 54.1%, stomach-ache 49.8%, backache 37%, and at least one of the three pains 74.4%. Girls had a higher prevalence of the three pains than boys and the prevalence of pain increased with age. Headache, stomach-ache and backache frequently coexist, for example, of those with headache: 21.2% had headache alone, 31% suffered from both headache and stomach-ache, 12.1% suffered from backache and headache, and 35.7% had all three pains.

Conclusions: Somatic pain is very common in adolescents, more often coexisting than occurring in isolation. Our data supports the need for further research to improve the understanding of these pains in adolescents.

Keywords: Pain, Adolescent, Prevalence, Epidemiology, World Health Organisation, HBSC

Background

Adolescence marks the transition from childhood to adult life. Pain during adolescence is an important predictor of future pain [1-3]. A Danish twins study [4] found adolescents with persistent low back pain were 3.5 times more likely to have low back pain in adulthood. Co-occurrence of low back pain and headache in adolescence further increases the risk of developing future pain which draws attention to the significance of multiple pains [4].

Similar to adults, substantial economic costs can be attributed to pain in adolescents by way of direct medical costs, parental work absence and childcare expenses [5,6]. In adulthood the estimated cost of pain-related lost productivity time is $61.2 billon a year in the United States [7] with headache and back pain the leading contributors to this cost. In Europe the total cost of headache alone is estimated to exceed €20 billion per year [8]. Given the apparent link between adolescent pain and pain in adult life, steps to better understand and prevent adolescent pain are appropriate. An important first step in public health management is to identify the extent of the problem.

A number of systematic literature reviews have previously investigated the prevalence of headache [9,10], abdominal pain [10] and back pain [10,11] in children and adolescents. However, meaningful synthesis of the research in this area is hampered by the poor quality of the original studies. King and colleagues' review [10] noted a considerable number of relatively small studies that yield imprecise estimates of prevalence, which are inadequate to make inferences at a global level. Between the studies there are large differences in the age range

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(children as young as 2 and as old as 18) and different instruments used to measure pain. Not surprisingly King et al's review noted that the estimates of chronic pain prevalence vary substantially between studies (headache 8–83%; abdominal pain 4–53% and back pain: 14–24%); and there were inconsistent conclusions on the effect of age, region, psychosocial, and demographic factors on pain prevalence.

The study of prevalence from large, generalisable samples is critical in epidemiology and a paucity of such studies exists with regard to pain in adolescence. The World Health Organisation (WHO) monitors the health and behaviour of school-aged children via a survey conducted every four years [12,13] which enables the exploration of adolescent pain from a more global perspective. This dataset has advantages over previous studies in this area because it is derived from a large multi-national study using standardised methods of data collection. The 'Health Behaviour in School-aged Children: WHO Collaborative Cross-National survey (HBSC)' dataset has advantages over previous studies in this area because it is derived from a large multi-national study across Europe, North America, and Israel, using standardised methods of data collection. The purpose of the current study is to estimate the prevalence of headache, stomach-ache and backache in adolescents as well as explore the extent to which these pain conditions coexist using this data.

Methods

Study design and sample

Data were obtained from three consecutive waves (1997/98, 2001/02 and 2005/06) of the 'Health Behaviour in School-aged Children: WHO Collaborative Cross-National Survey (HBSC)'. The HBSC research network is an international alliance of researchers that conduct four-yearly cross-national surveys. Data is collected from 11-, 13- and 15-year-olds regarding their health, well-being, social environments and health behaviours. A standardised research protocol has been developed by the HBSC research network for the purpose of securing valid, reliable, and comparable data.

The HBSC study design, methods and data collection dates have been described in detail elsewhere [14-16]. Three age groups – mean of 11.5, 13.5 and 15.5 years – are sampled via administration of surveys within school classes. For the majority of participating countries a nationally representative sample is drawn. The primary sampling unit is the school class or, where a sample frame of classes is not available, the whole school. In the latter circumstances sampling is performed across school grades to account for students that have been advanced or held back. Cluster sampling is therefore used in which the primary sampling unit is the class (or school) rather than the individual student. The desired sample size for each age group is 1500 students per country (750 per gender). Once data is collected from the participating countries files are exported to the HBSC data banks where data is checked and cleaned in accordance to strict criteria. A list of participating researchers, countries and select reports can be found at http://www.hbsc.org.

Instrument and variables

Data from 28 countries across Europe, North America and Israel were extracted for this study. In Belgium separate surveys were conducted for Flemish and French speaking regions. Respondent demographics (gender, age and country) and data from the HBSC symptoms checklist (HBSC-SCL) were accessed. Responses to questions pertaining to headache, stomach-ache and backache were extracted for evaluation. The frequency of the respective pains was listed as a single multipart question: "In the last 6 months, how often have you had the following?" a list of symptoms included: headache, stomach-ache and backache. For each type of pain, respondents were required to specify the frequency of pain in the last six months on a five point scale: (1) "about every day"; (2) "more than once a week"; (3) "about every week"; (4) "about every month"; or (5) "rarely or never". No details regarding the duration and intensity of somatic pain were available. The HBSC-SCL enables comparable assessment of pain across countries, age groups and genders [17].

Data analysis

The prevalence of headache, stomach-ache and backache was estimated by analysing the combined data from the 1997/98, 2001/02 and 2005/06 survey waves. Prevalence estimates are based upon adolescents who reported experiencing headache, stomach-ache or backache at least every month for the last 6 months. Prevalence rates were calculated and then plotted using SigmaPlot version 12. The extent to which the three forms of pain coexist in adolescents was explored by constructing frequency distribution tables and cross-tabulation using SPSS version 20. Membership of the clusters of coexisting pains was illustrated using a three set area-proportional Venn diagram using an applet based on the method described by Chow and Rogers [18]. Univariate logistic regression models were constructed to investigate the odds of experiencing an individual pain type which also coexisted with another pain type. These were carried out using Statistical Analysis System (SAS) version 9.3.

Results

Data from a total of 404,206 adolescents in 28 countries were available for analysis. Individual participants' age ranged from 9.8 years to 17.3 years. For 11-, 13-, and 15-year age groups the mean age of respondents was 11.6 years, 13.6 years and 15.6 years respectively. There

were slightly more girls (51.2%) than boys (48.8%) and the three waves were of similar size (Table 1).

Headache was the most prevalent of the three pain conditions in adolescents. The percentage of adolescents (95% confidence interval) who reported a headache monthly or more frequently was 54.1% (54.0% to 54.3%), stomach-ache was 49.8% (49.6% to 49.9%) and backache was 37% (36.8% to 37.1%). Figure 1 shows the frequency distribution of somatic pain in adolescents. The prevalence of headache, stomach-ache and backache stratified by country is presented as supplemental information (Additional file 1: Figure S1, Additional file 2: Figure S2 and Additional file 3: Figure S3). There was some variation in pain prevalence across the 28 countries, but in no countries were any of these three pains uncommon. The lowest pain prevalence was stomach-ache in Portuguese adolescents which affected 22.8% (22.0% to 23.6%).

Table 1 Descriptive statistics of participants

Age	Mean: 13.6 years (SD: 1.7 years)		
		n	%
Gender	Boy	197094	(48.8%)
	Girl	207112	(51.2%)
Country	Austria	13636	(3.4%)
	Belgium - Flemish	15424	(3.8%)
	Belgium - French	11304	(2.8%)
	Canada	16858	(4.2%)
	Czech republic	13497	(3.3%)
	Denmark	15479	(3.8%)
	England	17237	(4.3%)
	Estonia	10360	(2.6%)
	Finland	15501	(3.8%)
	France	19473	(4.8%)
	Germany	17716	(4.4%)
	Greece	11821	(2.9%)
	Greenland	3905	(1.0%)
	Hungary	11305	(2.8%)
	Israel	16401	(4.1%)
	Latvia	11501	(2.9%)
	Lithuania	15790	(3.9%)
	Norway	14760	(3.7%)
	Poland	16733	(4.1%)
	Portugal	10580	(2.6%)
	Rep. of Ireland	12163	(3.0%)
	Russia	20265	(5.0%)
	Scotland	16226	(4.0%)
	*Slovak republic	7671	(1.9%)
	*Spain	14718	(3.6%)
	Sweden	12143	(3.0%)
	Switzerland	14820	(3.7%)
	USA	14086	(3.5%)
	Wales	12833	(3.2%)
Wave	1997/98	122386	(30.3%)
	2001/02	135067	(33.4%)
	2005/06	146756	(36.3%)

(*Waves and countries without HBSC-SCL data: Spain 1997/98, Slovak republic 2001/02).

The three pains were more prevalent in girls and older adolescents (Figure 2). The prevalence in girls vs. boys was: headache 60.4% (60.1% to 60.6%) vs. 47.5% (47.3% to 47.7%); stomach-ache 59.5% (59.3% to 59.7%) vs. 39.4% (39.2% to 39.6%), and backache 38.9% (38.7% to 39.1%) vs. 35.0% (34.8% to 35.2%). The increase in prevalence from 11 to 13 to 15 years for headache was 48.3% (48.0% to 48.5%), 54.8% (54.5% to 55.1%) and 59.4% (59.1% to 59.7%); for stomach-ache was 45.1% (44.8% to 45.4%), 50.8% (50.5% to 51.1%) and 53.4% (53.2% to 53.7%); and for backache 27.4% (27.2% to 27.7%), 37.0% (36.7% to 37.2%) and 46.7% (46.5% to 47.0%).

The prevalence of having at least one of the three somatic pains was 74.4% (74.3% to 74.6%), with 47.3% (47.1% to 47.4%) of adolescents reporting two or more of the three pain conditions (Table 2). Girls experienced multiple pains more frequently than boys and multiple pains became more prevalent as age increased across adolescence. The prevalence of multiple pains stratified by gender and age is presented as supplemental information (Additional file 4: Figure S4).

Figure 3 proportionally represents the extent to which the three pains coexisted in adolescents. It can be seen that each of the three pains commonly coexist with one or both of the other pain conditions. For example, of the adolescents with headache: 21.2% (21.1% to 21.4%) had headache alone, 31.0% (30.8% to 31.2%) also suffered stomach-ache, 12.1% (12% to 12.3%) suffered from backache and headache, and 35.7% (35.4% to 35.8%) had all three pains. Univariate logistic modelling found adolescents with pain (headache, stomach-ache or backache) were at increased odds of experiencing coexisting pain. This was highest for headache and stomach-ache OR = 4.7 (4.6 to 4.7), followed by headache and backache OR = 2.9 (2.8 to 2.9) and stomach-ache and backache OR = 2.6 (2.6 to 2.7).

Discussion

Almost three-quarters of adolescents experience headache, stomach-ache or backache at least monthly. These pain conditions commonly coexist and are more prevalent in girls and older adolescents. While there was some variation in pain prevalence across the 28 countries there were no countries where these three pains were uncommon.

Our study is substantially larger than any previous study of the prevalence of pain in adolescents. It provides

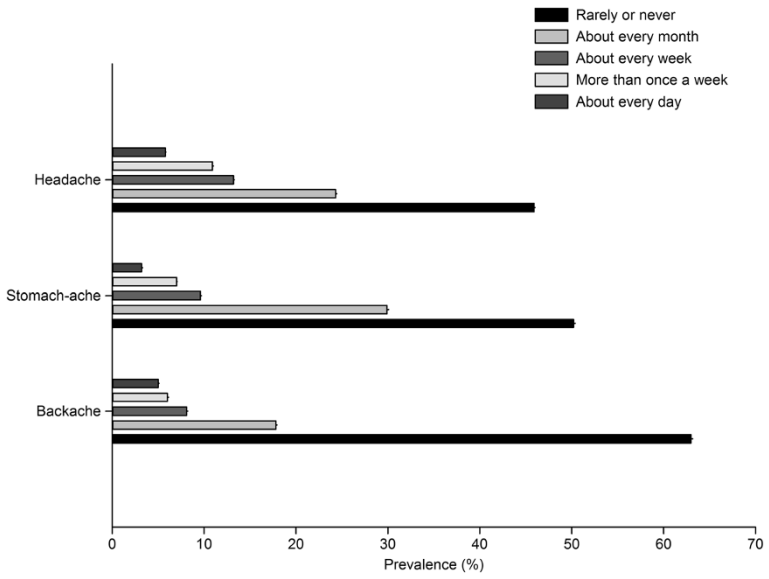

Figure 1 Prevalence of headache, stomach-ache and backache by frequency of occurrence. (Excluding adolescents who did not state: headache n = 5620, 1.4%; stomach-ache n = 6412, 1.6% and backache n = 7142, 1.8%).

robust estimates of prevalence and coexistence of pain as it draws from a large, multi-national and representative sample of adolescents and makes use of the standardised survey methods employed by the HBSC research network. These methods minimise sampling bias and enable extrapolation of the results across Europe, North America and Israel. An important feature of the study is that it provides information on the prevalence of each of the three types of pain separately as well as in combination.

The HBSC Symptoms Check List (HBSC-SCL) was primary developed for measuring the subjective experience of health and in this study it quantifies the subjective experience of pain among adolescents regardless of the cause. A limitation of relying upon a brief instrument like this is that it does not provide a precise medical diagnosis

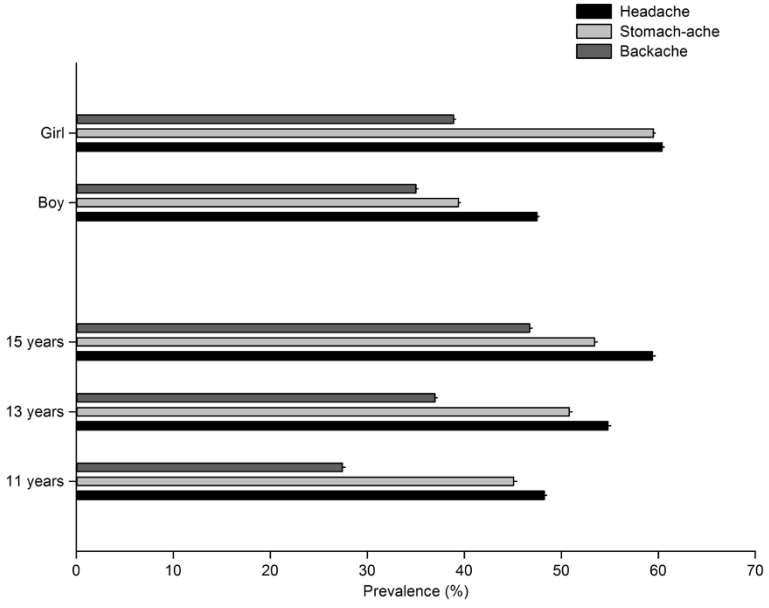

Figure 2 Prevalence of headache, stomach-ache and backache by gender and age-group. (Excluding adolescents who did not state: gender*headache n = 5620, 1.4%; gender*stomach-ache n = 6412, 1.6% and gender*backache n = 7142, 1.8%; age-group*headache n = 7590, 1.9%; age-group*stomach-ache n = 9096, 2.3%; age-group*backache n = 8378, 2.1%).

Table 2 Coexistence of somatic pain in adolescents

Number of somatic pains	Frequency (n)	Percent (%)	Cumulative percent (%)
1	107451	27.1	27.1
2	110792	28.0	55.1
3	76475	19.3	74.4
0	101253	25.6	100.0
Total	395971	100.0	

(Excluding 8235 adolescents whose pain frequency was not stated).

for each adolescent's pain or provide greater qualitative information on the pain experience. Given the broad nature of the pain measure, it is likely that physical ailments (such as sports injuries, menstrual issues and menstrual migraine) were among the causes of pain in this study. Having established the scale of the problem in this study we would encourage additional studies to further characterise these problems in adolescents.

Traditionally back pain is considered a condition of middle age and is regarded as being uncommon and/or short lived in adolescents. Reflecting this view current clinical practice guidelines specify that back pain in those younger than 20 years is a 'red flag' which should alert clinicians to the possibility of serious spinal pathology [19,20]. Further investigation via imaging and laboratory testing is then recommended. Our finding of a high prevalence of backache in adolescents questions the clinical utility of 'age of onset <20 years' as red flag to screen for serious disease [21]. Additionally many clinical practice guidelines explicitly state that their treatment recommendations only apply to adults [22]. Clinical practice guidelines should be reviewed to consider the implications of the high prevalence of pain in adolescents.

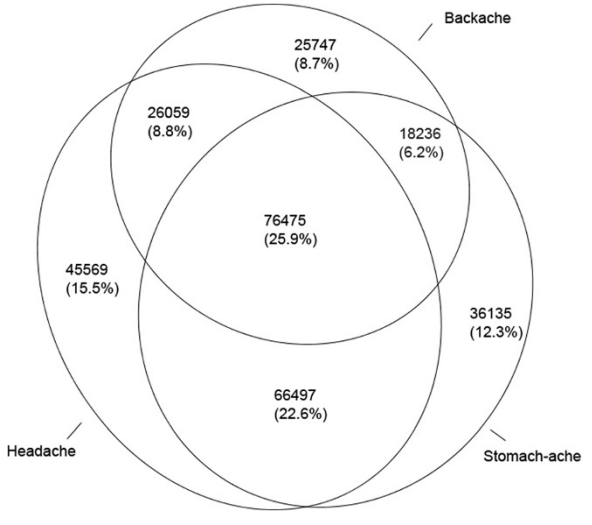

Figure 3 Proportional Venn diagram representing the coexistence of pain in adolescents. (Excluding 8235 adolescents whose pain frequency was not stated).

Our estimates of the prevalence of headache, stomach-ache and backache are at the upper bounds or higher than the wide range of previous estimates reported in King and colleagues' review of chronic pain [10]. These differences may be explained in part by differences in ages of the young people studied, case definition, and recall period [23]. The way in which different types of somatic pain are defined contributes to variations in previous prevalence estimates. A study [24] of low back pain in British school-children (11-14 years, girls 53.9%) illustrates the effect of a different operational definition. Directed by a pain diagram and the severity measure 'for one day or longer in the prior month', adolescents reported the prevalence of back pain as 26%, which is substantially less than the 37.0% backache estimate obtained for England in this analysis. Moreover, adolescence is defined by the WHO as the period between 10 and 19 years [25]. The HBSC study methods encompass a broad age range but ensure that a minimum of 95% of the eligible target population falls within the sample frame 11-15 years [12]. Given that the prevalence of somatic pain in children and adolescents increases with age it is reasonable to suggest that disparities in pain prevalence estimates may be explained by the variability in the age distribution of previous studies. For example, a Swedish study [26] reported the monthly prevalence of headache in children (7-16 years, girls 48.6%) to be 26%, which is substantially lower than this study's estimate of 63.1% from Sweden. The difference is likely due to the fact that 20% of the sample was aged below 11 years. A one-month time period for reporting prevalence was used in this study on the basis of recently published consensus [27] and empirically-based [28] recommendations in the field of back pain. Opportunity exists for a consensus approach to standardise important definitional components of paediatric somatic pain including the frequency and duration of pain and the age distribution in sampling strategies.

Our study found somatic pain in adolescents most commonly occurs in multiple-pain form. In particular young people had the greatest odds of coexisting pain when they experienced headache and stomach-ache, which appears to align with the prevailing knowledge [29]. Contrary to a previous study [29] we found girls have a higher prevalence of multiple-pains than boys and the prevalence of multiple-pains increases with age. Given the high prevalence of individual pains it is likely that some coexistence of individual pains will occur despite unrelated cause. Several potential physical, behavioural and mental developmental changes that coincide with pubertal development have been hypothesised to explain the age and gender differences that were observed in this study [11,30,31]. LeResche et al. [31]

found both the prevalence of one pain condition and the prevalence of two or more pain conditions increased with increasing physical maturity, which may explain the significant increase in the pain prevalence with age in our study. Very few studies have described the extent to which somatic pains coexist in adolescents and as a consequence there is a paucity of knowledge in this field.

Suffering and developmental consequences are important actual and potential implications of somatic pain in adolescence. Somatic pain has been associated with anxiety and depression as well as school absenteeism and poor quality of life [5]. The direct cost of health care is likely to already be apparent given the relationship between subjective health complaints and high medicine use in adolescents [32]. Somatic pain during adolescence is associated with re-occurrence later in life [1-4] and it appears that some groups of children are predisposed to ongoing pain-related problems, including work disruption, into adulthood [33]. Given that the majority of sick leave in adults is due to somatic pains [34], prevention and management of these problems in adolescence could conceivably have an important impact on disease burden in adults.

Conclusions

Our research has clearly established that headache, stomach-ache and backache are very common in adolescents and these pains more often coexist than occur in isolation. Somatic pain affects the health and well-being of adolescents in several countries across Europe and North America and as such poses a substantial public health challenge. However, research into the health of young people is recognised as a neglected priority in global health [35] and this is certainly the case in the pain field where there is an incomplete understanding of the epidemiology, mechanisms and management of these pains in adolescents. In regards to pain, large differences in prevalence exist across gender and age in adolescents. These findings are useful as they identify that girls are more likely to experience individual and multiple pains. Moreover, young people during late adolescence are commonly afflicted by multiple pains. Longitudinal investigations that coincide with the onset of pubertal development are now required to appropriately establish fundamental risk factors and mechanisms for adolescent pain. Once established, an evidence-based approached to prevention and intervention strategies can be explored in the interest of public health.

Additional files

Additional file 1: Figure S1. Prevalence of headache in adolescents by country. (Excluding 5620 adolescents whose headache frequency was not stated).

Additional file 2: Figure S2. Prevalence of stomach-ache in adolescents by country. (Excluding 6412 adolescents whose stomach-ache frequency was not stated).

Additional file 3: Figure S3. Prevalence of backache in adolescents by country. (Excluding 7142 adolescents whose backache frequency was not stated).

Additional file 4: Figure S4. The prevalence of multiple somatic pains stratified by (a) gender and (b) age. (Excluding 8235 adolescents whose pain frequency was not stated).

Abbreviations

HBSC: Health Behaviour in School-aged Children; HBSC-SCL: Health Behaviour in School-aged Children – symptoms checklist; WHO: World Health Organisation.

Competing interests

The authors have no competing interests to disclose.

Authors' contributions

MSS, NH and CGM conceptualised and designed the analyses. NH, IG and VO facilitated the data acquisition, MS conducted the analyses. All authors interpreted the data, critically reviewed and revised the manuscript. All authors approved the final manuscript and MS is the guarantor.

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References

1. Fearon P, Hotopf M: **Relation between headache in childhood and physical and psychiatric symptoms in adulthood: National birth cohort study.** *BMJ* 2001, **322:**1145–1148.
2. Gieteling MJ, Bierma-Zeinstra SM, Passchier J, Berger MY: **Prognosis of chronic or recurrent abdominal pain in children.** *J Pediatr Gastroenterol Nutr* 2008, **47:**316–326.
3. Hestbaek L, Leboeuf-Yde C, Kyvik KO, Manniche C: **The course of low back pain from adolescence to adulthood: eight-year follow-up of 9600 twins.** *Spine (Phila Pa 1976)* 2006, **31**(4):468–472.
4. Hestbaek L, Leboeuf-Yde C, Kyvik KO: **Is comorbidity in adolescence a predictor for adult low back pain? A prospective study of a young population.** *BMC Musculoskelet Disord* 2006, **7:**29.
5. Saps M, Seshadri R, Sztainberg M, Schaffer G, Marshall BM, Di Lorenzo C: **A Prospective School-based Study of Abdominal Pain and Other Common Somatic Complaints in Children.** *J Pediatr* 2009, **154:**322–326.
6. Sleed M, Eccleston C, Beecham J, Knapp M, Jordan A: **The economic impact of chronic pain in adolescence: methodological considerations and a preliminary costs-of-illness study.** *Pain* 2005, **119:**183–190.
7. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R: **Lost Productive Time and Cost Due to Common Pain Conditions in the US Workforce.** *JAMA* 2003, **290:**2443–2454.
8. Linde M, Gustavsson A, Stovner LJ, Steiner TJ, Barré J, Katsarava Z, Lainez JM, Lampl C, Lantéri-Minet M, Rastenyte D, Ruiz de la Torre E, Tassorelli C, Andrée C: **The cost of headache disorders in Europe: The Eurolight project.** *Eur J Neurol* 2012, **19:**703–711.
9. Abu-Arafeh I, Razak S, Sivaraman B, Graham C: **Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies.** *Dev Med Child Neurol* 2010, **52:**1088–1097.
10. King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, MacDonald AJ: **The epidemiology of chronic pain in children and adolescents revisited: a systematic review.** *Pain* 2011, **152:**2729–2738.
11. Jeffries LJ, Milanese SF, Grimmer-Somers KA: **Epidemiology of adolescent spinal pain: a systematic overview of the research literature.** *Spine (Phila Pa 1976)* 2007, **32:**2630–2637.
12. Roberts C, Freeman J, Samdal O, Schnohr CW, de Looze ME, Nic Gabhainn S, Iannotti R, Rasmussen M, International HSG: **The Health Behaviour in School-aged Children (HBSC) study: methodological developments and current tensions.** *Int J Public Health* 2009, **54**(Suppl 2):140–150.
13. Currie C, Gabhainn SN, Godeau E: **The Health Behaviour in School-aged Children: WHO Collaborative Cross-National (HBSC) study: origins, concept, history and development 1982-2008.** *Int J Public Health* 2009, **54**(Suppl 2):131–139.
14. Currie C, Hurrelmann K, Settertobulte W, Smith R, Todd J: *Health and health behaviour among young people*, Health Policy for Children and Adolescents, No. 1. Copenhagen: WHO Regional Office for Europe; 2000.
15. Currie C, Gabhainn SN, Godeau E, Roberts C, Smith R, Currie D, Pickett W, Richter M, Morgan A, Barnekow V: *Inequalities in young people's health: HBSC international report from the 2005/06 survey*, Health Policy for Children and Adolescents, No. 5. Copenhagen: WHO Regional Office for Europe; 2008.
16. Currie C, Roberts C, Morgan A, Smith R, Settertobulte W, Samdal O, Barnekow-Rasmussen V: *Young People's Health in Context: international report from the HBSC 2001/02 survey*, Health Policy for Children and Adolescents, No. 4. Copenhagen: WHO Regional Office for Europe; 2004.
17. Ravens-Sieberer U, Erhart M, Torsheim T, Hetland J, Freeman J, Danielson M, Thomas C: **An international scoring system for self-reported health complaints in adolescents.** *Eur J Public Health* 2008, **18:**294–299.
18. Micallef L, Rodgers P: **eulerAPE: Drawing Area-proportional 3-Venn Diagrams Using Ellipses.** *PLoS ONE* 2014, to appear. http://www.eulerdiagrams.org/eulerAPE.
19. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, Mannion AF, Reis S, Staal JB, Ursin H, Zanoli G: **Chapter 4: European guidelines for the management of chronic nonspecific low back pain.** *Eur Spine J* 2006, **15:**S192–S300.
20. Van Tulder M, Becker A, Bekkering T, Breen A, Del Real MTG, Hutchinson A, Koes B, Laerum E, Malmivaara A: **Chapter 3: European guidelines for the management of acute nonspecific low back pain in primary care.** *Eur Spine J* 2006, **15:**S169–S191.
21. Leeflang MMG, Bossuyt PMM, Irwig L: **Diagnostic test accuracy may vary with prevalence: implications for evidence-based diagnosis.** *J Clin Epidemiol* 2009, **62:**5–12.
22. Chou R, Qaseem A, Snow V, Casey D, Cross JT, Shekelle P, Owens DK: **Diagnosis and Treatment of Low Back Pain: A Joint Clinical Practice Guideline from the American College of Physicians and the American Pain Society.** *Ann Intern Med* 2007, **147:**478–491.
23. Goodman JE, McGrath PJ: **The epidemiology of pain in children and adolescents: A review.** *Pain* 1991, **46:**247–264.
24. Watson KD, Papageorgiou AC, Jones GT, Taylor S, Symmons DPM, Silman AJ, Macfarlane GJ: **Low back pain in schoolchildren: occurrence and characteristics.** *Pain* 2002, **97:**87–92.
25. WHO: **Adolescent health. [accessed: 11 December 2012].** 2012. Available from: http://www.who.int/topics/adolescent_health/en/.
26. Carlsson J: **Prevalence of headache in schoolchildren: relation to family and school factors.** *Acta Paediatr* 1996, **85**(6)**:**692–696.
27. Dionne CE, Dunn KM, Croft PR, Nachemson AL, Buchbinder R, Walker BF, Wyatt M, Cassidy JD, Rossignol M, Leboeuf-Yde C, Hartvigsen J, Leino-Arjas P, Latza U, Reis S, Gil Del Real MT, Kovacs FM, Öberg B, Cedraschi C, Bouter LM, Koes BW, Picavet HSJ, Van Tulder MW, Burton K, Foster NE, MacFarlane GJ, Thomas E, Underwood M, Waddell G, Shekelle P, Volinn E, *et al*: **A consensus approach toward the standardization of back pain definitions for use in prevalence studies.** *Spine (Phila Pa 1976)* 2008, **33:**95–103.
28. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, Woolf A, Vos T, Buchbinder R: **A systematic review of the global prevalence of low back pain.** *Arthritis Rheum* 2012, **64:**2028–2037.
29. Petersen S, Brulin C, Bergström E: **Recurrent pain symptoms in young schoolchildren are often multiple.** *Pain* 2006, **121:**145–150.
30. Feldman DE, Shrier I, Rossignol M, Abenhaim L: **Risk factors for the development of low back pain in adolescence.** *Am J Epidemiol* 2001, **154:**30–36.
31. LeResche L, Mancl LA, Drangsholt MT, Saunders K, Korff MV: **Relationship of pain and symptoms to pubertal development in adolescents.** *Pain* 2005, **118:**201–209.
32. Gobina IVR, Tynjala J, Villberg J, Villerusa A, Iannotti RJ, Godeau E, Gabhainn S, Andersen A, Holstein BE: **The medicine use and corresponding subjective health complaints among adolescents, a cross-national survey.** *Pharmacoepidemiol Drug Saf* 2011, **20:**424–431.
33. Walker LS, Sherman AL, Bruehl S, Garber J, Smith CA: **Functional abdominal pain patient subtypes in childhood predict functional gastrointestinal disorders with chronic pain and psychiatric comorbidities in adolescence and adulthood.** *Pain* 2012, **153:**1798–1806.
34. Roelen CAM, Koopmans PC, Groothoff JW: **Subjective health complaints in relation to sickness absence.** *Work* 2010, **37:**15–21.
35. Gore FM, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, Sawyer SM, Mathers CD: **Global burden of disease in young people aged 10-24 years: a systematic analysis.** *Lancet* 2011, **377**(9783):2093–2102.

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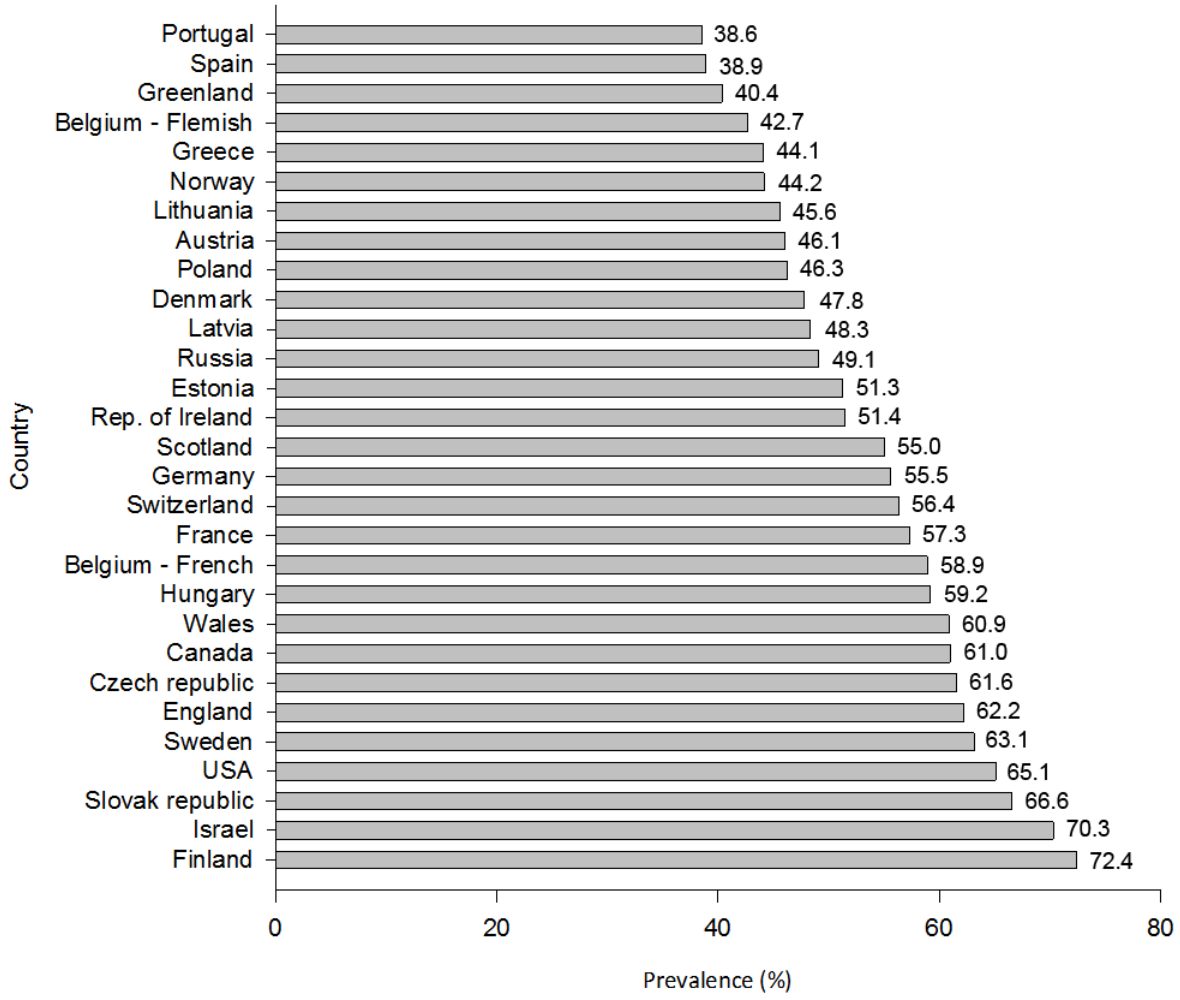
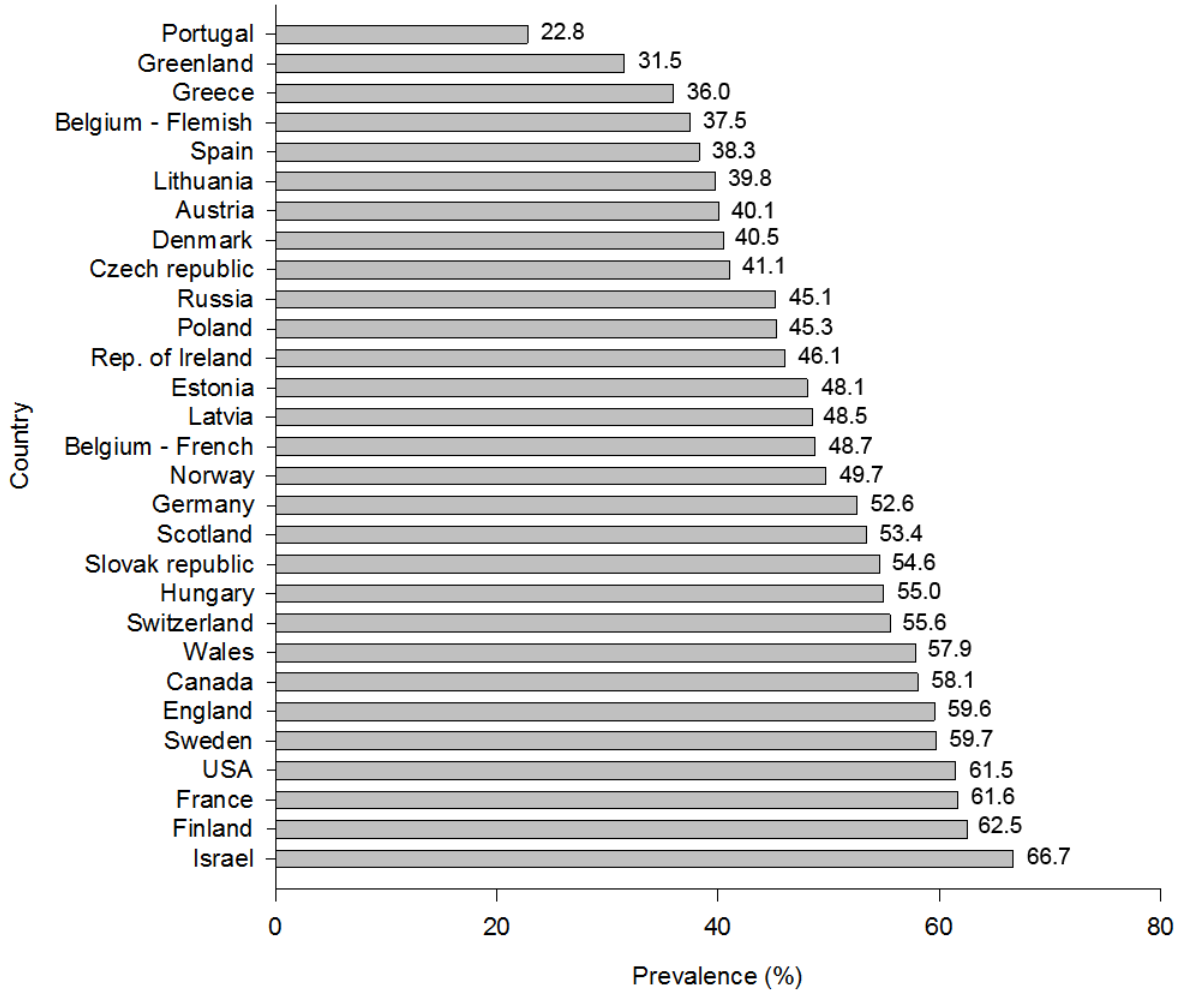
Appendix 1 (Figure S1. Prevalence of headache in adolescents by country.**)**

(Excluding 5620 adolescents whose headache frequency was not stated).



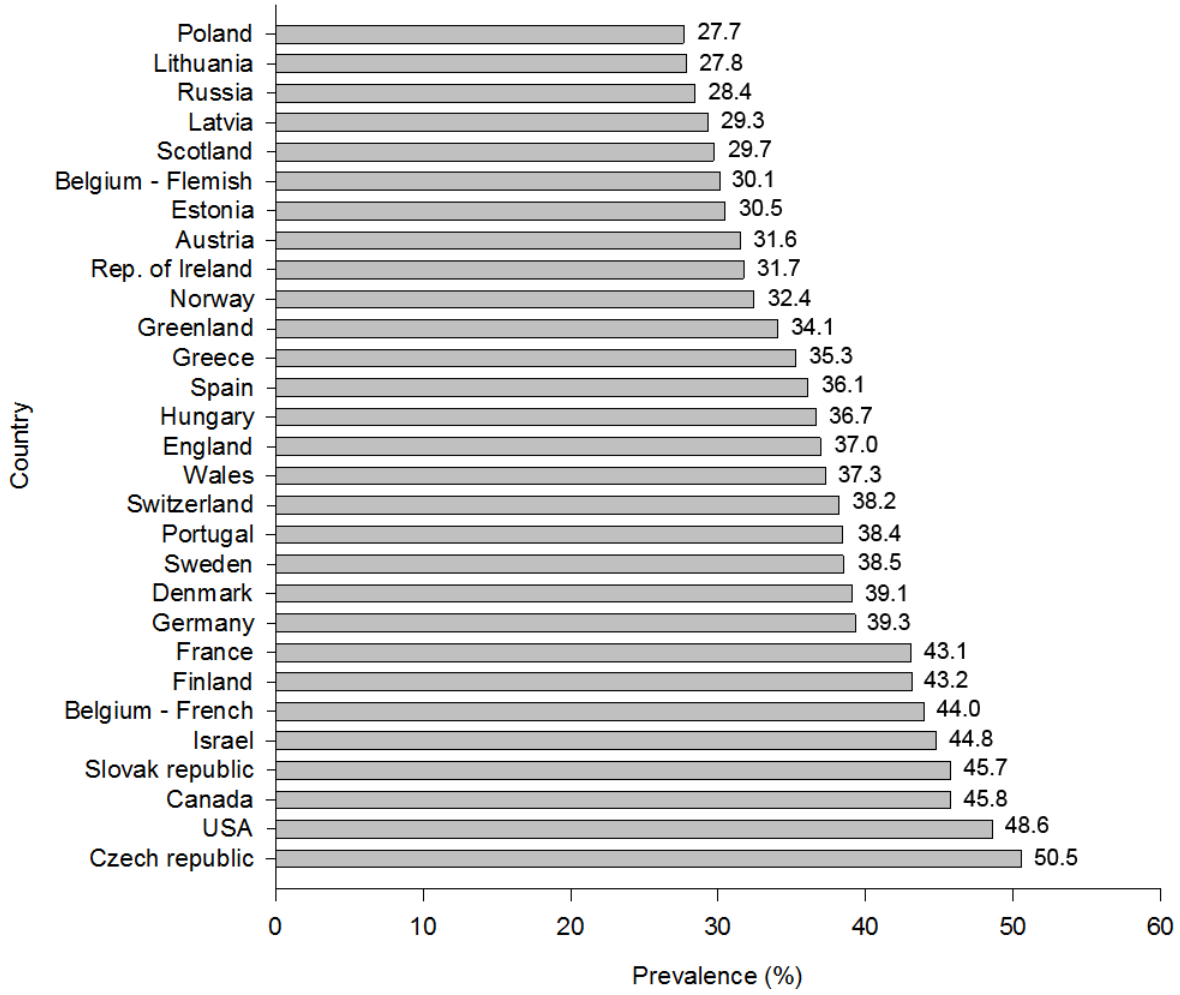
Appendix 2 (Figure S2. Prevalence of stomach-ache in adolescents by country.**)**

(Excluding 6412 adolescents whose stomach ache frequency was not stated).



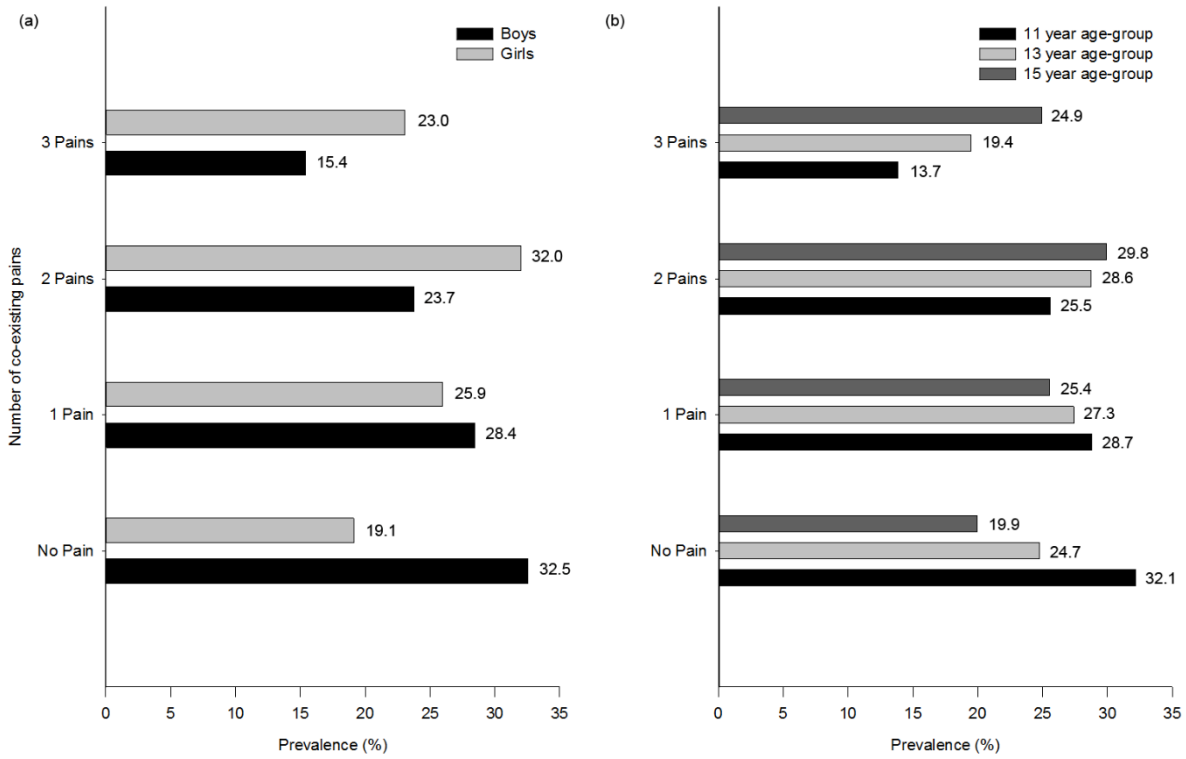
Appendix 3 (Figure S3. Prevalence of backache in adolescents by country.**)**

(Excluding 7142 adolescents whose backache frequency was not stated).



Appendix 4 (Figure S4. The prevalence of multiple somatic pains stratified by (a) gender and (b) age.**)**

(Excluding 8235 adolescents whose pain frequency was not stated).



Chapter Three

Pain and Moderate to Vigorous Physical Activity in Adolescence: An International Population-Based Survey

“The doctor of the future will give no medication but will interest his patients in the care of the human frame, diet and in the cause and prevention of disease.”

- Thomas A. Edison

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Original Research Article

Pain and Moderate to Vigorous Physical Activity in Adolescence: An International Population-Based Survey

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Abstract

Objective. To evaluate whether individual types of pain (headache, stomach-ache, and backache) or multiple pains affect the odds of young people achieving the recommended 60 minutes of moderate to vigorous physical activity (MVPA) per day in a large representative sample.

Design. Multicenter cross-sectional survey.

Setting. Twenty-eight countries across Europe and North America.

Subjects. Adolescents (N = 242,103).

Methods. An analysis of data collected in two waves (2001/02 and 2005/06) of the health behavior in school-aged children (HBSC) study was performed. Survey questions included the HBSC symptoms checklist and the amount of regular physical activity. Multilevel logistic regression was used to account for clustering effect of MVPA within countries. Models investigated the relationship between pain and physical activity, adjusted for the HBSC study year. Six models were conducted separately for gender and age-group (11, 13, and 15 years) strata.

Results. In general, the presence of pain was associated with reduced physical activity. Headache alone was associated with reduced physical activity in all six strata (odd ratios 0.77–0.84), stomach-ache alone in five strata (0.77–0.92), and backache alone in four strata (0.86–0.96). In 11- and 13-year-old girls, headache, stomach-ache, and backache, individually and in combination, were associated with decreased odds of being physically active (odds ratios ranging from 0.73 to 0.91). Within the other

four age and gender strata, the relationship was less consistent.

Conclusion. Pain is associated with reduced physical activity in adolescents but this association varies according to gender, age, and the type of pain experienced.

Key Words. Pain; Physical Activity; Adolescent; Epidemiology; Health Behavior in School-Aged Children

Introduction

The pandemic of physical inactivity in children and adolescents is an important priority for public health action [1]. Pain is a frequent experience during childhood and adolescence. Recent population-based studies [2,3] have found high prevalence rates of headache, stomach-ache, and backache in school-aged children; with higher rates found in girls and older children. Clustering of two or more pains also occurs frequently in young people [2], and tends to be the rule rather than the exception [4]. This is becoming a major public health concern as multiple pains in adolescence are a strong predictor of multiple pains in adulthood [5] and subsequent disability [6].

In the recent Global Burden of Disease study, various types of pain featured prominently as contributors to the number of years individuals live with disability [7]. In adolescence, physical and mental health, as well as school performance and quality of life can be affected by pain [2,8–12]. Studies that have assessed functional status via questionnaires have found that pain can also impair activities of daily functioning [13–15]. Physical inactivity has major health effects worldwide, causing noncommunicable diseases such as cardiovascular disease, diabetes, cancer, and depression [16].

Traditional fear-avoidance models of pain, as seen in acute/subacute backache assume disability will lead to reduced levels of physical activity [17,18]. However, cohort and cross-sectional studies published to date report conflicting evidence for the association between moderate to vigorous physical activity (MVPA) and low back pain in both adult populations and school children [19]. One possible consequence of pain in childhood and adolescence is that it can become a barrier to physical activity. The fact that more than 80% of adolescents (aged 13–15) do not meet the recommended 60 minutes of MVPA per day [20] is particularly alarming given that health behaviors in childhood are commonly retained in adulthood.

Few studies have investigated the association between individual or multiple pains and health behavior, specifically MVPA, in adolescents. The aim of this study is to evaluate whether individual (headache, stomach-ache, and backache), or multiple pains affect the odds of achieving the recommended 60 minutes of MVPA per day in a large representative sample of school-aged children.

Methods

Study Design, Setting, and Participants

A secondary analysis of data from two consecutive survey years (2001/02 and 2005/06) of the health behavior in school-aged children (HBSC) study [21], a multinational cross-sectional survey, was performed. The HBSC network conducts a large-scale four-yearly survey which collects health data from nationally representative samples of adolescents in Europe and North America. The necessary approvals from health/education authorities and research ethics Institutional Review Boards were negotiated at the national level by country team members. The level of consent in schools varied in accordance with national requirements. A list of participating researchers, countries, and selected reports can be found at http://www.hbsc.org.

All countries followed data collection procedures outlined in a standardized research protocol, which enables international comparison [22]. The HBSC study is a school-based survey in which data is collected via a self-completed questionnaire in the classroom setting. Cluster sampling was used in which the sample unit was the class (or the school when the class sample unit was not available). The target participants were adolescents aged 11, 13, and 15 years, which coincides with onset and early adolescence; a time of rapid physical and emotional change. For each survey year, the desired sample size per country was approximately 1,500 participants in each age-group (750 per gender). A single response rate is difficult to obtain given the use of multistage sampling (school, class, and student). For example, it was estimated across 35 countries that the 2001/2002 response rate at the level of the school was above 80% with additional nonresponse at the student-level ranging from 2.4% to 26.0% [23]. The combined and weighted response rates in 2001/2002 and 2005/06 both exceed 70% in the majority of countries [23,24].

Variables and Measures

Health and health related behavior data from the HBSC survey in 28 countries across Europe and North America was accessed along with demographic information (gender, age, and country).

The frequency of headache, stomach-ache, and backache, were measured by the pain items in the HBSC symptoms checklist. For each type of pain, respondents were required to specify the frequency of pain in the last 6 months on a five point scale: 1) about every day; 2) more than once a week; 3) about every week; 4) about every month; or 5) rarely or never. For the purposes of our analyses, pain frequencies were dichotomized as follows: 0 = pain rarely or never and 1 = pain at least every month. To facilitate investigation into the

clustering effect of symptoms, discrete and combined pain groups were created: 1) no pain; 2) headache only; 3) stomach-ache only; 4) backache only; 5) headache and stomach-ache; 6) headache and backache; 7) stomach-ache and backache; and 8) headache, stomach-ache, and backache. No details regarding the duration or intensity of pain were available.

The frequency of MVPA was measured using the question: *Over the past 7 days (week), on how many days were you physically active for a total of at least 60 min per day?* The question was preceded by explanatory text which defined MVPA as *"any activity that increases your heart rate and makes you get out of breath some of the time"* [25] with some examples of specific activities given. For the current analyses, responses were dichotomized (0–6 days = underactive, 7 days = active) to reflect the world health organisation's (WHO) recommendations on physical activity for children and young people, i.e., that people aged 5–17 years should accumulate at least 60 minutes of MVPA per day [26].

Statistical Analysis

Only participants with complete data for pain and physical activity measures were included in the analyses. Descriptive statistics of participants were stratified by age-group and gender, proportions related to individual and multiple pains, and physical activity, are reported. Risk differences and the unadjusted relative risk of adolescents with pain not meeting the MVPA guidelines were calculated. Multilevel logistic regression was used to account for assumed clustering effect (potentially correlated observations) of MVPA within countries. Multilevel models were constructed to investigate the relationship between pain groups and MVPA, adjusted for HBSC data collection wave. The multilevel models considered individuals as first-level units which are grouped into second-level units of country. Odds ratios and 95% confidence intervals were calculated separately for the different gender and age-groups to account for established differences. Prior to examining the relationship between pain and MVPA, the intraclass correlation coefficient (ICC) was calculated [27] in the null model to estimate how much of the total variation in adolescents meeting the recommended amount of MVPA is accounted for by country. All statistical analyses were performed using statistical analysis system version 9.4.

Results

Pain and MVPA Characteristics

After combining two waves (2001/02 and 2005/06) of HBSC data, a total of 242,103 adolescents (median age 13.6 years, interquartile range 3.4 years) from 28 countries were included in this analysis (Table 1). Across countries, there was variation in the proportion of young people that were physically active (range: 12.8–41.7%) and that reported no pain (range: 14.9–52.4%) (Supporting Information Table S1).

The proportion of young people with monthly or more frequent pain increased with age and the difference was more pronounced in girls (11 years 69.3% to 15 years 87.8%) than boys (11 years 61.1% to 15 years 69.5%). There was also an increase with age in the frequency of more than one type of pain in girls (11 years 40.1% to 15 years 64.7%) and boys (11 years 32.8% to 15 years 40.8%). Only 18.7% of participants met the recommended amount of 60 minutes of MVPA per day. Girls met the MVPA recommendations less often than boys; 14.4% vs 23.3%, respectively. The proportion of adolescents meeting MVPA recommendations was lower in older age-groups in boys (11 years; 28.2%, 15 years; 18.4%) and girls (11 years; 19.7%, 15 years; 10.2%). Table 1 reports the frequency of MVPA and pain (presented as discrete individual and combined pain clusters) in adolescent girls and boys.

Pain and Association with MVPA among Girls

The largest proportion of girls, 21.9%, experienced all three pains together (headache, stomach-ache, and backache) followed by no pain, 20.6%. In descending order, the frequencies of other pain types were: stomach-ache and headache 20.1%, stomach-ache alone 10.9%, headache alone 10.5%, headache and backache 6.0%, stomach-ache and backache 5.1%, and lastly backache alone 4.8%.

The association between pain and level of physical activity is displayed in Figure 1. After adjusting for HBSC survey year; headache, stomach-ache as well as combined headache and stomach-ache were all negatively associated with adolescent girls meeting MVPA recommendations. Risk differences and unadjusted relative risks of not meeting the MVPA guidelines were calculated between girls with and without pain (Supporting Information Table S2). The risk differences indicate that girls with pain have from 0.3% lower risk to a 4.3% higher risk of being underactive than those with no pain.

In girls aged 11 and 13 years, backache, combined backache and headache, combined backache and stomach-ache as well as combined backache, headache, and stomach-ache were also all negatively associated with MVPA. However, for girls aged 15 years, report of multiple pains was not associated with MVPA.

Pain and Association with MVPA among Boys

The largest proportion of boys did not experience pain 34.6%, with the second largest proportion the combined headache, stomach-ache and backache group 14.4%. The frequencies of other pain types were: headache alone 12.2%, headache and stomach-ache 11.6%, backache alone 8.8%, stomach-ache alone 7.3%, headache and backache 6.9%, and stomach-ache and backache 4.2%.

Table 1 Frequency of pain clusters and MVPA in adolescent girls and boys

	Girls			Boys		
	11 Years N = 40,417 % (95%CI)	13 Years N = 42,997 % (95%CI)	15 Years N = 42,222 % (95%CI)	11 Years N = 38,258 % (95%CI)	13 Years N = 39,804 % (95%CI)	15 Years N = 38,405 % (95%CI)
Pain						
No pain	30.7 (30.3–31.1)	19.2 (18.8–19.6)	12.2 (11.9–12.5)	38.9 (38.4–39.4)	34.5 (34–35)	30.5 (30–31)
Headache (HA)	12.5 (12.2–12.8)	10.3 (10–10.6)	8.9 (8.6–9.2)	12.6 (12.3–12.9)	12.6 (12.3–12.9)	11.4 (11.1–11.7)
Stomach-ache (SA)	11.9 (11.6–12.2)	11.5 (11.2–11.8)	9.4 (9.1–9.7)	9.7 (9.4–10)	6.9 (6.7–7.1)	5.3 (5.1–5.5)
Backache (BA)	4.7 (4.5–4.9)	4.9 (4.7–5.1)	4.8 (4.6–5)	6.1 (5.9–6.3)	8.3 (8–8.6)	12.1 (11.8–12.4)
HA + SA	18.5 (18.1–18.9)	20.9 (20.5–21.3)	20.7 (20.3–21.1)	13.2 (12.9–13.5)	12 (11.7–12.3)	9.5 (9.2–9.8)
HA + BA	4.7 (4.5–4.9)	5.9 (5.7–6.1)	7.4 (7.2–7.6)	4.6 (4.4–4.8)	6.7 (6.5–6.9)	9.4 (9.1–9.7)
SA + BA	3.7 (3.5–3.9)	5.4 (5.2–5.6)	6.3 (6.1–6.5)	3.5 (3.3–3.7)	4.2 (4–4.4)	4.9 (4.7–5.1)
HA + SA + BA	13.2 (12.9–13.5)	21.9 (21.5–22.3)	30.3 (29.9–30.7)	11.5 (11.2–11.8)	14.8 (14.5–15.1)	17 (16.6–17.4)
MVPA						
Active	19.7 (19.3–20.0)	13.5 (13.2–13.8)	10.2 (9.9–10.5)	28.2 (27.8–28.7)	23.3 (22.9–23.7)	18.4 (18.0–18.7)
Underactive	80.3 (79.9–80.7)	86.5 (86.2–86.8)	89.8 (89.5–90.1)	71.8 (71.3–72.3)	76.7 (76.3–77.1)	81.6 (81.2–82.0)

After adjusting for HBSC survey year; boys reporting headache or combined headache and stomach-ache had decreased odds of meeting the recommended level of MVPA, regardless of age. Boys aged 11 years who experienced backache or backache in combination with headache and stomach-ache had reduced odds of being active. However, the effect of backache was not associated with MVPA in boys 15 years of age (Figure 1). Risk differences and unadjusted relative risks of not meeting the MVPA guidelines between boys with and without pain are reported in Supporting Information Table S2. The risk differences indicate that boys with pain have from 0.4% to 4.6% higher risk of being underactive than those with no pain.

Multiple pains (combined headache, stomach-ache, and backache) were not associated with achieving the MVPA guideline in boys aged 11 years. However, at 13 and 15 years of age, boys reporting multiple pains had decreased odds of meeting the recommended level of MVPA.

The calculated ICCs indicate that approximately 4–6% of the variability in boys and girls meeting the recommended amount of MVPA is accounted for by country in our study.

Discussion

In a large representative sample of school-aged children, we showed that adolescents who experience pain typically have lower odds of meeting the WHO recommendation of 60 minutes of MVPA per day. The association seems to be influenced by the type of pain and the child's age and gender. An unexpected finding was that around 75% of the adolescents reported pain at least monthly and that the most common presentation was multiple areas of pain.

The large representative sample and standardized methods of the HBSC survey have enabled us to account for the considerable cross-regional variations in physical activity and pain. Health and physical activity differences in young boys and girls have been established in previous reports [28,29] and were also identified in our analysis. Perhaps of greatest concern is the dramatic increase in multiple pains experienced by girls between the ages of 11 and 15 years. By isolating pain clusters, we were able to see different frequencies in individual and multiple pains across age-groups in boys and girls. Our results suggest girls have a substantially lower probability than boys of remaining pain free, which is driven mostly by the increase in girls reporting multiple pains.

One limitation of the cross-sectional study design is the ability to only establish bidirectional associations without determining cause. Moreover, unlike studies that are restricted to pain specific disciplines, the HBSC study does not provide definitional boundaries to aspects of pain location, intensity, and duration. There are practical limitations to the nature of

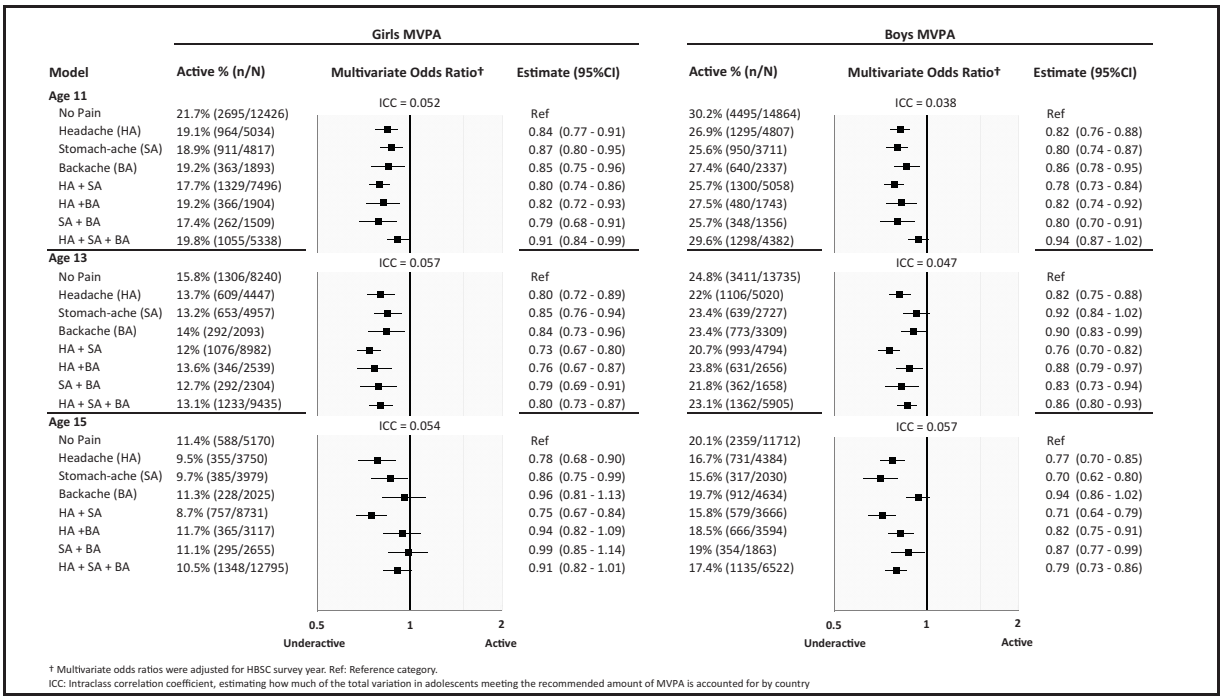

Figure 1 The association between pain and meeting the WHO's recommended level of physical activity in 11-, 13-, and 15-year-old boys and girls.

measures used to explore pain and physical activity in very large samples across different regions. It is plausible that acute vs chronic pain or high intensity pain may influence physical activity levels differently in adolescents and this was not explored in our study. In this study, the feasibility of self-reported items needs to be considered alongside adolescents' ability to accurately recall monthly pain and weekly physical activity. While the physical activity items used in this study are thought have acceptable reliability, aspects of validity are less clear [30,31]. Given these considerations, the associations identified in this study should be approached with caution at this time.

Galán et al. [32] recently analyzed a Spanish subset of 2006 HBSC survey data and found that increasing frequency of MVPA was associated with fewer health complaints, high life satisfaction, and better self-reported health. They found the benefits of MVPA were especially pronounced in boys. Our analysis differentiates the effect of individual and combined pain clusters. It suggests that the various pain experiences affect physical activity behavior in girls and boys differently across the adolescent life-span. One example is that multiple pains (headache, stomach-ache, and backache) tends to decrease the odds of meeting recommended levels of MVPA aged 11–15 years in boys, but not girls.

A systematic review by Sitthipornvorakul et al. [19] found conflicting evidence for the association between physical activity and low back pain in school children. Our findings may explain this conflict by illustrating the fact that the magnitude of the association between back pain and physical activity is quite small and influenced by age. There is an association between backache and insufficient MVPA in younger, but not older adolescents. While the effect of backache on meeting MVPA was lower in the older age-groups in our study, the longitudinal relationship between backache and physical activity from early to late adolescence remains unclear.

The concept that pain is a barrier to physical activity in children is of public health interest and has implications for clinicians and policymakers alike. Presumably primary prevention strategies can be initiated during childhood and adolescence. However, there is a lack of effective management strategies for pain in children and adolescents [33–35], with few randomized studies and numerous methodological limitations [33]. Given our findings, it is reasonable to speculate that pain might affect children's physical activity, this means identifying effective pain management strategies in adolescents is of even greater importance.

The research priorities for child and adolescent physical activity and sedentary behaviors have now been established via expert consensus [36]. The third ranked research priority from this Delphi procedure was future prospective and longitudinal studies to evaluate the independent effects of physical activity and sedentary behavior on health. Wedderkopp et al. [37] prospectively followed 9-year-old children and found that those with low levels of physical activity had higher odds of

backache at 12 years of age. High physical activity seemed to protect against backache in this study. Our analysis did not assess whether higher levels of physical activity, such as vigorous physical activity (VPA) are associated with pain. Notwithstanding the limitation of a cross-sectional study design, our analysis suggests pain may be implicated in reducing physical activity, particularly in early adolescence. Longitudinal study designs which evaluate the effect of pain (individual and combined) on MVPA as well as VPA in both early and late adolescence remain an area for future research.

Pain and physical inactivity continue to be two important public health issues. This study has established an association between the two in a large representative sample of adolescents. Our study showed that most adolescents do not meet the WHO recommendations for healthy levels of physical activity and that those with pain are even less likely to meet these goals. Public health initiatives to address physical inactivity in children and adolescents arguably need to consider pain as a barrier to uptake of physical activity.

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References

1 Kohl HW 3rd, Craig CL, Lambert EV, et al. The pandemic of physical inactivity: Global action for public health. Lancet. 2012;380:294–305.

2 Rathleff MS, Roos EM, Olesen JL, Rasmussen S. High prevalence of daily and multi-site pain–A cross-sectional population-based study among 3000 Danish adolescents. BMC Pediatr 2013;13:191.

3 Wober-Bingol C. Epidemiology of migraine and headache in children and adolescents. Curr Pain Headache Rep 2013;17:341.

4 Petersen S, Brulin C, Bergstrom E. Recurrent pain symptoms in young schoolchildren are often multiple. Pain 2006;121:145–50.

5 Kamaleri Y, Natvig B, Ihlebaek CM, Benth JS, Bruusgaard D. Change in the number of musculoskeletal pain sites: A 14-year prospective study. Pain 2009;141:25–30.

6 Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D. Does the number of musculoskeletal pain sites predict work disability? A 14-year prospective study. Eur J Pain 2009;13:426–30.

7 Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163–96.

8 Arruda MA, Bigal ME. Behavioral and emotional symptoms and primary headaches in children: A population-based study. Cephalalgia 2012;32:1093–100.

9 Dunn KM, Jordan KP, Mancl L, Drangsholt MT, Le Resche L. Trajectories of pain in adolescents: A prospective cohort study. Pain 2011;152:66–73.

10 Hunfeld JAM, Passchier J, Perquin CW, et al. Quality of life in adolescents with chronic pain in the head or at other locations. Cephalalgia 2001;21:201–6.

11 Kernick D, Reinhold D, Campbell JL. Impact of headache on young people in a school population. Br J Gen Pract 2009;59:678–81.

12 Wirth B, Knecht C, Humphreys K. Spine day 2012: Spinal pain in Swiss school children–epidemiology and risk factors. BMC Pediatr 2013;13:1–10.

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

14 Larsson B, Sund AM. Emotional/behavioural, social correlates and one-year predictors of frequent pains among early adolescents: Influences of pain characteristics. Eur J Pain 2007;11:57–65.

15 Palermo TM, Toliver-Sokol M, Fonareva I, Koh JL. Objective and subjective assessment of sleep in adolescents with chronic pain compared to healthy adolescents. Clin J Pain 2007;23:812–20.

16 Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. Lancet 2012;380:219–29.

17 Fritz JM, George SZ, Delitto A. The role of fear-avoidance beliefs in acute low back pain: Relationships with current and future disability and work status. Pain 2001;94:7–15.

18 Verbunt JA, Sieben JM, Seelen HA, et al. Decline in physical activity, disability and pain-related fear in subacute low back pain. Eur J Pain 2005;9:417–25.

19 Sitthipornvorakul E, Janwantanakul P, Purepong N, Pensri P, van der Beek AJ. The association between physical activity and neck and low back pain: A systematic review. Eur Spine J 2011;20:677–89.

20 Hallal PC, Andersen LB, Bull FC, et al. Global physical activity levels: Surveillance progress, pitfalls, and prospects. Lancet 2012;380:247–57.

21 Currie C, Gabhainn SN, Godeau E. The Health Behaviour in School-aged Children: WHO Collaborative Cross-National (HBSC) study: Origins, concept, history and development 1982-2008. Int J Public Health 2009;54:131–9.

22 Roberts C, Currie C, Samdal O, et al. Measuring the health and health behaviours of adolescents through cross-national survey research: Recent developments in the Health Behaviour in School-aged Children (HBSC) study. J Public Health 2007;15:179–86.

23 Ravens-Sieberer U, Erhart M, Torsheim T, et al. An international scoring system for self-reported health complaints in adolescents. Eur J Public Health 2008;18:294–9.

24 Roberts C, Freeman J, Samdal O, et al. The Health Behaviour in School-aged Children (HBSC) study: Methodological developments and current tensions. Int J Public Health 2009;54:140–50.

25 Prochaska JJ, Sallis JF, Long B. A physical activity screening measure for use with adolescents in primary care. Arch Pediatr Adolesc Med 2001;155:554–9.

26 World Health Organization. Global recommendations on physical activity for health. World Health Organization 2010. ISBN 9789241599979.

27 Snijders TAB, Bosker RJ. Multilevel Analysis. An Introduction to Basic and Advanced Multilevel Modeling. Thousand Oaks, CA: Sage; 1999.

28 Currie C, Gabhainn SN, Godeau E, et al. Inequalities in young people's health: HBSC international report from the 2005/06 survey. Health Policy for Children and Adolescents, No.5. Copenhagen: WHO Regional Office for Europe; 2008.

29 Currie C, Roberts C, Morgan A, et al. Young People's Health in Context: International report from the HBSC 2001/02 survey. Health Policy for Children and Adolescents, No.4. Copenhagen: WHO Regional Office for Europe; 2004.

30 Booth ML, Okely AD, Chey T, Bauman A. The reliability and validity of the physical activity questions in the WHO health behaviour in schoolchildren (HBSC) survey: A population study. Br J Sports Med 2001;35:263–7.

31 Rangul V, Holmen T, Kurtze N, Cuypers K, Midthjell K. Reliability and validity of two frequently used self-administered physical activity questionnaires in adolescents. BMC Med Res Methodol 2008;8:47.

32 Galán I, Boix R, Medrano MJ, et al. Physical activity and self-reported health status among adolescents: A cross-sectional population-based study. BMJ Open 2013;3:e002644.

33 Calvo-Munoz I, Gomez-Conesa A, Sanchez-Meca J. Physical therapy treatments for low back pain in children and adolescents: A meta-analysis. BMC Musculoskelet Disord 2013;14:55.

34 Verhagen AP, Damen L, Berger MY, et al. Conservative treatments of children with episodic tension–type headache. J Neurol 2005;252:1147–54.

35 Weydert JA, Ball TM, Davis MF. Systematic review of treatments for recurrent abdominal pain. Pediatrics 2003;111:e1–11.

36 Gillis L, Tomkinson G, Olds T, et al. Research priorities for child and adolescent physical activity and sedentary behaviours: An international perspective using a twin-panel Delphi procedure. Int J Behav Nutr Phys Act 2013;10:112.

37 Wedderkopp N, Kjaer P, Hestbaek L, Korsholm L, Leboeuf-Yde C. High-level physical activity in childhood seems to protect against low back pain in early adolescence. Spine J 2009;9:134–41.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's Website:

Table S1 Cross regional variation in moderate to vigorous physical activity and pain.

Table abbreviations: MVPA = moderate to vigorous physical activity; ha = headache; sa = stomach-ache; ba = backache.

Table S2. Risk of not meeting moderate to vigorous physical activity guidelines by pain experience.

Table abbreviations: Ref = reference category; HA = headache; SA = stomach-ache; BA = backache.

Table S1. Cross regional variation in moderate to vigorous physical activity and pain

	MVPA		Pain							
	Underactive	Active	no pain	ha	sa	ba	sa + ha	ha + ba	sa + ba	sa + ha + ba
Austria	79.9%	20.1%	37.7%	10.7%	11.0%	7.3%	11.7%	5.3%	4.8%	11.5%
Belgium - Flemish	87.2%	12.8%	35.0%	9.4%	10.5%	7.5%	14.0%	4.6%	4.9%	14.1%
Canada	77.4%	22.6%	22.7%	10.5%	8.6%	7.4%	14.9%	7.6%	6.1%	22.3%
Czech republic	75.8%	24.2%	19.9%	14.0%	4.7%	9.9%	11.2%	15.6%	4.2%	20.4%
Denmark	79.8%	20.2%	30.6%	11.9%	8.6%	11.3%	11.6%	8.3%	5.4%	12.3%
England	79.9%	20.1%	18.9%	10.5%	8.0%	4.2%	21.8%	5.4%	4.0%	27.1%
Estonia	85.2%	14.8%	31.8%	12.4%	10.0%	6.0%	15.9%	5.2%	4.4%	14.4%
Finland	80.7%	19.3%	14.9%	12.4%	5.3%	3.7%	23.0%	6.3%	2.8%	31.6%
France	86.6%	13.4%	16.6%	7.5%	10.7%	6.6%	18.8%	5.6%	8.0%	26.3%
Germany	85.4%	14.6%	23.2%	11.2%	10.2%	7.1%	16.2%	7.5%	5.1%	19.6%
Greece	84.1%	15.9%	34.3%	13.1%	7.0%	9.7%	10.5%	8.6%	4.7%	12.0%
Greenland	71.1%	28.9%	52.4%	11.7%	5.2%	8.4%	9.1%	4.3%	2.9%	6.1%
Hungary	82.4%	17.6%	21.4%	10.5%	9.6%	4.7%	20.2%	5.1%	4.5%	23.9%
Ireland	70.4%	29.6%	30.8%	12.9%	9.5%	6.2%	16.3%	6.0%	4.2%	14.3%
Israel	84.6%	15.4%	16.8%	8.8%	6.5%	2.5%	23.4%	3.9%	4.2%	33.8%
Latvia	80.8%	19.2%	30.7%	11.0%	11.4%	6.2%	15.7%	5.4%	4.7%	14.8%
Lithuania	77.7%	22.3%	36.8%	13.6%	9.4%	6.1%	12.9%	5.3%	3.5%	12.4%
Norway	86.7%	13.3%	27.8%	9.9%	14.2%	7.0%	15.2%	4.8%	6.6%	14.5%
Poland	82.9%	17.1%	31.9%	12.0%	11.5%	6.7%	16.4%	4.8%	3.9%	12.8%
Portugal	86.4%	13.6%	42.4%	12.3%	4.7%	14.2%	4.4%	11.5%	3.2%	7.3%
Russia	86.5%	13.5%	34.1%	12.5%	10.2%	5.3%	15.1%	4.9%	4.1%	13.8%
Scotland	79.1%	20.9%	27.2%	12.5%	11.6%	4.6%	20.2%	4.7%	4.1%	15.1%
Slovak republic	58.3%	41.7%	18.1%	17.7%	5.0%	6.8%	15.0%	14.9%	3.3%	19.1%
Spain	80.6%	19.4%	35.6%	9.0%	9.3%	10.2%	10.0%	6.8%	6.0%	13.2%
Sweden	85.3%	14.7%	19.7%	11.7%	9.0%	4.5%	21.1%	5.3%	4.6%	24.0%
Switzerland	86.1%	13.9%	21.7%	10.1%	9.3%	6.0%	18.8%	5.2%	5.4%	23.6%
USA	72.7%	27.3%	19.7%	10.5%	8.4%	6.5%	16.9%	7.6%	5.6%	24.9%
Wales	81.1%	18.9%	21.1%	11.5%	9.2%	4.9%	21.4%	5.5%	4.4%	21.9%

Table abbreviations: MVPA – moderate to vigorous physical activity; ha – headache; sa – stomach-ache; ba – backache.

Table S2. Risk of not meeting moderate to vigorous physical activity guidelines by pain experience

	Girls			Boys		
	Underactive % (n/N)	Risk Difference %	Unadjusted Relative Risk	Underactive % (n/N)	Risk Difference %	Unadjusted Relative Risk
Age 11						
No Pain	78.3% (9731/12426)	Ref	Ref	69.8% (10369/14864)	Ref	Ref
Headache (HA)	80.9% (4070/5034)	2.6%	0.97 (0.95-0.98)	73.1% (3512/4807)	3.3%	0.95 (0.94-0.97)
Stomach-ache (SA)	81.1% (3906/4817)	2.8%	0.97 (0.95-0.98)	74.4% (2761/3711)	4.6%	0.94 (0.92-0.96)
Backache (BA)	80.8% (1530/1893)	2.5%	0.97 (0.95-0.99)	72.6% (1697/2337)	2.8%	0.96 (0.94-0.99)
HA + SA	82.3% (6167/7496)	4.0%	0.95 (0.94-0.97)	74.3% (3758/5058)	4.5%	0.94 (0.92-0.96)
HA +BA	80.8% (1538/1904)	2.5%	0.97 (0.95-0.99)	72.5% (1263/1743)	2.7%	0.96 (0.93-0.99)
SA + BA	82.6% (1247/1509)	4.3%	0.95 (0.92-0.97)	74.3% (1008/1356)	4.5%	0.94 (0.91-0.97)
HA + SA + BA	80.2% (4283/5338)	1.9%	0.98 (0.96-0.99)	70.4% (3084/4382)	0.6%	0.99 (0.97-1.01)
Any pain	81.2% (22741/27991)	2.9%	0.96 (0.95-0.97)	73% (17083/23394)	3.2%	0.96 (0.94-0.97)
Age 13						
No Pain	84.2% (6934/8240)	Ref	Ref	75.2% (10324/13735)	Ref	Ref
Headache (HA)	86.3% (3838/4447)	2.1%	0.98 (0.96-0.99)	78% (3914/5020)	2.8%	0.96 (0.95-0.98)
Stomach-ache (SA)	86.8% (4304/4957)	2.6%	0.97 (0.96-0.98)	76.6% (2088/2727)	1.4%	0.98 (0.96-1)
Backache (BA)	86% (1801/2093)	1.8%	0.98 (0.96-1)	76.6% (2536/3309)	1.4%	0.98 (0.96-1)
HA + SA	88% (7906/8982)	3.8%	0.96 (0.94-0.97)	79.3% (3801/4794)	4.1%	0.95 (0.93-0.96)
HA +BA	86.4% (2193/2539)	2.2%	0.97 (0.96-0.99)	76.2% (2025/2656)	1.0%	0.99 (0.96-1.01)
SA + BA	87.3% (2012/2304)	3.1%	0.96 (0.95-0.98)	78.2% (1296/1658)	3.0%	0.96 (0.94-0.99)
HA + SA + BA	86.9% (8202/9435)	2.7%	0.97 (0.96-0.98)	76.9% (4543/5905)	1.7%	0.98 (0.96-0.99)
Any pain	87.1% (30256/34757)	2.9%	0.97 (0.96-0.98)	77.5% (20203/26069)	2.3%	0.97 (0.96-0.98)
Age 15						
No Pain	88.6% (4582/5170)	Ref	Ref	79.9% (9353/11712)	Ref	Ref
Headache (HA)	90.5% (3395/3750)	1.9%	0.98 (0.97-0.99)	83.3% (3653/4384)	3.4%	0.96 (0.94-0.97)
Stomach-ache (SA)	90.3% (3594/3979)	1.7%	0.98 (0.97-1)	84.4% (1713/2030)	4.5%	0.95 (0.93-0.97)
Backache (BA)	88.7% (1797/2025)	0.1%	1 (0.98-1.02)	80.3% (3722/4634)	0.4%	0.99 (0.98-1.01)
HA + SA	91.3% (7974/8731)	2.7%	0.97 (0.96-0.98)	84.2% (3087/3666)	4.3%	0.95 (0.93-0.96)
HA +BA	88.3% (2752/3117)	-0.3%	1 (0.99-1.02)	81.5% (2928/3594)	1.6%	0.98 (0.96-1)
SA + BA	88.9% (2360/2655)	0.3%	1 (0.98-1.01)	81% (1509/1863)	1.1%	0.99 (0.96-1.01)
HA + SA + BA	89.5% (11447/12795)	0.9%	0.99 (0.98-1)	82.6% (5387/6522)	2.7%	0.97 (0.95-0.98)
Any pain	90% (33319/37052)	1.4%	0.99 (0.98-1)	82.4% (21999/26693)	2.5%	0.97 (0.96-0.98)

Table abbreviations: Ref – Reference category; HA – headache; SA – stomach-ache; BA – backache.

Chapter Four

Relationship between growth, maturation, and musculoskeletal conditions in adolescents: a systematic review

“Without continual growth and progress, such words as improvement, achievement, and success have no meaning”.

- Benjamin Franklin

Relationship between growth, maturation and musculoskeletal conditions in adolescents: a systematic review

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ABSTRACT

Objective To determine whether there is a relationship between physical growth and development, as determined by markers of biological maturation, and musculoskeletal conditions in adolescents.

Design Systematic review.

Data sources Electronic databases (PubMed, EMBASE and the Cumulative Index to Nursing and Allied Health Literature) were searched up to 6 September 2017.

Eligibility criteria for selecting studies Studies that evaluated the association between biological maturation or growth and musculoskeletal conditions in adolescents (chronological age 10–19 years).

Results From 20 361 titles identified by the searches, 511 full-text articles were retrieved and assessed for eligibility; 56 studies, all at high risk of bias, evaluating the relationship between maturation and/or growth and musculoskeletal conditions were included. A total of 208 estimates of association were identified across the included studies, which generally indicated no association or an unclear association between maturation, growth and musculoskeletal conditions.

Summary/Conclusions While the relationship between maturation, growth and musculoskeletal conditions remains plausible, the available evidence is not supportive. The current body of knowledge is at high risk of bias, which impedes our ability to establish whether biological maturity and growth are independent risk factors for musculoskeletal conditions.

INTRODUCTION

Adolescence is defined by the WHO as the second decade of life,[1] and represents a key period of physical, psychosocial and cognitive development, yet also a period of physical and psychological vulnerability.[2 3] Puberty is a physical event that occurs during adolescence characterised by marked somatic growth, and significant musculoskeletal (MSK), physiological and sexual development,[4] sometimes considered of itself to define. The prevalence of MSK conditions such as spinal pain increases during adolescence,[5 6] and persistent problems in this period predict pain and disability later in life.[7–10] Understanding the role of biological development in the onset of MSK conditions in adolescents is important to guide preventative efforts.

Rapid physical growth (ie, 'the adolescent growth spurt') and biological maturity (eg, stage of skeletal or pubertal development) have been proposed as risk factors for MSK pain and injury.[11] At the anatomical level, the structural capacity of growth plates and developing bone may be exceeded during rapid periods of growth,[12 13] leading to pain, injuries, fracture or the development of non-specific MSK conditions. However, there is limited epidemiological evidence to support the hypothesis that rapid growth during adolescence influences the tolerance of growth plates and bones to excessive or repetitive load. It may be that the construct of biological maturity increases risk, underpinned by the physical and neurodevelopmental changes such as motor coordination, cognitive control or negative affect that occur during adolescence, as observed by associations between Tanner staging[14 15] and injury rates in adolescent athletes.[16 17] In addition to physical growth, puberty is also characterised by numerous hormonal, emotional and neurological changes,[4] which may also increase the risk of injury/pain.

Adolescents of the same chronological age can vary significantly in height, weight and pubertal stage. Given the wide variation in speed and timing of maturation and growth, chronological age may be less appropriate as a measure for the prediction of MSK conditions. Instead, longitudinal measures of growth such as height change velocity and cross-sectional measures of maturation such as bone age[18] may more accurately capture the constructs relevant to the hypothesis that the pubertal period carries an increased risk of the development of pain and injuries.

While multiple biological, psychological, social and developmental factors may be aetiologically linked with MSK conditions, this systematic review aims to specifically determine whether there is a relationship between physical growth and/or stage of development and MSK conditions in adolescents.

METHODS

A protocol for this review[19] was registered a priori at the International Prospective Register of Systematic Reviews—PROSPERO 2014:CRD42014014333.

Information sources and search methods

Electronic databases (PubMed, EMBASE and the Cumulative Index to Nursing and Allied Health Literature) were searched for eligible studies from inception to 6 September 2017. The search strategy was developed for PubMed and modified for other databases (online supplementary appendix table 1). The reference lists of all included publications and relevant systematic reviews were checked, and

forward citation searches (using the Scopus citation database) were performed. No unpublished studies were identified, nor was contact with experts made.

Eligibility criteria

Studies were considered eligible if they evaluated exposure factors of maturation and/or growth, and the outcome of MSK conditions, in adolescents (recruited within the chronological age range 10–19 years). Prospective, cross-sectional and retrospective studies were eligible for inclusion, while case-series were excluded.

Studies needed to quantitatively measure stage or timing of maturation and/or growth. Measures of biological maturity status, defined as a single measurement in time that assesses where a child is in the continuum of biological maturation, could include status of pubertal development such as Tanner staging, testicular volume (orchidometer) or radiographic analysis of skeletal age. Measures of maturity timing, defined as the chronological age at which specific maturational events occur, could include age at peak height velocity (PHV), age at menarche, estimated percentage of predicted adult height or maturity offsets. Growth rate, defined as change in physical stature within a specific time period, had to be measured longitudinally, for example repeated standing height measurements within a specified period. Measurements of growth spurt were also included, defined as a period of rapid somatic growth. Growth spurt measures were set within a study and could include a priori thresholds for rapid height or weight gain over a specific period, for example 5 cm of height growth in a 6-month period. Anthropometric measurements that did not account for temporal change (ie, growth) and studies that only measured chronological age were excluded.

Our definition of MSK condition was intentionally broad to accommodate non-specific pain (eg, back pain or headache), MSK injuries and fractures. We did not include typically asymptomatic conditions when pain was not an outcome measure, such as scoliosis, benign joint hypermobility, negative ulnar variance and low bone density, or conditions that were incidentally identified on imaging studies. Studies had to provide a measure of the association (eg, ratio (relative) or difference (absolute) measures) between the exposure and MSK condition.

Only full articles published in peer-reviewed journals were included. Studies published in all languages were eligible and translations were sought where necessary.

Study selection and data extraction

Pairs of authors (MSS and SJK, MSS and NH) independently screened all titles and abstracts identified in the searches. Full-text copies of potentially relevant articles were retrieved and evaluated against the eligibility criteria for final inclusion. Disagreements regarding inclusion were resolved by consensus.

One review author (MSS) extracted data from all included studies, and two review authors (NH, SJK) checked the extracted data. Data were extracted using a specifically designed spreadsheet that included study design and characteristics, sample characteristics (participant source, setting, and age and gender distribution), MSK condition (type, definition, assessment method, frequency and/or duration), measures of maturation and/or growth (type, definition and categories), and measures of association such as ORs and CIs. Confounders were extracted where reported, and where multiple measures of association were presented we extracted the most adjusted estimates.

Risk of bias in individual studies

The Quality in Prognosis Studies (QUIPS) tool[20] was modified to assess the quality of the included studies by substituting risk factors for prognostic factors. The modified QUIPS tool rated risk of bias in six domains: (1) study participation, (2) study attrition, (3) aetiological factor measurement, (4) outcome measurement, (5) confounding measurement and account, and (6) analysis. The risk of bias tool guide includes a series of statements to direct reviewers to issues that may introduce bias within each of the six domains, for example, 'whether the source population was adequately described for key characteristics' within the study participation domain, and 'whether attempts to collect information on participants who dropped out of the study were described' within the study attrition domain. A complete list of the guiding statements is described by Hayden *et al*.[20] The risk of bias in each domain was rated as 'low', 'moderate' and 'high'. Overall risk of bias for each included study was rated as either low risk or high risk. A low risk of bias study satisfied the following criteria: (1) low risk of bias on domain 2 (study attrition) and domain 5 (study confounding), and (2) low risk of bias on at least four of the six domains. Pairs of reviewers (MSS and SJK, MSS and NH) independently assessed the risk of bias of each included study. Discrepancies were resolved by consensus. The consensus process involved discussion between authors regarding their independent responses to the guiding statements and their impression of the impact of these on the overall risk of bias relevant to each domain.

Synthesis of results

Studies were divided according to type of MSK condition—pain, injury or fracture—as follows:

1. pain, if the outcome definition specified pain, painful episodes or symptoms pertaining to pain without reference to a specific precipitating injury
2. injury, if the outcome definition specified injury due to an organised activity or event (usually sport or performance); injuries could include sprains, strains or injuries from single event, or stress fractures or overuse injuries from repeated trauma; studies were not included in this category if the outcome was exclusively fracture
3. fracture, if the outcome definition specified fracture exclusively.

It was recognised that some studies in category 2 could include participants whose injury included fracture, and that some studies in category 3 could include patients whose fracture was sustained during a sporting event or activity. However, it was assumed that these cases would make up only small proportions in the included studies. Where disagreements among review authors occurred in the categorisation of studies, consensus was reached via discussion. Further details of the outcome definitions within studies are reported in online supplementary appendix table 2.

Associations were grouped separately for maturity and growth. In studies that evaluated pain as the outcome, the associations were grouped by region of pain, for example, back pain, extremity pain and neck pain. Typically, maturity or growth was dichotomised in primary studies; where reported we present ORs that quantify the association between these exposures and outcome. Conclusions were based on data from prospective, longitudinal studies where exposure measurement preceded outcome measurement because this study design provides the most robust estimates of causal association. Studies with cross-sectional and retrospective design were included but given

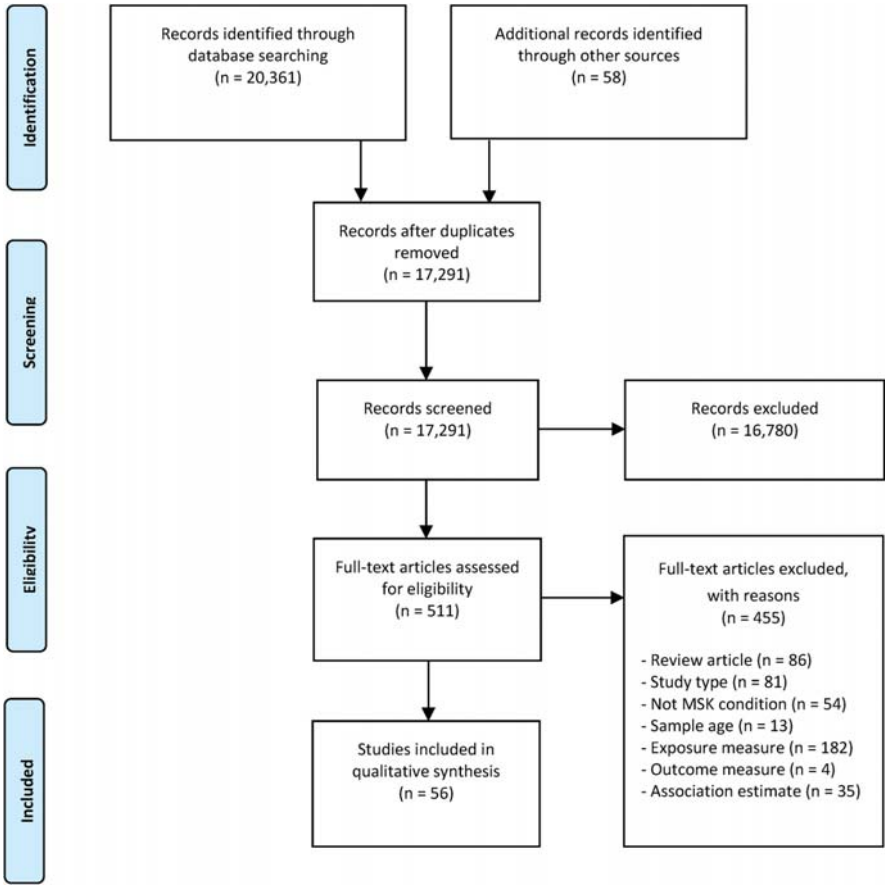

Figure 1 PRISMA flow diagram of studies through the review. MSK, musculoskeletal; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

less weight. Where available, gender-specific associations were presented separately. This decision was not prespecified, but taken post hoc due to the way data were reported in the included studies. For studies that evaluated univariate and multivariate associations, the fully adjusted or final model was presented along with all reported covariates. Homogeneity was assessed subjectively based on population, measurement and methodological aspects of the included studies. No quantitative data synthesis (meta-analysis) was performed due to heterogeneous study designs and measures (online supplementary appendix table 2). We performed a narrative synthesis, taking study quality into account. Summary statements were generated as follows: associated (along with direction), no association or unclear. Statistically significant associations were based on primary study findings; the level of significance was typically set at P value <0.05.

RESULTS

Study selection

Database searches retrieved 20 361 citations, of which 17 291 remained after duplicates were removed (figure 1). After screening, 511 articles were retrieved in full text, along with 58 articles identified through forward and backward citation tracking. Fifty-six articles were finally included, of which 55 were published in English[16 17 21–74] and 1 in Spanish.[59]

Description of included studies

Of the 56 included articles, 25 (20 discrete samples) evaluated associations with pain,[21–45] 22 articles (19 samples) with injury[16 17 46–65] and 9 articles (8 samples) with fracture.[66–74] Table 1 reports the exposure measures and outcomes, while the study design, sample size, characteristics of participants, measurement of maturation or growth, and measurement of MSK conditions are presented in online supplementary appendix table 2.

Risk of bias assessment

No article adequately addressed all bias domains (online supplementary appendix table 3). High risk of bias was identified in 23 articles for study participation, 35 for study attrition, 10 for aetiological factor measurement, 9 for outcome measure, 27 for study confounding, and 15 for statistical analysis and reporting. Regarding overall study risk of bias, only two studies were at low risk of bias in at least four of the six QUIPS domains; neither study was at low risk in relation to study attrition. Therefore, all included studies were judged to be at high risk of bias.

Associations between biological maturity or growth, and pain

MSK pain

A total of 101 associations (52 longitudinal, 49 cross-sectional) from 21 studies[23–32 34–44] evaluated relationships between adolescent development and back, neck or extremity pain, or any report of MSK pain. There were 58 associations between

Table 1 Exposure measures and outcomes

	Biological maturity		Growth	
Outcome	**Maturity status**	**Maturity timing**	**Growth rate**	**Growth spurt**
Pain				
Back pain[23 24 26 29–31 34–38 43 44]	PDS[24 29 30 34 37] Pubertal stage (breast development)[44] Maturity status classification[23] Genital development[31] Pubic hair staging[31]	Age at first ejaculation/menstruation[35 43] Height-for-age[29 37] Weight-for-age[37] Predicted growth remaining[23] Years from age at PHV[23]	Standing height (6 months and 12 months)[26 29 36 38] Body mass (kg/m^2/year)[36 38] Sitting height (cm/year)[36 38] Weight (kg/year)[29]	Growth spurt item—PDS[30] Height spurt (>5 cm in 6 months)[26] Upper 20% of weight gain[37] Upper 20% of height gain[37]
Neck pain[25 43 44]	Pubertal stage (breast development)[44]	Age at first ejaculation/menstruation[43]		Height spurt (>5 cm in 6 months)[25]
Extremity pain[27 29 37 40]	PDS[29 37] Skeletal age[27]	Height-for-age[29 37] Weight-for-age[37]	Height (cm/year)[29] Weight (kg/year)[29]	Height spurt (>5 cm in 6 months)[40] Upper 20% of weight gain[37] Upper 20% of height gain[37]
Head/face pain[21 22 24 28 30 33 34 39 45]	PDS[24 28 30 34] Pubertal status questions[39] Tanner stage[45]	Menarche status[22 33] Late menarche (>12 years)[21] Pubertal timing question[39] Age at first menstruation[21]		
Chest pain[39]	Pubertal status questions[39]	Pubertal timing questions[39]		
Any or multiple pain[28 29 32 34 37 39 41 42]	PDS[28 29 34 37] Tanner stage[41 42] Pubertal status questions[39]	Pubertal timing questions[39] Height-for-age[29 37] Weight-for-age[37] Perceived physical maturation timing[32] Age at menarche[32]	Height (cm/year)[29] Weight (kg/year)[29]	Upper 20% of weight gain[37] Upper 20% of height gain[37]
Injuries				
Football injuries[16 54–56 58 61 64 65]	Skeletal age[61] Tanner stage[16]	Maturity algorithm[64 65] Skeletal age vs chronological age[54 56] % predicted mature height[58] Period of PHV[65]		Height (≥0.6 cm/month)[55] Body mass index (>0.3 kg/m^2/month)[55]
Ballet/dance injuries[47 53]	Tanner stage[47]	Age at first menstruation[47 53]		Foot length (0.5 cm)[47]
Gymnastics injuries[17 50]	Tanner stage[17] Skeletal age[50]			
Athletic injuries[52 62 63]		Age at first menstruation[62 63] Late age at menarche (>15 years)[63] Age at PHV[52]		
Stress fracture[51 57]		Age at first menstruation[51 57]		
Ice hockey injuries[49]		Menarche status[49]		
Handball injuries[59]	Bone age[59] Tanner stage[59] Change in Tanner stage[59] Pubertal stage[59] Testicular volume (cm)[3 59]		Testicular volume (cm)[3 59]	Peak growth rate (cm/6 months)[59]
Multisport injuries[46 48 60]	Tanner stage[46]	Age at first menstruation[60] Chronological age minus age at menarche[60] Bone maturity[48] Bone age[48] Maturity offset algorithm[48]		
Fracture	Tanner stage[66 67 70 74] Bone age[73] Skeletal age[74]	Age at first menstruation[66 68] Age at PHV[71] Age at peak height estimate[66] Index of maturation[70] Years from PHV estimate[69]		

PDS, Pubertal Development Scale; PHV, peak height velocity.

biological maturity (35 status, 23 timing) and MSK pain, and 43 associations between growth (26 rate, 17 spurt) and MSK pain.

Three studies[24 30 35] (n=62 970) reported nine longitudinal associations between maturity and back, neck or extremity pain, or any report of MSK pain (online supplementary appendix table 4). Two studies[24 30] reported seven associations that indicated increased pain frequency with later maturity, while one study[35] reported no association between pain frequency and maturity timing.

Eight studies[25 26 29 30 36–38 40] (n=12 212) reported 43 longitudinal associations between growth and back, neck or extremity pain (online supplementary appendix table 4). There were no

consistent patterns of association; 3 studies[26 29 38] reported 5 associations indicating increased pain with higher rates of growth, and 8 studies[25 26 29 30 36–38 40] reported 38 associations indicating no relationship.

Thirteen studies[23 27–29 31 32 34 37 39 41–44] (n=44 266) reported 49 cross-sectional associations between maturity and back, neck or extremity pain, or any report of MSK pain (online supplementary appendix table 4). There were no consistent patterns of association.

Head/face or chest pain

A total of 32 associations (9 longitudinal, 23 cross-sectional) from 8 studies[21 22 24 28 30 33 39 45] evaluated relationships between adolescent development and head/face or chest pain. All associations were between maturity (21 status, 11 timing) and pain.

Three studies[24 30 33] (n=6692) reported nine longitudinal associations between maturity and head/face pain (online supplementary appendix table 4). There was no consistent pattern of association; one study[24] reported two associations that indicated increased pain probability with later maturity, and two studies[30 33] reported seven associations indicating no relationship.

Six studies[21 22 28 34 39 45] (n=25 990) reported 23 cross-sectional associations between maturity and head/face or chest pain (online supplementary appendix table 4). There was no consistent pattern of association.

Associations between biological maturity or growth, and injury

Sporting injuries

A total of 46 associations (40 longitudinal, 5 cross-sectional, 1 retrospective) from 18 studies[16 17 46 48–50 52 54–56 58–65] evaluated relationships between adolescent development and sporting injuries (athletic, football, gymnastics, handball, ice hockey and multisport injuries). There were 42 associations between maturity (12 status, 30 timing) and sporting injuries, and 4 between growth (1 rate, 3 spurt) and sporting injuries.

Fourteen studies[16 17 46 49 52 54 56 58–61 63–65] (n=3363) reported 36 longitudinal associations between maturity and sporting injuries (online supplementary appendix table 4). There was no consistent pattern of association; 5 studies[16 17 49 56 65] reported 5 associations indicating higher injury rates/severity with later maturity/early pubertal timing, 11 studies[17 46 54 56 58–61 63–65] reported 26 associations indicating no relationship, and 4 studies[52 56 63 64] reported 5 associations indicating higher injury rates/severity with early maturity/late pubertal timing.

Two studies[55 59] (n=265) reported four longitudinal associations between growth and sporting injuries (online supplementary appendix table 4). There was no consistent pattern of association; one study[55] reported two associations indicating higher football injury rates with growth spurt, and one study[59] reported two associations indicating no relationship between handball injury rate and growth spurt.

Three studies[48 50 62] (n=772) reported five cross-sectional and one retrospective association between biological maturity and sporting injuries (athletic, gymnastic and organised physical activity injuries) (online supplementary appendix table 4). There was no consistent pattern of association; one study reported three associations indicating higher organised physical activity injury rates with early maturity, two studies[50 62] found no association between biological maturity and sporting injury (gymnastics and athletics) frequency, and one study[48] reported one association indicating higher organised physical activity injury rates with earlier maturity offset timing.

Ballet injuries

A total of four associations (three longitudinal, one retrospective) from two studies[47 53] evaluated relationships between adolescent development and ballet injuries (online supplementary appendix table 4). Both studies (n=334) found no association between adolescent development and ballet injury rate.

Stress fracture

Two studies[51 57] (n=12 292) reported two longitudinal associations between maturity (maturity timing) and stress fracture injuries (online supplementary appendix table 4). One study[57] reported no relationship, and the other[51] reported higher injury rates with late pubertal timing.

Associations between biological maturity or growth, and fracture

A total of 23 associations (3 longitudinal, 20 retrospective) from 9 studies[66–74] evaluated relationships between adolescent development and fracture. All associations evaluated aspects of maturity (13 status, 10 timing) and fracture.

Two studies[72 74] (n=1654) reported three longitudinal associations between maturity and fracture (online supplementary appendix table 4). There was no consistent pattern of association; one study[74] found advanced maturation (both Tanner stage and bone age) was associated with a higher incidence of fracture, and one study[72] found no association between age at PHV and fracture.

Seven studies[66–71 73] (n=4042) reported 20 retrospective associations between biological maturity and fracture (online supplementary appendix table 4). There were no consistent patterns of association.

Summary of associations

A total of 208 associations were identified. Table 2 provides an overall summary of the associations between biological maturity, growth and MSK conditions.

DISCUSSION

Despite being a commonly held theory, there is little published empirical evidence that biological maturity and growth in adolescence are associated with MSK conditions. While 56 articles were identified in our searches, there remain knowledge gaps for common conditions. The data that are available provide limited evidence due to high risk of bias in prospective studies and the inherent limitations in studying risk in cross-sectional studies.

A strength of this review was the comprehensive evaluation of both biological maturation and growth as risk factors for specific types of MSK pain, injury and fracture. We separated specific exposures and types of conditions (ie, between factors and effects) to appropriately evaluate studies that propose causality. The ability to conclusively answer our question was constrained by limitations in included studies; these included poor reporting quality, high loss to follow-up, lack of clarity regarding the number of participants providing aetiological and outcome measures, and variable analytical methods.

ORs for the association between maturity status versus back pain ranged from 1.1 to 1.9, which indicates a small risk of advanced maturation.[75] ORs were seldom below 0.6 or above 1.6. We presented covariates (when included) alongside estimates of association to assess whether potential confounders such as age, sex and history of MSK disorder were included in study designs and statistical models.[76] The included studies generally did a poor job of accounting for potentially confounding factors.

Table 2 Associations between maturity, growth and musculoskeletal conditions

	Biological maturity		Growth	
	Maturity status	**Maturity timing**	**Growth rate**	**Growth spurt**
Pain				
Back pain	↑Maturity, ↑Back Pain[24 30]	Unclear[35]	Unclear[26 29 36 38]	Unclear[26 30 37]
Neck pain	*No association[44]	*No association[43]	–	No association[25]
Extremity pain	*Unclear[27 29 37]	*Unclear[29 37]	Unclear[29]	No association[37 40]
Head/face pain	Unclear[24 30]	No association[33]	–	–
Chest pain	*No association[39]	*Unclear[39]	–	–
Any or multiple pain	*Unclear[28 29 34 37 39 41 42]	*Unclear[29 32 37 39]	No association[29]	No association[37]
Injuries				
Football	Unclear[16 61]	Unclear[54 56 58 64 65]	–	↑Growth, ↑Injury[55]
Ballet/dance injuries	No association[47]	No association[47]	–	No association[47]
Gymnastics injuries	Unclear[17]	–	–	–
Athletic injuries	–	Unclear[62 63]	–	–
Stress fracture	–	Unclear[51 57]	–	–
Ice hockey injuries	–	Early timing, ↑injury[49]	–	–
Handball injuries	No association[59]	–	No association[59]	No association[59]
Multisport injuries	No association[46]	No association[60]	–	–
Fractures	↑Maturity, ↑Fracture[74]	No association[72]	–	–

Summaries are based on 100% consistency for longitudinal associations, that is, all longitudinal associations are in the same direction.
*Summaries based on cross-sectional or retrospective associations, where longitudinal associations are not available.
–, no data available.

For example, of the 208 associations identified, 111 (~53%) were univariate, 157 (~75%) did not account for chronological age, and the factors in the model were unclear in 11 (~5%) of associations. This issue is reflected in the risk of bias domain for study confounding, where three-quarters of studies in this review were deemed at moderate-to-high risk. Regardless, the general lack of strength and consistency of the associations raises doubts about the hypothesised causal relationship between biological maturation and MSK pain and injuries.

Measurement of maturity and growth were generally found to be at moderate-to-high risk of bias. For example, arbitrary thresholds and categories were often set for maturity timing. In one study,[35] timing of puberty was measured via questions about age at the time of the first ejaculation (boys) and the first menstruation (girls), and timing of puberty was grouped into three categories: early (12 years or younger for boys and 11 years or younger for girls), average (13 or 14 years for boys and 12 or 13 years for girls) and late (15 years or older for boys and 14 years or older for girls). Other studies used different thresholds for 'late' puberty, including menarche at >12 years[21] and at ≥15 years.[63] Similarly, measurement of growth spurt was commonly categorised as 'high growth spurt', arbitrarily defined as >5 cm in a 6-month period (not accounting for baseline height or other factors). The arbitrary cut-point for high-growth spurt in this example may be erroneously high as this growth rate is typically only attained by the top three per cent of adolescents.[77] The issue of measurement error (misclassification) also negatively impacts confidence in this body of knowledge. The validity and reliability of self-reported measures of pubertal status and timing have been queried in previous research.[78–80] Pubertal assessment by children or their parents may not be reliable and should be augmented by a physical examination.[79] Ensuring that measures are valid and reliable, in addition to addressing other sources of bias (such as measurement recall bias), is required before the relationship between biological maturation and MSK conditions can be clarified.

In addition to considerations of reliability and validity of the maturity and growth measures used in included studies, there is also the question of heterogeneity. We decided a priori to separate exposure measures into the broad categories of 'growth' and 'maturity'; this was performed via a process of consensus among the authors. While we contend that this represents a sensible and meaningful division, there was heterogeneity between measures within each category. In the context of our findings, it may be that the lack of consistent direction and magnitude of associations could be partly due to this heterogeneity. We cannot be sure of the importance of the variability between measures, but this provides reason to be somewhat cautious in our conclusions.

Timing of information (temporality) was typically not well considered in studies that evaluated biological maturation as risk factor for adolescent MSK conditions. Per the Bradford-Hill criteria for causal inference,[81] the exposure must precede the onset of the disease. Studies in this review seldom established whether participants had a history free of the MSK condition at enrolment; only 8 of the 208 associations adjusted for physical complaints,[23] functional somatic syndromes,[30 43] previous low back pain[43] or fracture history.[63] There were studies that measured the exposure after the occurrence of the outcome, and this was particularly common in studies on fracture.[66–69 71 73] The timing of maturation and growth events in relation to conditions needs to be properly addressed in future studies that aim to evaluate biological maturation factors for adolescent MSK conditions.

Several previous epidemiological reviews link adolescent growth and development with MSK conditions, such as back pain and sports injuries.[11 82–86] A position statement from the American Medical Society for Sports Medicine states that overuse injuries may be more likely during the adolescent growth spurt.[87] This has led to the recommendation to monitor adolescent growth rate and limit training workloads during rapid growth periods.[87] This recommendation does not appear to be based on robust published research evidence. To

date only one other focused review has systematically evaluated puberty specifically as a risk factor for MSK conditions (limited to back pain) in the young.[84] The authors concluded that a causal link between puberty and back pain is possible. That review found five studies (all included in the current review) that were all deemed to be of high quality based on their methodological checklist that evaluated study sample, data collection, study factor, outcome measure, modifiers/confounders and biological gradient. In contrast, we deemed all studies to be at high risk of bias based on the QUIPS steering questions. We also applied a consistency threshold of 100% for association, which differed from the previous review of 75%. Like us, the authors of the previous systematic review did not perform meta-analysis due to heterogeneous study designs.

Our review demonstrates that there is considerable uncertainty regarding the aetiological role of maturation and growth in adolescent MSK conditions, and highlights the knowledge gaps. For example, periods of rapid growth have been linked to the onset of traction apophysitis, such as Osgood-Schlatter disease.[88] We found only one article that explored this question[27]; skeletal age and disorders of the knee extensor mechanism were studied in 40 young male soccer players, and no association was found. Perhaps the most biologically plausible relationship is between rapid growth and fracture, given a reduction in cortical bone mineral density occurs as growth increases during early-mid puberty.[13] Only two prospective studies attempted to determine whether maturation was associated with fracture in adolescents.[72 74] In one study,[74] Tanner stage and skeletal age measures were positively associated with a higher hazard of fracture over a 6-year follow-up period, while the other study found no association between age at PHV and fracture.[72] Nevertheless, the role of rapid growth in the aetiology of fracture is still to be determined.

Future research should be designed to observe change in individuals over a sufficient period to account for the wide variation in tempo and timing of maturation and growth. Measurements need to be adequately valid and reliable, and frequent enough to capture rapid change. It may be that frequent repeated measurement to ascertain growth velocity in adolescence (while logistically difficult) provides a better measure than measuring the multifactorial construct of maturation. Large samples of adolescents need to be selected to adequately capture the MSK outcomes of interest and appropriate measure taken to minimise attrition. Many of these issues relate back to developing an appropriately clear research question. Researchers must clearly delineate the specific exposure construct of interest in the formulation of their research question, and ensure appropriate covariates are included in the analysis to limit issues with confounding.

What is already known?

- Adolescence is characterised by marked somatic growth, and significant musculoskeletal, physiological and pubertal development.
- Musculoskeletal conditions become increasingly prevalent during adolescence and commonly predict pain and disability later in life.

What are the findings?

- A meaningful association between biological maturation, growth and musculoskeletal conditions in adolescence is doubtful.
- Clinicians should refrain from inferring a causal relationship between maturity, growth and musculoskeletal conditions in adolescents.
- The data that are available on this topic provide limited evidence due to high risk of bias.

CONCLUSION

Our study did not find clear association between maturation, growth and MSK conditions in adolescents. Clinicians should avoid supposing a causal relationship as studies on the topic report inconsistent findings and are at high risk of bias.

Contributors All authors conceived the study and wrote the study protocol. MSS, NH and SJK selected the studies. MSS extracted the data. NH and SJK checked the extracted data. MSS analysed the data. All authors interpreted the data. MSS wrote the first draft of the manuscript and all authors contributed to the writing of the final version.

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Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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REFERENCES

1 World Health Organization. Heatlh topics - adolescent health. 2017 http://www.who.int/topics/adolescent_health/en/ (accessed 1 Aug 2017).
2 Blum RW, McNeely C, Nonnemaker J. Vulnerability, risk, and protection. *J Adolesc Health* 2002;31:28–39.
3 Resnick MD, Bearman PS, Blum RW, *et al*. Protecting adolescents from harm. Findings from the National Longitudinal Study on Adolescent Health. *JAMA* 1997;278:823–32.
4 Patton GC, Viner R. Pubertal transitions in health. *Lancet* 2007;369:1130–9.
5 Kamper SJ, Yamato TP, Williams CM. The prevalence, risk factors, prognosis and treatment for back pain in children and adolescents: An overview of systematic reviews. *Best Pract Res Clin Rheumatol* 2016;30:1021–36.
6 Swain MS, Henschke N, Kamper SJ, *et al*. An international survey of pain in adolescents. *BMC Public Health* 2014;14:447.
7 Hestbaek L, Leboeuf-Yde C, Kyvik KO. Is comorbidity in adolescence a predictor for adult low back pain? A prospective study of a young population. *BMC Musculoskelet Disord* 2006;7:29.
8 Hestbaek L, Leboeuf-Yde C, Kyvik KO, *et al*. The course of low back pain from adolescence to adulthood: eight-year follow-up of 9600 twins. *Spine* 2006;31:468–72.
9 Kamaleri Y, Natvig B, Ihlebaek CM, *et al*. Change in the number of musculoskeletal pain sites: A 14-year prospective study. *Pain* 2009;141:25–30.
10 Kamaleri Y, Natvig B, Ihlebaek CM, *et al*. Does the number of musculoskeletal pain sites predict work disability? A 14-year prospective study. *Eur J Pain* 2009;13:426–30.
11 Caine D, Maffulli N, Caine C. Epidemiology of injury in child and adolescent sports: injury rates, risk factors, and prevention. *Clin Sports Med* 2008;27:19–50.
12 Wang Q, Seeman E. Growth-related cortical fragility at metaphyseal regions. *IBMS Bonekey* 2009;6:429–433.
13 Wang Q, Wang XF, Iuliano-Burns S, *et al*. Rapid growth produces transient cortical weakness: a risk factor for metaphyseal fractures during puberty. *J Bone Miner Res* 2010;25:1521–6.
14 Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. *Arch Dis Child* 1969;44:291–303.
15 Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;45:13–23.
16 Linder MM, Townsend DJ, Jones JC, *et al*. Incidence of adolescent injuries in junior high school football and its relationship to sexual maturity. *Clin J Sport Med* 1995;5:167–70.

17 Caine D, Cochrane B, Caine C, *et al*. An epidemiologic investigation of injuries affecting young competitive female gymnasts. *Am J Sports Med* 1989;17:811–20.
18 Malina RM, Rogol AD, Cumming SP, *et al*. Biological maturation of youth athletes: assessment and implications. *Br J Sports Med* 2015;49:852–9.
19 Swain M, Kamper S, Maher C, *et al*. The relationship between growth, maturity, and musculoskeletal conditions in adolescents: a systematic review. 2014 http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014014333 (accessed 1 Aug 2017).
20 Hayden JA, van der Windt DA, Cartwright JL, *et al*. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280–6.
21 Aegidius KL, Zwart JA, Hagen K, *et al*. Increased headache prevalence in female adolescents and adult women with early menarche. The Head-HUNT Studies. *Eur J Neurol* 2011;18:321–8.
22 Deubner DC. An epidemiologic study of migraine and headache in 10-20 year olds. *Headache* 1977;17:173–80.
23 Dolphens M, Vansteelandt S, Cagnie B, *et al*. Multivariable modeling of factors associated with spinal pain in young adolescence. *Eur Spine J* 2016;25:2809–21.
24 Dunn KM, Jordan KP, Mancl L, *et al*. Trajectories of pain in adolescents: a prospective cohort study. *Pain* 2011;152:66–73.
25 Ehrmann Feldman D, Shrier I, Rossignol M, *et al*. Risk factors for the development of neck and upper limb pain in adolescents. *Spine* 2002;27:523–8.
26 Feldman DE, Shrier I, Rossignol M, *et al*. Risk factors for the development of low back pain in adolescence. *Am J Epidemiol* 2001;154:30–6.
27 Hirano A, Fukubayashi T, Ishii T, *et al*. Relationship between the patellar height and the disorder of the knee extensor mechanism in immature athletes. *J Pediatr Orthop* 2001;21:541–4.
28 Hirsch C, Hoffmann J, Türp JC. Are temporomandibular disorder symptoms and diagnoses associated with pubertal development in adolescents? An epidemiological study. *J Orofac Orthop* 2012;73:6–18.
29 Hulsegge G, van Oostrom SH, Picavet HS, *et al*. Musculoskeletal complaints among 11-year-old children and associated factors: the PIAMA birth cohort study. *Am J Epidemiol* 2011;174:877–84.
30 Janssens KA, Rosmalen JG, Ormel J, *et al*. Pubertal status predicts back pain, overtiredness, and dizziness in American and Dutch adolescents. *Pediatrics* 2011;128:553–9.
31 Jones MA, Stratton G, Reilly T, *et al*. Biological risk indicators for recurrent non-specific low back pain in adolescents. *Br J Sports Med* 2005;39:137–40.
32 Kløven B, Hoftun GB, Romundstad PR, *et al*. Relationship between pubertal timing and chronic nonspecific pain in adolescent girls: the Young-HUNT3 study (2006-2008). *Pain* 2017;158:1554–60.
33 Kröner-Herwig B, Vath N. Menarche in girls and headache–a longitudinal analysis. *Headache* 2009;49:860–7.
34 LeResche L, Mancl LA, Drangsholt MT, *et al*. Relationship of pain and symptoms to pubertal development in adolescents. *Pain* 2005;118:201–9.
35 Mattila VM, Saarni L, Parkkari J, *et al*. Predictors of low back pain hospitalization–a prospective follow-up of 57,408 adolescents. *Pain* 2008;139:209–17.
36 Nissinen M, Heliövaara M, Seitsamo J, *et al*. Anthropometric measurements and the incidence of low back pain in a cohort of pubertal children. *Spine* 1994;19:1367–70.
37 Picavet HS, Berentzen N, Scheuer N, *et al*. Musculoskeletal complaints while growing up from age 11 to age 14: the PIAMA birth cohort study. *Pain* 2016;157:2826–33.
38 Poussa MS, Heliövaara MM, Seitsamo JT, *et al*. Anthropometric measurements and growth as predictors of low-back pain: a cohort study of children followed up from the age of 11 to 22 years. *Eur Spine J* 2005;14:595–8.
39 Rhee H. Relationships between physical symptoms and pubertal development. *J Pediatr Health Care* 2005;19:95–103.
40 Shrier I, Ehrmann-Feldman D, Rossignol M, *et al*. Risk factors for development of lower limb pain in adolescents. *J Rheumatol* 2001;28:604–9.
41 Sperotto F, Balzarin M, Parolin M, *et al*. Joint hypermobility, growing pain and obesity are mutually exclusive as causes of musculoskeletal pain in schoolchildren. *Clin Exp Rheumatol* 2014;32:131–6.
42 Sperotto F, Brachi S, Vittadello F, *et al*. Musculoskeletal pain in schoolchildren across puberty: a 3-year follow-up study. *Pediatr Rheumatol Online J* 2015;13:16.
43 Vikat A, Rimpelä M, Salminen JJ, *et al*. Neck or shoulder pain and low back pain in Finnish adolescents. *Scand J Public Health* 2000;28:164–73.
44 Wedderkopp N, Andersen LB, Froberg K, *et al*. Back pain reporting in young girls appears to be puberty-related. *BMC Musculoskelet Disord* 2005;6:52.
45 Weiler RM, Vitalle MS, Mori M, *et al*. Prevalence of signs and symptoms of temporomandibular dysfunction in male adolescent athletes and non-athletes. *Int J Pediatr Otorhinolaryngol* 2010;74:896–900.
46 Baxter-Jones A, Maffulli N, Helms P. Low injury rates in elite athletes. *Arch Dis Child* 1993;68:130–2.
47 Bowerman E, Whatman C, Harris N, *et al*. Are maturation, growth and lower extremity alignment associated with overuse injury in elite adolescent ballet dancers? *Phys Ther Sport* 2014;15:234–41.
48 Costa E Silva L, Fragoso MI, Teles J. Physical Activity-Related Injury Profile in Children and Adolescents According to Their Age, Maturation, and Level of Sports Participation. *Sports Health* 2017;9:118–25.
49 Decloe MD, Meeuwisse WH, Hagel BE, *et al*. Injury rates, types, mechanisms and risk factors in female youth ice hockey. *Br J Sports Med* 2014;48:51–6.
50 DiFiori JP, Puffer JC, Mandelbaum BR, *et al*. Distal radial growth plate injury and positive ulnar variance in nonelite gymnasts. *Am J Sports Med* 1997;25:763–8.
51 Field AE, Gordon CM, Pierce LM, *et al*. Prospective study of physical activity and risk of developing a stress fracture among preadolescent and adolescent girls. *Arch Pediatr Adolesc Med* 2011;165:723–8.
52 Fourchet F, Horobeanu C, Loepelt H, *et al*. Foot, Ankle, and Lower Leg Injuries in Young Male Track and Field Athletes. *Int J Athl Train* 2011;16:19–23.
53 Gamboa JM, Roberts LA, Maring J, *et al*. Injury patterns in elite preprofessional ballet dancers and the utility of screening programs to identify risk characteristics. *J Orthop Sports Phys Ther* 2008;38:126–36.
54 Johnson A, Doherty PJ, Freemont A. Investigation of growth, development, and factors associated with injury in elite schoolboy footballers: prospective study. *BMJ* 2009;338:b490.
55 Kemper GL, van der Sluis A, Brink MS, *et al*. Anthropometric Injury Risk Factors in Elite-standard Youth Soccer. *Int J Sports Med* 2015;36:1112–7.
56 Le Gall F, Carling C, Reilly T. Biological maturity and injury in elite youth football. *Scand J Med Sci Sports* 2007;17:564–72.
57 Loud KJ, Gordon CM, Micheli LJ, *et al*. Correlates of stress fractures among preadolescent and adolescent girls. *Pediatrics* 2005;115:e399–e406.
58 Malina RM, Morano PJ, Barron M, *et al*. Incidence and player risk factors for injury in youth football. *Clin J Sport Med* 2006;16:214–22.
59 Mónaco M, Gutiérrez Rincón JA, Montoro Ronsano JB, *et al*. Estudio prospectivo de maduración, desarrollo e incidencia lesional en balonmano formativo de élite. ¿Puede el estado madurativo ser un factor determinante de la incidencia lesional en balonmano?. *Apunts Medicina de l'Esport* 2015;50:5–14.
60 Rauh MJ, Nichols JF, Barrack MT. Relationships among injury and disordered eating, menstrual dysfunction, and low bone mineral density in high school athletes: a prospective study. *J Athl Train* 2010;45:243–52.
61 Rochelle RH, Kelliher MS, Thornton R. Relationship of Maturation Age to Incidence of Injury in Tackle Football. *Res Q* 1961;32:78–82.
62 Tenforde AS, Sayres LC, McCurdy ML, *et al*. Overuse injuries in high school runners: lifetime prevalence and prevention strategies. *Pm R* 2011;3:125–31.
63 Tenforde AS, Sayres LC, McCurdy ML, *et al*. Identifying sex-specific risk factors for stress fractures in adolescent runners. *Med Sci Sports Exerc* 2013;45:1843–51.
64 van der Sluis A, Elferink-Gemser MT, Brink MS, *et al*. Importance of peak height velocity timing in terms of injuries in talented soccer players. *Int J Sports Med* 2015;36:327–32.
65 van der Sluis A, Elferink-Gemser MT, Coelho-e-Silva MJ, *et al*. Sport injuries aligned to peak height velocity in talented pubertal soccer players. *Int J Sports Med* 2014;35:351–5.
66 Cheng S, Xu L, Nicholson PH, *et al*. Low volumetric BMD is linked to upper-limb fracture in pubertal girls and persists into adulthood: a seven-year cohort study. *Bone* 2009;45:480–6.
67 Chevalley T, Bonjour JP, van Rietbergen B, *et al*. Fractures during childhood and adolescence in healthy boys: relation with bone mass, microstructure, and strength. *J Clin Endocrinol Metab* 2011;96:3134–42.
68 Chevalley T, Bonjour JP, van Rietbergen B, *et al*. Fractures in healthy females followed from childhood to early adulthood are associated with later menarcheal age and with impaired bone microstructure at peak bone mass. *J Clin Endocrinol Metab* 2012;97:4174–81.
69 Darelid A, Ohlsson C, Rudäng R, *et al*. Trabecular volumetric bone mineral density is associated with previous fracture during childhood and adolescence in males: the GOOD study. *J Bone Miner Res* 2010;25:537–44.
70 Farr JN, Tomás R, Chen Z, *et al*. Lower trabecular volumetric BMD at metaphyseal regions of weight-bearing bones is associated with prior fracture in young girls. *J Bone Miner Res* 2011;26:380–7.
71 Kindblom JM, Lorentzon M, Norjavaara E, *et al*. Pubertal timing predicts previous fractures and BMD in young adult men: the GOOD study. *J Bone Miner Res* 2006;21:790–5.
72 Lynch KR, Kemper HCG, Turi-Lynch B, *et al*. Impact sports and bone fractures among adolescents. *J Sports Sci* 2017.35.
73 Thandrayen K, Norris SA, Micklesfield LK, *et al*. Heterogeneity of fracture pathogenesis in urban South African children: the birth to twenty cohort. *J Bone Miner Res* 2011;26:2834–42.
74 Wren TA, Shepherd JA, Kalkwarf HJ, *et al*. Racial disparity in fracture risk between white and nonwhite children in the United States. *J Pediatr* 2012;161:1035–40.
75 Chen H, Cohen P, Chen S. How big is a big odds ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. *Commun Stat Simul Comput* 2010;39:860–4.
76 Grimes DA, Schulz KF. False alarms and pseudo-epidemics: the limitations of observational epidemiology. *Obstet Gynecol* 2012;120:920–7.
77 Baumgartner RN, Roche AF, Himes JH. Incremental growth tables: supplementary to previously published charts. *Am J Clin Nutr* 1986;43:711–22.
78 Cooper R, Blell M, Hardy R, *et al*. Validity of age at menarche self-reported in adulthood. *J Epidemiol Community Health* 2006;60:993–7.
79 Rasmussen AR, Wohlfahrt-Veje C, Tefre de Renzy-Martin K, *et al*. Validity of self-assessment of pubertal maturation. *Pediatrics* 2015;135:86–93.

80 Dorn LD, Dahl RE, Woodward HR, *et al*. Defining the boundaries of early adolescence: a user's guide to assessing pubertal status and pubertal timing in research with adolescents. *Appl Dev Sci* 2006;10:30–56.
81 Fedak KM, Bernal A, Capshaw ZA, *et al*. Applying the bradford hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol* 2015;12:14.
82 Bowerman EA, Whatman C, Harris N, *et al*. A review of the risk factors for lower extremity overuse injuries in young elite female ballet dancers. *J Dance Med Sci* 2015;19:51–6.
83 Jeffries LJ, Milanese SF, Grimmer-Somers KA. Epidemiology of adolescent spinal pain: a systematic overview of the research literature. *Spine* 2007;32:2630–7.
84 Lardon A, Leboeuf-Yde C, Le Scanff C, *et al*. Is puberty a risk factor for back pain in the young? a systematic critical literature review. *Chiropr Man Therap* 2014;22:27.
85 Read P, Oliver JL, De Ste Croix MBA, *et al*. Injury risk factors in male youth soccer players. *Strength Cond J* 2015;37:1–7.
86 Zwick EB, Kocher R. Growth dynamics in the context of pediatric sports injuries and overuse. *Semin Musculoskelet Radiol* 2014;18:465–8.
87 DiFiori JP, Benjamin HJ, Brenner JS, *et al*. Overuse injuries and burnout in youth sports: a position statement from the American medical society for sports medicine. *Br J Sports Med* 2014;48:287–8.
88 Adirim TA, Cheng TL. Overview of injuries in the young athlete. *Sports Med* 2003;33:75–81.

Appendix Table 1. PubMed Search String

((((((((((sports) OR athletic) OR soft tissue) OR overuse) OR musculoskeletal) OR back) OR lower extremity) OR upper extremity) OR neck)) AND (((pain) OR injury) OR fracture)) AND ((((((((((((((((((bone age) OR skeletal age) OR body size) OR peak height velocity) OR height velocity) OR growth spurt) OR maturation) OR skeletal maturity) OR biologic maturity) OR sexual maturity) OR Tanner stage) OR Tanner staging) OR puberty) OR somatic growth) OR pubertal development) OR pubertal spurt) OR sex factor) OR risk factor) OR anthropometr*)) AND ((child*) OR adolescen*)

Appendix Table 2. Characteristics of included studies

Characteristics of studies that evaluate pain				
Author Year	**Study design**	**Participants**	**Exposure factor**	**Outcome – Pain**
Aegidius 2011[21]	Cross-sectional population-based study, Norway	Female (n=2,766) school students age-range 12-19 years	Female students were interviewed about the age at onset of menarche.	Participants were asked (interview or questionnaire) if they had experienced recurring headaches that were not related to cold, fever or any other disease in the last 12-months. Participants were classified according to their headache(s) descriptions.
Deubner 1977[22]	Cross-sectional study, Wales	Girls (n=303), age 10-20 years, who had attended city or parochial schools	Menarcheal status (pre vs. post menarche) was assessed by self-report and categorised by age-group (10-12 years and 13-15 years)	Headache and migraine (not otherwise defined) were assessed via home interview. Parents also completed a questionnaire about their child's headaches.
Dolphens 2016[23]	Cross-sectional population-based study, Belgium	Boys (n=461) and girls (n=385), mean age 11.7±1.1 years, who are school students	Rough indicators of biological age (years from age at peak height velocity, maturity status classification, percentage of adult stature and predicted growth remaining) were collected. In girls, information was gathered on whether they had started menstruating. Measure not otherwise described.	The 1-month period prevalence of low back pain was determined by self-complete questions including a pre-shaded manikin. The questions relevant to this study included the following: "Has your low back been painful in the last 4 weeks?".
Dunn 2011[24]	Three-year prospective cohort study, USA	Boys and girls (n=1,336), aged 11 years, from the Group Health database	Pubertal development was self-reported at interview using the Pubertal Development Scale.[89]	History and presence of back pain, headache, and facial pain in the past 3-months were collected from children via telephone survey. Severity criteria and a frequency measure (''almost every day," ''more than half the days" or ''fewer than half the days" in the past 3 months) were used.
Ehrmann Feldman 2002[25]	Twelve-month prospective cohort study, Canada	Boys (n=264) and girls (n=238), mean age 13.8±0.1 years, who are school students	Height was measured during physical education class and a high growth spurt was defined as more than 5 cm of growth in a 6-month period.[90]	Pain in the neck, upper back, shoulder and arm were assessment by self-report questionnaire. Pain was defined occurring at least once a week within the preceding 6-months.
Feldman 2001[26]	Twelve-month prospective cohort study, Canada	Boys (n=264) and girls (n=238), mean age 13.8±0.1 years, who are school students	Height was measured. A high growth spurt was defined as having grown more than 5 cm in a 6-month period, in line with the findings of average peak velocity of growth of 10 cm/year.[90]	Low back pain was assessment by self-report questionnaire. It was defined at a frequency of at least once a week within the past 6-months.
Hirano 2001[27]	Two-year prospective cohort study, Japan	Boys (n=40), mean age 12.8±1.6 years, who are junior soccer players	Skeletal age was assessed by radiograph of the radius, ulna, short bones method score of the Tanner/Whitehouse 2 method. Scores were converted to skeletal age using the Murata method.[91]	Disorders of the knee extensor mechanism such as Osgood-Schlatter Disease, Sinding-Larsen-Johansson disease, and bipartite were diagnosed by radiographs taken three times during the observation period. Knees were grouped by stage of disorder as: 1.predisorder, 2.painful, 3.healed and 4.normal.
Hirsch 2012[28]	Cross-sectional study, Germany	Boys (n=486) and girls (n=525), age 10-17 years, from the general population	A modified German version of the Pubertal Development Scale (PDS)[89] was used to assess menarche in girls (asked by a study nurse) and voice change and facial hair growth in boys (assessed by the examiner).	Temporomandibular disorder (TMD) symptoms were assessed by the German version of the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) questionnaire. Assessment for the presence of TMD signs was also carried out by three calibrated dentists.
Hulsegge 2011[29]	Population based birth cohort study, Netherlands	Boys (n=1,325) and girls (n=1,313), mean age 11.3±0.2 years, from the general population	Pubertal status was measured via self-report with the Pubertal Development Scale.[89] Height-for-age was based on reference growth curves. Weight change in kilograms per year and height change in centimeters per year were measured between ages 8 and 11 years.	Musculoskeletal pain (back, upper extremities, and lower extremities) of ≥1-month duration was measured as part of a 15-item list of diseases and complaints self-report questionnaire. Participant recall was past 12-months and included whether they visited a doctor for pain.
Janssens 2011a[30]	Two to three-year prospective cohort study, Netherlands	Boys (n=1,093) and girls (n=1,137), mean age 13.6±0.5 years, from the general population	Pubertal development was self-reported using the Pubertal Development Scale.[89] Growth spurt was measured using the growth spurt item from the Pubertal Development Scale.	Back pain, and headache frequency in the past 3-months were measured using the Youth Self-report questionnaire. Response categories: "not at all;" "less than once a month;" "once a month;" "two to three times a month;" "once a week;" "two to six times a week;" and "almost every day."
Janssens 2011b[30]	Three-year prospective cohort study, USA	Boys (n=1,004) and girls (n=992), mean age 11.6±0.3 years, from the general population	Pubertal development was assessed via telephone interview using the Pubertal Development Scale.[89] Growth spurt was measured using the growth spurt item from the Pubertal Development Scale.	Back pain, and headache frequency in the past 3 months were assessed by telephone interview using the Symptom Checklist-90. Response categories: "not at all;" "fewer than half of the days;" "more than half of the days;" and "almost every day."
Jones 2005[31]	Case-control study, England	Boys (n=30) and girls (n=26), mean age 14.9±0.7, who are school children	Sexual maturity was measured using a self-assessment procedure. Each subject was asked to observe drawings of the stage of secondary sex characteristics during puberty.[92]	Cases of recurrent non-specific low back pain were identified by self-reported questionnaire and follow-up interview. Asymptomatic controls were matched to the symptomatic subjects for chronological age, sex, and school class.
Kløven 2017[32]	Cross-sectional population-based study, Norway	Girls (n=3,982), age 13 to 18 years, who are school students from the general population	Menarche and perceived physical maturation were used as exposure measures. Early menarche was defined as, <12-years, normal menarche as ≥12 and <14-years, and late menarche as ≥14-years. Perceived physical maturation (as maturing earlier or later than others of their own age) was divided into maturing earlier, the same or later than others of their own age.[93]	Adolescents were asked if they had experienced pain in one of 10 locations during the last 3-months, not related to any known disease or injury. Chronic nonspecific pain was defined as pain in at least one location not related to any known disease or injury for at least once a week during the last 3 months.
Kröner-Herwig 2009[33]	Two-year longitudinal cohort study, Germany	Girls (n=1,130), mean age 11.4±2 years, from the general population	Occurrence of menarche was assessed by a question posed to the parents of girls. "Has your child already experienced her first menstruation? Yes/no."	Headache frequency was assessed on the basis of retrospective self-reports for a period of 6-months Further questions aimed at the identification of type of headache (migraine, tension-type headache) given by the International Classification of Headache Disorders (ICHD) (2004) by a single item.
LeResche 2005[34]	Cross-sectional population-based survey, USA	Boys (n=1,553) and girls (n=1,548), age 11-17 years, from the Group Health Database	Pubertal development was assessed using the Pubertal Development Scale[89] via telephone interview.	Back pain, headache, and facial pain experience in the past 3 months was asked via telephone interview.
Mattila 2008[35]	Eleven-year prospective follow-up study, Finland	Boys (n=26,688) and girls (n=30,719), aged 14-18 years, from the general population	The timing of puberty was assessed by questions about the respondent's age at the time of the first ejaculation (boys) and the first menstruation (girls).	Low back pain hospitalization data were obtained from the statutory, computer-based National Hospital Discharge Register of Finland. LBP hospitalization was defined by the ICD-10 codes (or earlier equivalent) lumbar and other intervertebral disc disorders with radiculopathy, low back pain, and dorsalgia.
Nissinen 1994[36]	Two-year prospective cohort study, Finland	Boys (n=451) and girls (n=408), mean age 10.8±0.3 years, who are school children	Growth over a one-year period was assessed by repeat measurement of standing height, sitting height, and weight. Measurements were taken by school nurses.	Low back pain was self-reported via a pain questionnaire. The children were asked, "Have you ever had pain in your lower back?" Those who responded positively to the question were asked further whether the pain had occurred over a year ago, less than a year ago, during the last month, during the last week or during that day.
Picavet 2016[37]	Birth cohort study, Netherlands	Boys (n=1,266) and girls (n=1,251), mean age 14.8±0.3 years, from the general population	Pubertal development status was measured with the Pubertal Development Scale.[89] During data collection the parents were asked to measure the weight (in kilogram) and height (in centimetres) of their child and to report this. Height-for-age z-scores and weight-for-age z-scores were calculated using reference values from the fourth Dutch National Growth Study.[94] Weight and height gain between the 11 and 14 years were calculated using the difference in days between the 2 measurements and expressed as gain per year. In the analyses, children in the highest quintile of weight and height gain were compared with those in the lower quintiles (the reference groups).	Musculoskeletal complaints were measured as part of a list of 15 conditions (and 1 open category) with the following introduction: would you indicate whether or not you (have) had one of the following diseases or disorders in the past 12-months (5 past year). If "long lasting" is mentioned, this refers to disorders with a total duration of at least 1 month. The phrases were long-lasting complaints of the back, long-lasting complaints of the upper extremities (the neck, shoulders, elbows, wrists, or hands), and long-lasting complaints of the lower extremities (hip, knees, ankles, or feet). The 3 response categories were "no," "yes, but no visit to the doctor," and "yes, visit to the doctor." The last 2 were combined to "yes." Any of the complaints were summarised as "any MSCs.

Poussa 2005[38]	Eleven-year prospective cohort study, Finland	Men (n=222) and women (n=208), mean age 21.9±0.3 years, who participated in a cohort study as school children	Growth between ages 11 to 14 years was assessed by annual (repeated) measurement of standing height, sitting height, and weight. Measurements were taken by school nurses. Growth between ages 14 to 22 years was assessed by re-examination at mean age 21.9 years.	Low back pain history was assessed by questionnaire. Low back pain region was pictured in the questionnaire and shown by the investigator. The duration of pain was defined by pain days in the previous year. The incidence of low back pain was defined as pain occurring in eight or more days during the past year.
Rhee 2005[39]	Cross-sectional analysis of the Add Health study, USA	Boys (n=9,193) and girls (n=9,529), mean age 16.2±1.7 years, who are high school students	Pubertal status was assessed by self-report. Three questions were asked of each sex: boys rated personal axillary hair growth, facial hair, and voice change, and girls rated personal breast growth, body curve, and menarche. Pubertal timing was assessed by a single item: "How advanced is your physical development compared to other boys/girls of your age?"	Symptoms (headache, musculoskeletal pain and chest pain) were assessed from a general health survey. An In-Home Interview asked individual questions, adolescents rated the frequency of having experienced the 10 physical symptoms during the past 12-months.
Shrier 2001[40]	Twelve-month prospective cohort study, Canada	Boys (n=264) and girls (n=238), mean age 13.8±0.1 years, who are high school students	Growth was measured via height and weight during physical education class. A high growth spurt was defined as having grown >5cm in a 6-month period.	Lower limb pain was assessed by self-administered questionnaire, defined as occurring at a frequency of at least once a week within the past 6-months.
Sperotto 2014[41]	Cross-sectional study, Italy	Boys (n=146) and girls (n=143), mean age 10.6 years, who are school children	The pubertal stage was visually assessed by the presence of secondary signs of pubertal development. For females, puberty was defined by the stage of breast development (Tanner stage ≥3) and menarche. For males, puberty was defined in presence of a testicles volume ≥12ml and presence of pubic and underarm hair.[95]	Chronic musculoskeletal pain, assessed by medical history and physical examination, was defined as continuous or recurrent pain lasting more than 3-months, during the previous 6-months, with an intensity so high to interfere with the regular activities of daily living.
Sperotto 2015[42]	Three-year follow-up study, Italy	Boys (n=41) and girls (n=29), mean age 14 years (range 11–16), who were symptomatic in the baseline study.	The pubertal stage was assessed by the presence of secondary signs of pubertal development. For females, puberty was defined by the stage of breast development (Tanner stage ≥3) and menarche. For males, puberty was defined in presence of a testicles volume ≥12ml and presence of pubic and underarm hair.[95]	Patients were asked to refer about presence and sites of chronic musculoskeletal pain in the previous 6 months by using a standardised form. According to the International Association for the Study of Pain, chronic musculoskeletal pain was defined as continuous or recurrent pain lasting more than 3-months and heavily interfering with daily life activities.
Vikat 2000[43]	Cross-sectional study, Finland	Boys (n=5,063) and girls (n=6,032), age 12-18 years, from the general population	Timing of puberty was formed by classifying girls' age at menarche and boys' age at first ejaculation into three categories: early, average and late.	Low back pain and neck or shoulder pain were assessed by self-report questionnaire. The questions were phrased: Have you had [type] pain during the past half year?" The provided alternatives were 1=``seldom or not at all'', 2=``about once a month'', 3=``about once a week'', and 4=``almost daily''.
Wedderkopp 2005[44]	Cross-sectional study, Denmark	Girls (n=254) aged 8-10 years and girls (n=165) aged 14-16 years, who are school children	Start of puberty was assessed according to Tanner[96] based on breast development.	Back pain (low back, mid back and/or neck region) was assessed by questionnaire and interview. The 1-month period prevalence of back pain was established by asking the pupils to point to any area of discomfort in the back reported to have occurred within the month preceding the interview.
Weiler 2010[45]	Case-control study, Brazil	Boys (n=87), age 10-18 years, who were basketball players and non-athletic patients of an Adolescent Medicine Clinic	Pubertal status was assessed by physical examination by physicians.[92] Adolescents were classified according to Tanner stages into three subgroups: 1. before the growth spurt, 2. growth spurt period, 3. end of growth spurt. The gonadal stage was chosen for the classification instead of pubic hair growth.	Temporomandibular dysfunction was assessed via a questionnaire. Adolescents with signs and symptoms present were submitted to a standardised functional examination of the masticatory system by the same examiner.

Characteristics of studies that evaluate injury

Author Year	Study design	Participants	Exposure factor	Outcome – Injury
Baxter-Jones 1993[46]	Two-year, prospective cohort. England.	Boys (n=231) and girls (n=222), age 8-16 years, who play football, gymnastics, swimming and tennis.	Sexual maturity was visually assessed using the indices developed by Tanner.[92] Pubertal stage was not otherwise specified.	Self-reported sports injury, defined as occurring as a result of participation in sport which had one or both of the following consequences: (1) a reduction in the amount or level of sports activity or (2) need for treatment or advice.
Bowerman 2014[47]	Six-month, prospective cohort. Australia	Boys (n=16) and girls (n=30), age 16±1.6 years, who are elite ballet dancers	Growth, measured as foot length change.[97] Sexual maturity was self-reported using the Tanner scale.[98] Age at onset of menarche.	Ballet injury, recorded by a physiotherapist, defined as any physical harm resulting in pain or discomfort that required a dance to modify their dance activity during one or more classes, or which required a dancer to cease all dance related activity.
Caine 1989[17]	One-year, prospective cohort. USA	Girls (n=50), mean age 12.6 years, who are competitive gymnasts	Sexual maturity (stage of breast development) was assessed by registered nurses in conjunction with menarcheal information to determine maturation rate. i.e. Tanner stages used as a proxy for growth rate.[99]	Self-reported and coach-reported injury with investigator interview. Defined as any gymnastics-related incident that resulted in the gymnast missing any portion of a workout or competitive event.
Costa 2017[48]	Cross-sectional study, Portugal	Boys (n=340) and girls (n=307), mean age 13.7±1.8 years, who are school students	Maturity measures determined maturity offset during adolescence (time before or after peak height velocity, according to Mirwald et al) and in calculating the bone age from radiographs of left hand and wrist using the Tanner-Whitehouse III bone age estimates. Bone age were divided into 3 bone maturity categories: late maturing, when the bone age was inferior to the decimal age over 1-year; normal maturing, when the difference between the bone and decimal age was 1 year at most; and early maturing, when the bone age was superior to the decimal age over 1-year.[100 101]	Any musculoskeletal condition or symptom that occurred as a result of participation in an organized practice, competition, or physical education class and entailed at least 1 of the following consequences: (1) resulted in PA restriction for at least 24-hours, (2) did not result in time lost from sports participation but determined changes in performance either in quantitative or qualitative terms, or (3) required medical attention by a health professional. Injury rates were defined as the number of sports injuries per 1000 hours of exposure (training and competition), as also reported by several studies.
Decloe 2014[49]	One season, prospective cohort. Canada	Girls (n=324), age 9-17 years, who play PeeWee ice hockey	Menarcheal status was assessed by a self-report questionnaire. Participants were either pre-menarche or post-menarche at age 11-12 years.	Ice hockey-related injuries were recorded by therapists, defined as any injury occurring in ice hockey in the season that required medical attention, removal from a session and/or resulted in a player missing a subsequent session.
DiFiori 1997[50]	Cross-sectional survey. USA	Boys (n=17) and girls (n=27), mean age 11.6 years, range 5-16), who are non-elite gymnasts	Skeletal age (years) not otherwise defined.	Stress injury of the distal radial growth plate was assessed by radiograph defined as characteristic changes that include widening of the growth plate, metaphyseal sclerosis, cystic changes, a beaked effect of the distal epiphysis, and irregularity of the margins of the growth plate.
Field 2011[51]	Seven-year, prospective cohort. USA.	Girls (n=6,831), mean age 12.0±1.6 years, from the general population	Menstrual status was assessed annually. Girls were asked whether their menstrual periods had started. Girls who answered yes were asked for the age when periods began (age at menarche).	Stress fracture incident were reported by mothers of participants via questionnaire. They were asked whether a doctor has ever said that their child had a stress fracture.
Fourchet 2011[52]	Three-year, prospective cohort study. Country not reported	Boys (n=110), mean age 15.7±1.7 years, who are track and field athletes	Age of peak height velocity (PHV) was used to define maturation.[102] Age of PHV was subtracted from chronologic age to classify the athletes in three maturation categories: early, normal, or late.	Injury was defined as a trauma occurring during track and field training or competition, which required one or more physiotherapy treatments and prevented the athlete from participating in one or more training sessions or competitive events.
Gamboa 2008[53]	Five-year, retrospective cohort study, USA	Girls (n=288), mean age 14.7±1.9 years, who are elite ballet dancers	Menstrual status was assessed annually. Age of menarche was determined via subjective history.	Injuries were recorded by physical therapists. An injury was considered to have occurred when a dancer sought at least one treatment session from a physical therapist.
Johnson 2009[54]	Six-year, prospective cohort study. England	Boys (n=292), mean age 11.7±2.4, who are elite schoolboy footballers	Skeletal age was determined using the Fels method.[103] Maturity status was grouped into three categories (early, normal, or late) based on whether skeletal age was more than a year younger/older than chronological age.	Injury not defined. Medical staff at the club maintained computerised confidential medical records for each player.
Kemper 2015[55]	One season prospective cohort study, Netherlands	101 male elite youth soccer players between 11-19 years of age	Height and body mass were measured monthly. Monthly growth rates were calculated to the nearest 0.1 decimal place (cm growth/month).	Injuries were defined following the recommendations of the FIFA Consensus Model for Injury Registration. Medical staff recorded the injuries.

Le Gall 2007[56]	Ten-season, prospective cohort study. France	Boys (n=233), mean age 13.3±0.3 years, who play elite youth football	Skeletal age was determined using the Greulich–Pyle method.[104] Maturity status was grouped into three categories (early, normal, or late) according to an individual's skeletal age compared with chronological age.	Injuries were recorded by a physician, defined as one received during training or competition and that prevented the injured player from participating in normal training or competition for more than 48 hours, not including the day of the injury.
Linder 1995[16]	Two-season, prospective cohort study. USA	Boys (n=340), mean age 12.6 years, who play school football	Sexual maturity was visually assessed (genital exam) by trained examiners, using Tanner's methods.[92]	Injuries were recorded by team coaches, defined as any sports-related mishap occurring during practice, drills, scrimmages, or games resulting in removal from a practice or game and/or missing a subsequent practice or game.
Loud 2005[57]	Two-year, prospective cohort study, USA.	Girls (n=5,461), mean age 13.9±1.6 years, from the general population	Menstrual status was assessed by self-report. Girls were asked whether their menstrual periods had started. Girls who marked "yes" were asked the age when periods began (age at menarche).	History of a stress fracture was assessed by questionnaire to the mothers, who were asked: "Has a doctor ever said that this child had any of the following conditions?" The orthopedic conditions were tendonitis, stress fracture, Osgood-Schlatter syndrome, and anterior cruciate ligament tear.
Malina 2006[58]	Two-season, prospective cohort study. USA	Boys (n=677) and one girl, mean age 11.5 years, who play youth football	Height as a percentage of predicted mature height was used as an estimate of biological maturity status and expressed as a Z-score.[105] Percentage of predicted height was based on the height of the biological parent.	Injuries were recorded by athletic trainers, that cause cessation of participation in the current game or practice and prevents the player's return to that session … any injury that causes cessation of a player's customary participation on the day following the day of onset.
Mónaco 2015[59]	Two-season, prospective study, Spain	164 male handball players, mean age 15.5 ± 2.9 years	Testicular volume measured by orchidometer. Tanner stage genital appearance was assessed by visual inspection. Bone age was measured via the method of Tanner Whitehouse III with left hand radiography. Puberty was categorized according to testicular volume as P1 pre-puberty, P2 initial puberty, P3 average puberty and P4 final stage puberty. Peak growth rate was considered 4 or more inches in 6 months, which corresponds to a gain of 8-12 cm / year.	Injury definition aligned with UEFA Football Safety Project. The diagnosis and registry of injuries was performed by two sports medicine doctors.
Rauh 2010[60]	One-season, prospective cohort study. USA	Girls (n=163), mean age 15.7±1.3 years, who compete in multisport high school athletes	Menarcheal status was assessed by a self-report questionnaire. Participants reported age (in years) at menarche. Gynecological age (in years) was determined (chronological age minus age at menarche).	Injuries were recorded by coaches and athletic trainers, defined as any reported muscle, joint, or bone problem or injury resulting from participation in a practice, game, or meet and requiring the athlete to be removed from a practice, game, or meet or to miss a subsequent one
Rochelle 1961[61]	One-season, prospective cohort study. USA	Boys (n=62), age 13-16 years, who play junior high-school football	Skeletal age determined by an X-ray of the right hand and wrist. X-ray films were assessed for skeletal age by a medical doctor using Todd's Atlas as a standard for levels of maturation.	Injuries were recorded (method not described) and defined in this study as skeletal injuries involving fractures, dislocations, and sprains
Tenforde 2011[62]	14-months, retrospective study. USA	Girls (n=442), mean age 15.4±1 years, who are cross-country and track and field athletes	Menarcheal status was assessed by self-report and age at menarche in years was reported for girls who had reached mena.	An online survey was designed to assess previous overuse injuries. Each subject was asked to indicate which form of injury he or she had previously sustained from a list of the most common overuse injuries in long-distance runners.
Tenforde 2013[63]	Four-season, prospective cohort. USA	Girls (n=442), mean age 15.4±1 years, who are cross-country and track and field athletes	Menarcheal status was assessed by self-report and age at menarche in years was reported by girls who had reached mena. Late menarche was defined as age of menarche ≥15-years.	Stress fractures were self-reported prospectively. Subjects were asked if he or she had sustained a stress fracture injury and imaging used to confirm diagnosis (eg, magnetic resonance imaging, radiography, and bone scan).
van der Sluis 2014[65]	Three-year, prospective study, Netherlands	26 elite male soccer players, mean age 11.9 ± 0.8 years	Standing and sitting height was measured. Maturity offset was derived from an algorithm used to predict the time (years) a player spent in a state before peak height velocity.[102] After calculating maturity offset, predicted age at PHV was estimated as chronological age (CA) plus maturity offset.	The club physician diagnosed and recorded injuries defined as "any physical complaint sustained by a player that results from a soccer match or a soccer training, irrespective of the need for medical attention or time loss from soccer activities".
van der Sluis 2015[64]	Three-year, Prospective study, Netherlands	26 elite male soccer players, mean age 11.9 ± 0.8 years	Standing and sitting height was measured. Maturity offset was derived from an algorithm used to predict the time (years) a player spent in a state before peak height velocity.[102] After calculating maturity offset, predicted age at PHV was estimated as chronological age (CA) plus maturity offset.	The club physician diagnosed and recorded injuries defined as "any physical complaint sustained by a player that results from a soccer match or a soccer training, irrespective of the need for medical attention or time loss from soccer activities".

Characteristics of studies that evaluate fracture

Author Year	Study design	Participants	Exposure factor	Outcome – Fracture
Cheng 2009[66]	Seven-year, prospective study. Finland.	Girls (n=1,034) aged 10-13 years, who are school students.	Sexual development was determined by a nurse using the Tanner grading. The age at onset of menarche was determined by questionnaire and phone call. Growth chart data obtained via the school health care system from birth to the ages of 16–20. The age at peak height of each individual as an indicator of somatic maturity was determined by fitting a cubic spline curve over the age period 9–15 years (age at peak height velocity in years).	Fracture history (lifetime) was collected first by a self-reported questionnaire (with parental assistance) and then verified by medical records.
Chevalley 2011[67]	Eight-year, prospective study. Switzerland	Boys (n=176), mean age 15.2±0.5 years, from the general population	Tanner's pubertal stage was determined by a pediatrician.	Fracture history (age 7.4±0.5 to 15.2±0.5 years), including skeletal site, year of event, and type of treatment, was recorded from the children and their parents.
Chevalley 2012[68]	Twelve-year, prospective study. Switzerland	Girls (n=124), mean age 7.9±0.5 to 20.4±0.6 years, from the general population	Menarcheal age was assessed prospectively by direct interview.	Fracture history since birth was recorded at baseline and then at each follow-up visit from the children and their parents.
Darelid 2010[69]	Population based cross-sectional study. Sweden	Men (n=1,068), mean age 18.9±0.6 years, from the general population	Peak height velocity was available for 600 participants. Detailed growth and weight charts from birth until age 19-years were obtained from a central archive containing public school health records. These growth charts were used to calculate peak height velocity according to the infancy-childhood puberty model.[106]	Fracture history (lifetime) verified by x-ray records collected from hospitals and clinics.
Farr 2011[70]	Prospective trial study design, USA	Girls (n=465), aged 8-13 years, who are school students	Maturity was assessed via self-report (with available assistance) of breast development based on Tanner stages.[107] An index of maturation was also used that estimated years from peak height velocity, using Mirwald's equation.[102]	Fracture history was assessed via a health history questionnaire, completed by a parent/guardian.
Kindblom 2006[71]	Population based cross-sectional study, Sweden.	642 men (18.9 ±0.6 years of age) from the general population	Growth charts from birth until 19 years of age were used for estimation of peak height velocity (PHV) according to the infancy-childhood-puberty model. Age at PHV was defined as the age at maximum growth velocity during puberty and was estimated by the algorithm.[106]	Questionnaires were used to assess the occurrence of previous fractures.
Lynch 2016[72]	Nine-month prospective cohort study, Brazil	Boys (n=116) and girls (n=68), age 11 to 17 years, from schools and sports clubs	Maturity offsets were used to estimate time (years) from/to peak of height velocity.[102]	The occurrence of stress fractures was assessed during the follow-up period. The participants were asked "During the past 9 months, have you experienced any broken bones?"
Thandrayen 2011[73]	Retrospective analysis of a longitudinal study, South Africa	Boys and girls (n=533) at 15 years of age, from the general community	Skeletal maturity was assessed at 10 years of age, by a trained expert by scoring bone age from hand radiographs using the Tanner-Whitehouse bone-specific scoring technique.[108]	Fracture history (lifetime) was assessed by self-report questionnaire at age 15-years (with the help parent/guardian).
Wren 2012[74]	Six-year, longitudinal study, USA	Boys (n=726) and girls (n=744), mean age 11.0±3.1 years, from the general population. Children ≤10 years old with	All subjects underwent a physical examination by a pediatrician or pediatric endocrinologist to determine their stage of sexual maturation based on Tanner stages.[109] Skeletal maturity	Fracture incident was assessed at each visit, the participants were asked, "During the past year, has the child broken any bones?"

	a history of >1 fracture or >10 years old with >2 prior fractures were excluded	was assessed by pediatric radiologists on the basis of roentgenograms of the left hand and wrist according to the method of Greulich and Pyle.[110]		

Appendix 3

Appendix Table 3. Risk of bias scores based on the modified QUIPS tool

		1. Study Participation	2. Study Attrition	3. Aetiological Factor Measurement	4. Outcome Measurement	5. Study Confounding	6. Statistical Analysis and Reporting	Overall risk of bias (High/Low)
Pain	**Aegidius 2011 //**	low	N/A	moderate	moderate	low	low	**High risk of bias**
	Deubner 1977	moderate	high	high	moderate	high	high	**High risk of bias**
	Dolphens 2016	low	N/A	high	moderate	low	low	**High risk of bias**
	Dunn 2011 †	moderate	high	low	low	high	low	**High risk of bias**
	Ehrmann Feldman 2002 *	moderate	high	high	moderate	low	low	**High risk of bias**
	Feldman 2001 *	moderate	high	high	moderate	low	low	**High risk of bias**
	Hirano 2001	high	high	moderate	moderate	high	high	**High risk of bias**
	Hirsch 2012	low	N/A	moderate	low	high	moderate	**High risk of bias**
	Hulsegge 2011 ¦	moderate	high	low	moderate	low	low	**High risk of bias**
	Janssens 2011	moderate	high	low	moderate	moderate	low	**High risk of bias**
	Jones 2005	high	N/A	moderate	high	high	moderate	**High risk of bias**
	Kloven 2017 //	low	N/A	low	low	moderate	moderate	**High risk of bias**
	Kröner-Herwig 2009	moderate	high	moderate	moderate	high	low	**High risk of bias**
	LeResche 2005 †	moderate	N/A	low	moderate	moderate	low	**High risk of bias**
	Mattila 2008	low	high	high	moderate	moderate	moderate	**High risk of bias**
	Nissinen 1994 ‡	high	high	moderate	high	moderate	moderate	**High risk of bias**
	Picavet 2016 ¦	moderate	high	moderate	moderate	low	low	**High risk of bias**
	Poussa 2005 ‡	high	high	moderate	high	high	high	**High risk of bias**
	Rhee 2005	low	N/A	moderate	moderate	high	moderate	**High risk of bias**
	Shrier 2001 *	moderate	high	moderate	high	moderate	moderate	**High risk of bias**
	Sperotto 2014 §	moderate	N/A	moderate	low	high	low	**High risk of bias**
	Sperotto 2015 §	high	high	moderate	low	high	low	**High risk of bias**
	Vikat 2000	moderate	N/A	high	moderate	low	low	**High risk of bias**
	Wedderkopp 2005	high	N/A	low	moderate	moderate	low	**High risk of bias**
	Weiler 2010	high	N/A	low	moderate	high	high	**High risk of bias**
Injury	**Baxter-Jones 1993**	high	high	moderate	moderate	high	high	**High risk of bias**
	Bowerman 2014	high	moderate	moderate	moderate	high	low	**High risk of bias**
	Caine 1989	moderate	high	moderate	low	high	moderate	**High risk of bias**
	Costa 2017	high	N/A	moderate	low	high	high	**High risk of bias**
	Decloe 2014	moderate	Moderate	low	low	high	high	**High risk of bias**
	DiFiori 1997	high	high	moderate	moderate	high	high	**High risk of bias**
	Field 2011 ¶	moderate	high	low	moderate	low	low	**High risk of bias**
	Fourchet 2011	high	high	high	moderate	high	high	**High risk of bias**
	Gamboa 2008	high	N/A	low	moderate	high	high	**High risk of bias**
	Johnson 2009	high	high	low	high	high	high	**High risk of bias**
	Kemper 2015	high	high	low	low	high	low	**High risk of bias**
	Le Gall 2007	moderate	high	low	moderate	high	moderate	**High risk of bias**
	Linder 1995	high	high	moderate	moderate	high	high	**High risk of bias**
	Loud 2005 ¶	moderate	N/A	low	high	moderate	low	**High risk of bias**
	Malina 2006	high	high	moderate	low	low	low	**High risk of bias**
	Mónaco 2015	high	high	low	low	moderate	moderate	**High risk of bias**
	Rauh 2010	moderate	high	low	low	low	low	**High risk of bias**
	Rochelle 1961	high	high	low	high	high	moderate	**High risk of bias**
	Tenforde 2011 ¤	moderate	N/A	moderate	high	moderate	low	**High risk of bias**
	Tenforde 2013 ¤	moderate	high	moderate	high	moderate	low	**High risk of bias**
	van der Sluis 2014 ¢	high	high	high	low	high	moderate	**High risk of bias**
	van der Sluis 2015 ¢	high	high	high	low	high	moderate	**High risk of bias**
Fracture	**Cheng 2009**	high	high	moderate	low	low	low	**High risk of bias**
	Chevalley 2011	moderate	high	moderate	low	moderate	low	**High risk of bias**
	Chevalley 2012	high	high	moderate	moderate	low	moderate	**High risk of bias**
	Darelid 2010 ¥	moderate	N/A	high	low	moderate	high	**High risk of bias**
	Farr 2011	moderate	N/A	low	moderate	high	high	**High risk of bias**
	Kindblom 2006 ¥	moderate	N/A	low	moderate	low	low	**High risk of bias**
	Lynch 2016	moderate	low	moderate	low	low	moderate	**High risk of bias**
	Thandrayen 2011	moderate	high	low	low	moderate	high	**High risk of bias**
	Wren 2012	moderate	high	low	low	low	low	**High risk of bias**

Symbols indicates studies with the same sample of participants.

Appendix Table 4. Associations between maturity, growth, and musculoskeletal conditions

Prospective associations between biological maturity and back, neck or extremity pain, or any report of MSK pain

Pain type	Maturity	Article - Analysis	Association	Strength of Association	Adjusted for	Direction
Back pain	Status	Dunn 2011 - LCGA	↑PDS score, ↑%back pain (3-years)	↓%back pain PDS=2.02 vs. ↑%back pain PDS=2.07-2.42		Positive
		Janssens 2011a - Ord Log Reg	↑PDS score, ↑back pain (2-3-years)	*OR 1.34 [1.13-1.57]	Gender	Positive
			Boys: ↑PDS score, ↑back pain (2-3-years)	OR 1.37 [1.05–1.79]		Positive
			Girls: ↑PDS score, ↑back pain (2-3-years)	OR 1.31 [1.07–1.61]		Positive
		Janssens 2011b - Ord Log Reg	↑PDS score, ↑back pain (2-3-years)	*OR 1.61 [1.30-1.99]	Gender	Positive
			Boys: ↑PDS score, ↑back pain (2-3-years)	OR 1.90 [1.28–2.82]		Positive
			Girls: ↑PDS score, ↑back pain (2-3-years)	OR 1.50 [1.16–1.93]		Positive
	Timing	Mattila 2008 - Cox Reg	Boys: Late pubertal timing (first ejaculation), ↓LBP hospitalisation (mean 11-years)	Late puberty: HR 0.6 [0.5-0.8]		Positive
			Girls: No association. Puberty timing (first menstruation), LBP hospitalisation (mean 11-years)	Late puberty: HR 0.9 [0.6-1.6]		No association

Prospective associations between growth and back, neck or extremity pain, or any report of MSK pain

Pain type	Growth	Article - Analysis	Association	Strength of Association	Adjusted for	Direction
Back Pain	Spurt	Feldman 2001 – GEE & Descriptive	High growth spurt (>5cm in a 6-month period), ↑LBP (12-months)	*OR 3.09 [1.53, 6.01]	Age, gender, smoking, initial height, and mental health score	Positive
		Janssens 2011a – Log Reg	No association. Growth spurt (single item - PDS), back pain (2-3-years)	*OR 1.13 [0.98-1.31]	unclear: gender, age, functional somatic symptoms	No association
		Janssens 2011b – Log Reg	No association. Growth spurt (single item - PDS), back pain (2-3-years)	*OR 1.04 [0.89-1.21]	unclear: gender, age, functional somatic symptoms	No association
		Picavet 2016 - Log Reg	No association. Upper 20% weight gain, Back complaints (3-years)	*OR 1.25 [0.82-1.91]	Sex, age	No association
			No association. Upper 20% height gain, Back complaints (3-years)	*OR 1.08 [0.67-1.73]	Sex, age	No association
	Rate	Feldman 2001 – GEE & Descriptive	↑ absolute growth (cm in 6-months), ↑LBP (12-months)	LBP=1.7cm vs. no-LBP =1.0cm		Positive
			No Association. Absolute growth (cm in 12-months), LBP (18-months)	LBP=3.4cm vs. no-LBP=2.8cm		No association
		Nissinen 1994 – Log Reg	Boys: No association. Standing height growth (cm/year), LBP (2-years)	OR 1.01 [0.98-1.04]		No association
			Girls: No association. Standing height growth (cm/year), LBP (2-years)	OR 0.99 [0.97-1.02]		No association
			Boys: No association. Sitting height growth (cm/year), LBP (2-years)	OR 1.01 [0.98-1.03]		No association
			Girls: No association. Sitting height growth (cm/year), LBP (2-years)	OR 1.01 [0.98-1.03]		No association
			No association. Body mass growth (kg/m^2/year), LBP (2-years)	*OR 1.22 [0.93-1.57]	Sitting height, BMI, growth BMI, Kyphosis, Increase kyphosis, Hump size	No association
			Boys: No association. Body mass growth (kg/m^2/year), LBP (2-years)	OR 1.12 [0.88-1.43]		No association
			Girls: No association. Body mass growth (kg/m^2/year), LBP (2-years)	OR 1.37 [0.87-1.96]		No association
		Poussa 2005 – Log Reg	↑Growth of body height (11 to 14 years-of-age), ↑LBP (at 22 years of age)	*OR 1.32 [1.06–1.66]	unclear	Positive
			Men: ↑Growth of body height (11 to 14 years-of-age), ↑LBP (at 22 years of age)	*OR 1.36 [1.01–1.85]	unclear	Positive
			Women: No association. Growth of body height (11 to 14 years-of-age), LBP (at 22 years of age)	*OR 1.25 [0.92–1.69]	unclear	No association
			No association. Sitting height growth (11 to 14 years-of-age), LBP (at 22 years of age)	*OR 1.11 [0.89–1.38]	unclear	No association
			Men: No association. Sitting height growth (11 to 14 years-of-age), LBP (at 22 years of age)	*OR 1.21 [0.89–1.65]	unclear	No association
			Women: No association. Sitting height growth (11 to 14 years-of-age), LBP (at 22 years of age)	*OR 0.99 [0.73–1.36]	unclear	No association
			No association. BMI change (11 to 14 years-of-age), LBP (at 22 years of age)	*OR 1.07 [0.83–1.36]	unclear	No association
			Men: No association. BMI change (11 to 14 years-of-age), LBP (at 22 years of age)	*OR 0.99 [0.72–1.36]	unclear	No association
			Women: No association. BMI change (11 to 14 years-of-age), LBP (at 22 years of age)	*OR 1.15 [0.80–1.67]	unclear	No association
		Hulsegge 2011 - Imp Reg	No association. Height growth (cm/year), Back complaint (3-years)	OR 0.97 [0.77-1.22]		No association
			No association. Weight growth (kg/year), Back complaint (3-years)	OR 1.05 [0.86-1.29]		No association
Any MSK condition	Spurt	Picavet 2016 - Log Reg	No association. Upper 20% weight gain, Any musculoskeletal complaint (3-years)	*OR 1.05 [0.77-1.42]	Sex, age	No association
			No association. Upper 20% height gain, Any musculoskeletal complaint (3-years)	*OR 1.05 [1.00-1.10]	Sex, age	No association
	Rate	Hulsegge 2011 - Imp Reg	No association. Height growth (cm/year), Any musculoskeletal complaint (3-years)	OR 1.04 [0.94-1.15]		No association
			No association. Weight growth (kg/year), Any musculoskeletal complaint (3-years)	OR 1.10 [1.01-1.21]		No association
Neck-limb pain	Spurt	Ehrmann Feldman 2002 - GEE	No association. High growth spurt (>5cm in a 6-month period), Neck and upper limb pain (12-months)	*OR 1.80 [0.93, 3.48]	age, gender, height, body mass index, smoking, activity participation and mental health index	No association
Extremity pain	Spurt	Shrier 2001 - GEE	No association. High growth spurt (>5cm in 6months), Lower limb pain (12-months)	*OR 0.93 [0.50-1.71]	age, sex, smoking, activity participation, smoking, and mental health status	No association
			No association. High growth spurt (>5cm in 6months), Hip pain (12-months)	*OR 0.50 [0.13-2.18]	age, sex, smoking, activity participation, smoking, and mental health status	No association
			No association. High growth spurt (>5cm in 6months), Knee pain (12-months)	*OR 1.17 [0.53-2.59]	age, sex, smoking, activity participation, smoking, and mental health status	No association

			No association. High growth spurt (>5cm in 6months), Leg pain (12-months)	*OR 1.57 [0.65-3.91]	age, sex, smoking, activity participation, smoking, and mental health status	No association
			No association. High growth spurt (>5cm in 6months), Ankle & Foot pain (12-months)	*OR 1.37 [0.75-2.49]	age, sex, smoking, activity participation, smoking, and mental health status	No association
		Picavet 2016 - Log Reg	No association. Upper 20% weight gain, Upper extremity complaint (3-years)	*OR 1.10 [0.70-1.75]	Sex, age	No association
			No association. Upper 20% weight gain, Lower extremity complaint (3-years)	*OR 1.13 [0.80-1.59]	Sex, age	No association
			No association. Upper 20% height gain, Upper extremity complaint (3-years)	*OR 1.48 [0.92-2.39]	Sex, age	No association
			No association. Upper 20% height gain, Lower extremity complaint (3-years)	*OR 1.09 [0.75-1.58]	Sex, age	No association
	Rate	Hulsegge 2011 - Imp Reg	No association. Height growth (cm/year), Lower extremity complaint (3-years)	OR 1.05 [0.93-1.18]		No association
			↑Weight growth (kg/year), ↑lower extremity complaints (3-years)	*OR 1.16 [1.05-1.29]	age, sex, physical activity, daytime tiredness, mental health status	Positive
			No association. Height growth (cm/year), Upper extremity complaint (3-years)	OR 1.02 [0.86-1.22]		No association
			No association. Weight growth (kg/year), Upper extremity complaint (3-years)	OR 1.04 [0.88-1.22]		No association
Cross-sectional associations between biological maturity and back, neck or extremity pain, or any report of MSK pain						
Pain type	**Maturity**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Back Pain	Status	Dolphens 2016 - Log Reg	No association. Maturity status (early vs average maturers; method undefined), LBP	*OR 1.83 [0.38–8.72]	Physical characteristics, sociodemographic, lifestyle factors, psychosocial characteristics, and other pain complaints	No association
			No association. Maturity status (late vs average maturers; method undefined), LBP	*OR 1.15 [0.16–8.15]	Physical characteristics, sociodemographic, lifestyle factors, psychosocial characteristics, and other pain complaints	No association
		Hulsegge 2011 - Imp Reg	No association. PDS, back complaints	OR 1.23 [0.77-1.96]		No association
			Boys: ↑PDS score, ↑back complaints	OR 2.86 [1.14-7.15]		Positive
			Girls: No association. PDS, back complaints	OR 1.09 [0.65-1.84]		No association
		Jones 2005 - Log Reg	No association. Genital development, Recurrent NSLBP	controls 3.3[0.9] vs. recurrent-LBP 3.7[0.7]		No association
			No association. Pubic hair staging, Recurrent NSLBP	controls 3.2[0.7] vs. recurrent-LBP 3.6[0.7]		No association
		LeResche 2005 - Log Reg	Boys: ↑PDS score, ↑%back pain	OR 1.9		Positive
			Girls: ↑PDS score, ↑%back pain	OR 2.0		Positive
		Picavet 2016 - Log Reg	No association. PDS, Back complaint	*OR 1.21 [0.92-1.59]	Sex, age	No association
		Wedderkopp 2005 - Log Reg	Girls: Advancing pubertal stages (breast development), ↑back pain anywhere	Puberty stages 2 to 5 OR 1.1-2.6		Positive
			Girls: Advanced pubertal stages (breast development), ↑LBP	Puberty stages 2 to 5 OR 0.9-19.6		Positive
			Girls: No association. Pubertal stage (breast development), mid back pain	Puberty stage 2 to 5 OR 1.0-1.6		No association
	Timing	Dolphens 2016 - Log Reg	No association. Years from age at PHV, LBP	*OR 1.42 [0.14–14.50]	Physical characteristics, sociodemographic, lifestyle factors, psychosocial characteristics, and other pain complaints	No association
			No association. Predicted growth remaining, LBP	*OR 1.04 [0.79–1.36]	Physical characteristics, sociodemographic, lifestyle factors, psychosocial characteristics, and other pain complaints	No association
		Hulsegge 2011 - Imp Reg	No association. Height-for-age/sex based on reference growth curves, Back complaint	OR 1.08 [0.85-1.38]		No association
		Picavet 2016 - Log Reg	No association. Height-for-age, Back complaint	*OR 1.13 [0.98-1.30]	Sex, age	No association
			↑Weight-for-age, ↑Back complaints	*OR 1.31 [1.12-1.53]	Sex, Age, Being bullied, Sleeping problems, Smoking (>1/mo), Back complaint at 11 years	Positive
		Vikat 2000 - Log Reg	Earlier timing of puberty (age at menarche / first ejaculation), ↑%LBP	Early timing: OR 1.2		Positive
Neck-shoulder	Status	Wedderkopp 2005 - Log Reg	Girls: No association. Pubertal stage (breast development), neck pain	Puberty stages 2 to 5 OR 0.5-1.2		No association
	Timing	Vikat 2000 - Log Reg	No association. Timing of puberty (age at menarche or first ejaculation), neck-shoulder pain ("best-fitting model")	early timing: *OR 1.1	sex, age, psychosomatic symptoms, LBP, long-term illness, cold, vision, smoking	No association
Extremity Pain	Status	Hirano 2001 – t-test	Boys: No association. Skeletal age, Disorder of the knee extensor mechanism	normal knees 12.99±1.89 years vs. painful knees 12.13±1.29 years		No association
		Hulsegge 2011 - Imp Reg	Advanced pubertal status (PDS), ↑upper extremity complaints	OR 1.46 [1.03-2.05]		Positive
			Advanced pubertal status (PDS), ↑lower extremity complaints	OR 1.45 [1.13-1.86]		Positive
		Picavet 2016 - Log Reg	No association. PDS, Upper extremity complaint	*OR 1.22 [0.91-1.63]	Sex, age	No association
			No association. PDS, Lower extremity complaint	*OR 1.04 [0.84-1.29]	Sex, age	No association
	Timing	Hulsegge 2011 - Imp Reg	↑Height-for-age scores, ↑lower extremity complaints	OR 1.16 [1.01-1.32]		Positive
			No association. Height-for-age score, Upper extremity complaint	OR 1.16 [0.96-1.42]		No association
		Picavet 2016 - Log Reg	No association. Height-for-age, Upper extremity complaint	*OR 1.03 [0.88-1.19]	Sex, age	No association
			↑Height-for-age, ↑Lower extremity complaints	*OR 1.13 [1.01-1.27]	Sex, age	Positive
			No association. Weight-for-age, Upper extremity complaint	*OR 1.16 [0.99-1.35]	Sex, age	No association
			↑Weight-for-age, ↑Lower extremity complaints	*OR 1.15 [1.03-1.29]	Sex, age	Positive
MSK pains	Status	Hirsch 2012 - X^2	Later pubertal stage (PDS), ↑pain (outside the face)	*OR 1.61 [1.21-2.13]	Gender, school type	Positive

		Hulsegge 2011 - Imp Reg	Advanced pubertal status (PDS), ↑ any musculoskeletal complaints	*OR 1.36 [1.09-1.70]	Weight-for-height z score, mental health status, daytime tiredness, physical activity	Positive
		LeResche 2005 - Log Reg	Girls: ↑Level of puberty (PDS), ↑%one or more pains	*OR 1.37 [1.12-1.68]	Child age, parent education	Positive
			Boys: ↑Level of puberty (PDS), ↑%one or more pains	*OR 1.37 [1.07-1.75]	Child age, parent education	Positive
		Picavet 2016 - Log Reg	No association. PDS, Any musculoskeletal complaint	*OR 1.02 [0.86-1.22]	Sex, age	No association
		Rhee 2005 - Log Reg	Boys: Advanced pubertal status, ↑musculoskeletal pain	*OR 1.61 [1.37-1.89]	Sampling probability and design factors	Positive
			Girls: Advanced pubertal status, ↑musculoskeletal pain	*OR 1.50 [1.32-1.71]	Sampling probability and design factors	Positive
		Sperotto 2014 - X^2	↓Pubertal stage, ↑chronic musculoskeletal pain symptoms	Pre-pubertal 83.0% vs. Pubertal 17.0%		Negative
		Sperotto 2015 -X^2	↑Pubertal stage, ↑%Persistent musculoskeletal pain	Pre-pubertal -10% vs. Pubertal +4%		Positive
	Timing	Hulsegge 2011 - Imp Reg	↑height-for-age scores, ↑any musculoskeletal complaints	OR 1.15 [1.03-1.29]		Positive
		Rhee 2005 - Log Reg	Boys: Early pubertal timing, ↑musculoskeletal pain	*OR 1.41 [1.23-1.62]	Sampling probability and design factors	Positive
			Girls: Early pubertal timing, ↑musculoskeletal pain	*OR 1.29 [1.11-1.50]	Sampling probability and design factors	Positive
		Picavet 2016 - Log Reg	No association. Height-for-age, Any musculoskeletal complaint	*OR 1.10 [1.00-1.21]	Sex, age	No association
			↑Weight-for-age, ↑Any musculoskeletal complaint	*OR 1.19 [1.08-1.31]	Sex, age	Positive
		Kloven 2017 - Log Reg	Girls: Early menarche, ↑Chronic non-specific pain	*OR 1.5 [1.2-1.9]	Age, BMI, parents' combined income, both parents' highest education, anxiety and depressive symptoms	Positive
			Girls: Early physical maturation, ↑Chronic non-specific pain	*OR 1.6 [1.3-1.9]	Age, BMI, parents' combined income, both parents' highest education, anxiety and depressive symptoms	Positive
			Girls: Early menarcheal age, ↑Chronic non-specific pain	OR 0.84 [0.79-0.90]		Positive
Prospective associations between biological maturity and head/face pain						
Pain Type	**Maturity**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Head or face pain	Status	Dunn 2011 - LCGA	↑PDS score, ↑%headache (3-years)	↓%Headache PDS=2.04 vs. ↑%Headache PDS=2.02-2.29		Positive
			↑PDS score, ↑%facial pain (3-years)	↓%facial pain PDS=2.02 vs. ↑%fascial pain PDS=2.13-2.29		Positive
		Janssens 2011a - Ord Log Reg	No association. PDS, headache (2-3-years)	*OR 1.07 [0.93-1.25]	Gender	No association
			Girls: No association. PDS, headache (2-3-years)	OR 1.14 [0.95–1.37]		No association
			Boys: No association. PDS, headache (2-3-years)	OR 0.96 [0.75–1.23]		No association
		Janssens 2011b - Ord Log Reg	No association. PDS, headache (2-3-years)	*OR 1.18 [0.94-1.48]	Gender	No association
			Girls: No association. PDS, headache (2-3-years)	OR 1.24 [0.94–1.61]		No association
			Boys: No association. PDS, headache (2-3-years)	OR 1.02 [0.66–1.59]		No association
	Timing	Kröner-Herwig 2009 - Log Reg	Girls: Inconsistent association. Occurrence of menarche, headache (migraine, tension-type headache) (3-years)	OR 0.75 - 1.65		No association
Cross-sectional associations between biological maturity and head/face or chest pain						
Pain Type	**Maturity**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Head or face	Status	Rhee 2005 - Log Reg	Boys: Advanced pubertal group, ↑ headaches	*OR 1.14 [0.96-1.35]	Sampling probability and design factors	Positive
			Girls: Advanced pubertal group, ↑ headaches	*OR 1.78 [1.52-2.08]	Sampling probability and design factors	Positive
		LeResche 2005 - Log Reg	Girls: ↑ pubertal stage (PDS), ↑%headache	OR 1.4		Positive
			Boys: No association. PDS, headache	OR 1.0		No association
			Girls: ↑pubertal stage (PDS), ↑%facial pain	OR 1.6		Positive
			Boys: ↑pubertal stage (PDS), ↑%facial pain	OR 1.5		Positive
		Hirsch 2012 - X^2	No association. PDS, temporomandibular pain	*OR 1.13 [0.80-1.60]	Gender, school type	No association
			Advanced pubertal stage (PDS), ↑ any TMD diagnosis	*OR 1.58 [1.03-2.42]	Gender, school type	Positive
			Advanced pubertal stage (PDS), ↑ IIa TMD diagnosis	*OR 2.00 [1.21–3.26]	Gender, school type	Positive
			No association. PDS, I/III TMD diagnoses	*OR 0.74 [0.32–1.71]	Gender, school type	No association
		Weiler 2010 - Fisher	Boys: No association. Pubertal status (Tanner), TMD	Before the growth spurt: no TMD 17% vs. ≥ one sign or symptom of TMD 12%;		No association
				During growth spurt period: no TMD 70% vs. ≥ one sign or symptom of TMD 71%;		
				End of growth spurt: no s TMD 13% vs. ≥ one sign or symptom of TMD 18%		
	Timing	Aegidus 2011 - Log Reg	Girls: Late menarche (>12 years), ↓%Headache among adolescents	*OR 0.8 [0.7–0.9]	age, body mass index, and for use of oral contraceptives	Positive
			Girls: Late menarche (>12 years), ↓%Migraine among adolescents	*OR 0.7 [0.5–0.9]	age, body mass index, and for use of oral contraceptives	Positive
			Girls: Late menarche (>12 years), ↓%Tension type headache among adolescents	*OR 0.8 [0.6–0.9]	age, body mass index, and for use of oral contraceptives	Positive
			Girls: No association. Age at menarche, Non-classifiable headache among adolescents	*OR 0.9 [0.6–1.2]	age, body mass index, and for use of oral contraceptives	No association

		Rhee 2005 - Log Reg	Boys: No association. Pubertal timing, headache	late timing 20.56% vs. on-time=20.56% vs. early timing 21.28%	Sampling probability and design factors	No association
			Girls: Early timing of puberty, ↑ headache	*OR 1.39 [1.22-1.58]	Sampling probability and design factors	Positive
		Deubner 1977 - X^2	Girls: No association. Menarchial status, Headache	pre- 78.5% vs. post- 84.2% menarche		No association
			Girls: No association. Menarchial status, Migraine	pre- 21.5% vs. post- 15.8% menarche		No association
Chest pain	Status	Rhee 2005 - Log Reg	Boys: No association. Pubertal status, chest pain	early pubertal 3.36% vs. mid-pubertal 3.36% vs. advanced pubertal 3.01%	Sampling probability and design factors	No association
			Girls: No association. Pubertal status, chest pain	early pubertal 4.43% vs. mid-pubertal 4.45% vs. advanced pubertal 5.04%	Sampling probability and design factors	No association
	Timing	Rhee 2005 - Log Reg	Boys: No association. Pubertal timing, chest pain	late timing 3.61% vs. on-time 2.69% vs. early timing 3.66%	Sampling probability and design factors	No association
			Girls: Late pubertal timing, ↑chest pain	*OR 1.79 [1.25-2.57]	Sampling probability and design factors	Negative
Prospective associations between biological maturity and sports injuries						
Sports Injury	**Maturity**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Athletic injury	Timing	Fourchet 2011 - ANOVA	Boys: Late maturation (age at peak height velocity), ↑foot/ankle/lower leg injury rate (3-years)	Late maturity IR 1.3 [0.4-2.2] vs. Normal maturity IR 0.4 [-0.1-1.4] vs. Early maturity IR 0.5 [-1.0-1.5]		Negative
		Tenforde 2013 – Descriptive & Cox Reg	Girls: No association. Age at menarche, Stress fracture (4-season)	Stress fracture 13.4[±1.5] vs. no stress fracture 12.6[±1.3]		No association
			Girls: Late age at menarche (>15yrs), Stress fracture (4-season)	*HR 2.49 [1.01-6.17]	Menstrual history, BMI, eating disorders, dietary intake of dairy and calcium, history of fracture, training variables, and prior sports participation	Negative
Football injury	Status	Linder 1995 - Fisher	Boys: ↑Maturity (Tanner stage), ↑Rate of football injury (2-season)	Stage I 0% vs. Stage II 3% vs. Stage III 16% vs. Stage IV 17% vs. Stage V 20%		Positive
		Rochelle 1961 - t test	Boys: No association. Skeletal age, Football injury (1-season)	Non-injured 183 vs. Injured 185, difference 2.0 months, S.E. Diff. 4.84		No association
	Timing	Johnson 2009 - ANCOVA & Poisson Reg	Boys: No association. Maturity status (chronological age minus skeletal age), Soccer injury rate (6-yeasrs)	Late Maturity IR 1.4 [1.2-1.6] vs. Normal Maturity IR 1.5 [1.39-1.61] vs. Early Maturity IR 1.8 [1.59-2.0]		No association
		Le Gall 2007 - Kruskal–Wallis & SNK	Boys: No association. Maturity status (skeletal age vs. chronological age), Soccer injury rate (10-seasons)	Early maturity IR 13.2 [9.3–17.6] vs. Normal maturity IR 12.3 [9.6–14.7] vs. Late maturity IR 6.5 [2.5–10.6]		No association
			Boys: Early maturity (skeletal age vs. chronological age), ↑Soccer re-injury rate (10-seasons)	Early maturity IR 0.35 vs. Normal maturity IR 0.12 vs. Late maturity IR 0.08		Positive
			Boys: No association. Maturity status (skeletal age vs. chronological age), Moderate severity soccer injury rate (10-seasons)	Early maturity IR 1.7 vs. Normal maturity IR 2.0 vs. Late Maturity IR 0.6		No association
			Boys: Late maturity (skeletal age vs. chronological age), ↑Severe soccer injury (10-seasons)	Early maturity IR 0.3 vs. Normal maturity IR 0.6 vs. Late maturity IR 0.9		Negative
		Malina 2006 -MANCOVA	No association. Percentage of predicted mature height, Football injury (2-seasons)	Mean maturity z-score: non-injured 0.28-0.73 vs. injured 0.06-0.69	age	No association
		van der Sluis 2014 - ANOVA	Boys: Period of PHV, ↑N traumatic injuries (3-years)	Pre-PHV 0.81 [±1.10] vs. PHV 1.42 [±1.33] vs. Post-PHV 1.39 [±1.50]		Positive
			Boys: No association. Maturity, N overuse injuries (3-years)	Pre-PHV 0.81 [±1.41] vs. PHV 1.15 [±1.29] vs. Post-PHV 1.42 [±1.50]		No association
			Boys: No association. Maturity, N missed days (3-years)	Pre-PHV 7.27 [±10.05] vs. PHV 15.69 [±19.93] vs. Post-PHV 10.73 [±17.77]		No association
			Boys: No association. Maturity, training IR (3-years)	Pre-PHV 2.57 [±3.22] vs. PHV 4.19 [±4.13] vs. Post-PHV 3.84 [±3.48]		No association
			Boys: No association. Maturity, training IR (time loss) (3-years)	Pre-PHV 1.59 [±2.04] vs. PHV 2.80 [±3.28] vs. Post-PHV 1.86 [±2.41]		No association
			Boys: No association. Maturity, match IR (3-years)	Pre-PHV 12.49 [±26.06] vs. PHV 20.50 [±28.00] vs. Post-PHV 23.08 [±28.80]		No association
			Boys: No association. Maturity, match IR (time loss) (3-years)	Pre-PHV 9.43 [±19.06] vs. PHV 11.77 [±19.86] vs. Post-PHV 15.91 [±21.03]		No association
		van der Sluis 2015 -Mann-Whitney	Boys: No association. Maturity, traumatic injury pre-PHV (3-years)	IR 1.14 [±1.97] vs. 2.33 [±3.40]		No association
			Boys: No association. Maturity, traumatic injury at PHV (3-years)	IR 3.14 [±3.52] vs. 3.96 [±2.57]		No association
			Boys: No association. Maturity, traumatic injury post-PHV (3-years)	IR 2.95 [±3.59] vs. 2.97 [±3.74]		No association
			Boys: Late maturity, ↑overuse injury pre-PHV (3-years)	IR 0.49 [±0.94] vs. 3.53 [±4.63]		Negative
			Boys: Late maturity, ↑overuse injury at PHV (3-years)	IR 1.56 [±1.92] vs. 3.97 [±3.11]		Negative
			Boys: No association. Maturity, overuse injury post-PHV (3-years)	IR 2.73 [±3.84] vs. 3.60 [±2.73]		No association
Gymnastics injury	Status	Caine 1989 - Discrim	Girls: No association. Sexual maturity (Tanner stage), Gymnastics injury rate (1-year)	Stage one IR 2.27-2.54 vs. Stage 2-3 IR 4.17-5.22		No association
			Girls: ↑Sexual maturity (Tanner stage), ↑Gymnastics injury severity (% time-loss injuries) (1-year)	Stage one 14.9%-15.5% vs. Stages two-to-three 28.5%-36.6%		Positive
Handball injury	Status	Mónaco 2015 - Descriptive & MANOVA	Boys: No association. Testicular volume (cm^3), Overall IR (2-seasons)	*$IR_{6\text{-}10cm^3}$ 8.6 vs. $IR_{10\text{-}15cm^3}$ 5.8 vs. $IR_{20\text{-}25cm^3}$ 5.3	Age, Category, Tanner stage, Δtanner stage, Testicular volume, Pubertal Stage	No association
			Boys: No association. Tanner Stage, Overall IR (2-seasons)	*IR_{G2} 4.5 vs. IR_{G3} 6.5 vs. IR_{G4} 5.6 vs. IR_{G5} 5.3	Age, Category, Tanner stage, Δtanner stage, Testicular volume, Pubertal Stage	No association
			Boys: Unclear. Bone age, Overall IR (2-seasons)	$IR_{Slow(<1)}$ 2.9 vs. IR_{Normal} 5.1 vs. $IR_{Advanced(>1)}$ 6.1		No association

			Boys: No association. Pubertal stage, Overall IR (2-seasons)	*IR_{P2} 7.0 vs. IR_{P3} 6.2 vs. IR_{P4} 5.4	Age, Category, Tanner stage, Δtanner stage, Testicular volume, Pubertal Stage	No association
			Boys: No association. Change in Tanner Stage, Overall IR (2-seasons)	*IR_0 4.3 vs. IR_1 6.5 vs. IR_2 6	Age, Category, Tanner stage, Δtanner stage, Testicular volume, Pubertal Stage	No association
Ice-hockey	Timing	Decloe 2014 - Poisson Reg	Girls (PeeWee): Early menarche, ↑Ice hockey injury rate (1-season)	*IIR 4.1 [1.0-16.8]	Cluster (i.e. team)	Positive
Multisport injury	Status	Baxter-Jones 1993 - X^2	No association. Sexual maturity (Tanner stage), Sports injury rate (gymnastics, football (soccer), swimming, and tennis) (2-years)	Not reported		No association
			No association. Sexual maturity (Tanner stage), Sports injury severity (gymnastics, football (soccer), swimming, and tennis) (2-years)	Not reported		No association
	Timing	Rauh 2010 - t test	Girls: No association. Age at menarche, Multisport injury (1-season)	Uninjured 12.3±1.2 vs. Injured 12.6±1.2		No association
			Girls: No association Gynaecological age (chronological age minus age at menarche), Multisport injury (1-season)	Uninjured 3.4±1.7 vs. Injured 3.1±1.9 years		No association
Prospective associations between growth and sports injuries						
Sports Injury	**Growth**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Football injury	Spurt	Kemper 2015 - Log Reg	Boys: ↑Growth of body height (≥ 0.6 cm/month), ↑Injury occurrence (1-season)	*OR 1.63 [1.06–2.52]	Age	Positive
			Boys: ↑Growth of BMI (> 0.3 kg/m²/month), ↑Injury occurrence (1-season)	*OR 1.61 [1.04–2.49]	Age	Positive
Handball injury	Rate	Mónaco 2015 - Descriptive & MANOVA	Boys: No association. Change in testicular volume (cm3), Overall IR (2-seasons)	$IR_{Δ0-4}$ 9.6 vs. $IR_{Δ5-8}$ 7.4 vs. $IR_{Δ>8}$ 4.7		No association
	Spurt		Boys: No association. Peak growth rate (cm/6-months), Overall IR (2-seasons)	IR_{0cm} 4.7 vs. $IR_{0.5-3cm}$ 4.8 vs. IR_{4-6cm} 5.5		No association
Cross-sectional associations between biological maturity and sports injuries						
Sports injury	**Maturity**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Gymnastics injury	Status	DiFiori 1997 - Descriptive	No association. Skeletal age, Distal radial stress injury	Injury 11.1[±2.3] vs. Normal 10.9[±3.3]		No association
Organised physical activity	Timing	Costa 2017 – Log Reg	Girls: Higher maturity offset, ↑Injury	*OR 2.1 [1.2-3.7]	Physical activity level	Positive
		Costa 2017 - Gam Reg	Girls: Early maturity, ↑Injury rate	*β -0.70 [-1.22, -0.19]	Physical activity level, bone age, maturity offset	Positive
			Girls: ↑Bone age, ↑Injury rate	*β 0.18 [0.04, 0.32]	Physical activity level, maturation level, maturity offset	Positive
			Girls: Lower maturity offset, ↑Injury rate	*β −0.21 [−0.39, −0. 16]	Physical activity level, maturation level, bone age	Negative
Retrospective associations between biological maturity and sports injuries						
Athletic injury	Timing	Tenforde 2011 - t test	Girls: No association. Age at menarche, Running injury (14-months)	No injury 12.7±1.3 vs. Previous injury 12.7±1.3		No association
Prospective associations between biological maturity and ballet injuries						
Injury	**Maturity /Growth**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Ballet injury	Status	Bowerman 2014 - Poisson Reg	No (trivial) association. Sexual maturity (Tanner scale), Ballet injury rate (6-months)	*RR 1.06 [0.59-1.90]	gender, age, height, body mass, occurrence of menarche, and change in foot length	No association
	Timing	Bowerman 2014 - Poisson Reg	Girls: No (trivial) association. Age at menarche, Ballet injury rate (6-months)	*RR 1.03 [0.10-8.95]	gender, age, height, body mass, Tanner stage, change in foot length	No association
	Spurt	Bowerman 2014 - Poisson Reg	No (unclear) association. Foot length growth (0.5cm), Ballet injury rate (6-months)	Right: *RR 1.41 [0.93-2.13] Left: *RR 1.37 [0.77-2.44]	gender, age, height, body mass, Tanner stage, occurrence of menarche	No association
Retrospective associations between biological maturity and ballet injuries						
Ballet injury	Timing	Gamboa 2008 – t-test	Girls: No association. Age at menarche, Ballet Injury (5-year)	Non-injured 13.5±1.2 vs. Injured 13.0±1.5		No association
Prospective associations between biological maturity and stress fracture injuries						
Injury	**Maturity**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Stress fracture	Timing	Field 2011 – Cox Reg	Girls: ↑Age at menarche, ↑Stress fracture (7-years)	*HR 1.35 [1.12-1.63]	Family history, Activity, age BMI, low bone mineral density	Negative
		Loud 2005 - GEE	Girls: No association. Age at menarche, stress fracture (2-years)	*OR 0.99 [0.94-1.17]	age	No association
Prospective associations between biological maturity and fractures						
Fracture	**Maturity**	**Article - Analysis**	**Association**	**Strength of Association**	**Adjusted for**	**Direction**
Past year	Status	Wren 2012 - Cox Reg	↑Sexual maturation (Tanner stages 2-4), ↑Fracture risk (6-years)	HR 1.74 [1.32-2.29]		Positive
			↑Skeletal age (10-14 years), ↑Fracture risk (6-years)	HR 2.17 [1.65-2.85]		Positive
Past nine months	Timing	Lynch 2016 - Descriptive	No association. PHV, Fracture (9-months)	No fracture -1.24±1.2 years vs. fracture -1.12±1.5 years		No association
Retrospective associations between biological maturity and fractures						
At 7-15 years	Status	Chevalley 2011 - Descriptive	Boys: No association. Sexual development (Tanner stage), Fracture history (7-15 years-of-age)	Without fracture: P2 (n=1), P3 (n=7), P4 (n=49), P5 (n=32). With fracture: P2 (4), P3 (n=6), P4 (n=44), P5 (n=33)		No association
Lifetime	Status	Cheng 2009 – Descriptive & ANOVA	No association. Sexual development (Tanner grade), Fraction history (lifetime)	No fracture P1=49%, P2=45%, P3=6%. Upper limb fracture P1=49%, P2=43%, P3=8%.Upper limb fracture at 8-14 years P1=50%, P2=40%, P3=10%. Other fracture P1=64%, P2=36%, P3=0%		No association
		Farr 2011 - t test	Girls: ↑Maturity (Tanner stage), ↑prior fracture	Fracture 2.5±0.9 vs. without fracture 2.0±1.0		Positive
		Thandrayen 2011 - Descriptive	Black females at 10 years: No association. Skeletal maturity (Bone age), Fracture history (lifetime)	With fracture 9.8±0.88 years vs. without fracture 9.9±1.1 years		No association
			Black females at 15 years: No association. Skeletal maturity (Bone age), Fracture history (lifetime)	With fracture 14.7±0.5 years vs. without fracture 14.7±0.62 years		No association

			Black males at 10 years: No association. Skeletal maturity (Bone age), Fracture history (lifetime)	with fracture 9.9±0.76 years vs. without fracture 9.9±0.70 years		No association
			Black males at 15 years: No association. Skeletal maturity, Fracture history (lifetime)	with fracture 14.73±1.16 years vs. without fracture 14.8±1.30 years		No association
			White females at 10 years: No association. Skeletal maturity, Fracture history (lifetime)	with fracture 10.2 ±1.26 years vs. without fracture 10.0±1.24 years		No association
			White females at 15 years: No association. Skeletal maturity, Fracture history (lifetime)	with fracture 14.8±0.48 years vs. without fracture 14.6±0.71 years		No association
			White males at 10 years: No association. Skeletal maturity, Fracture history (lifetime)	with fracture 10.2±0.72 years vs. without fracture 10.1 ±0.66 years		No association
			White males at 15 years: No association. Skeletal maturity, Fracture history (lifetime)	with fracture 15.8±0.86 years vs. without fracture 15.3±1.06 years		No association
	Timing	Chevalley 2012 - Descriptive	Girls: Late maturation (age at menarche), ↑Fracture history (lifetime)	With fracture 13.45±1.11 years vs. without fracture 12.78±1.19 years		Negative
		Cheng 2009 – Descriptive & ANOVA	No association. Age at menarche, Fracture history (lifetime)	No fracture 13.0[0.9] years vs. upper limb fracture 13.2[1.0] years vs. upper limb fracture at 8-14years 13.4[1.1] years vs. other fracture 12.9[0.7] years		No association
			No association. Age at peak height estimate, Fracture history (lifetime)	No fracture 12.4[1.2] years vs. upper limb fracture 12.3[1.0] years vs. upper limb fracture at 8-14 years 12.3[1.1] vs. other fracture 12.3[1.3]		No association
		Farr 2011 - t test	Girls: ↑Maturity (Maturity offset - Index of maturation), ↑prior fracture	Fracture -0.6±1.0 years vs. without fracture -1.2±1.0 years		Positive
Not defined	Timing	Kindblom 2006 – Log reg	Men: No association. Age at PHV, previous fracture	*OR 1.08 [0.89–1.31]	radius areal bone mass density	No association
			Men: No association. Age at PHV, previous upper limb fracture	*OR 0.35 [0.00–8.77]	radius areal bone mass density	No association
			Men: ↑Age at PHV, ↑%previous fracture	*OR 1.19 [1.00–1.42]	age at bone analysis, height, weight, smoking status, physical activity, and calcium intake for osteopenia variables and for age at bone analysis for fractures	Negative
			Men: ↑Age at PHV, ↑%Previous upper limb fracture	*OR 1.39 [1.08–1.79]	age at bone analysis, height, weight, smoking status, physical activity, and calcium intake for osteopenia variables and for age at bone analysis for fractures	Negative
		Darelid 2010 - Descriptive	Men: Coincided. Age at PHV (Years from peak height velocity estimate), ↑fracture incidence (period not defined)	Peak height velocity: -11years = 8 fractures*; ≥11<-9years = 17 fractures*; ≥9<-7years = 16 fractures*; ≥7<-5years = 27 fractures*; ≥5<-3years = 31 fractures*; ≥3<-1years = 42 fractures*; +/-1years = 58 fractures*; ≥1<3years = 24 fractures*; ≥3<5years = 10 fractures*; ≥5years = 2 fractures		Positive

Abbreviations: ANCOVA Analysis of covariance; ANOVA Analysis of variance; BMI Body mass index; CM Centimetre; Cox Reg Cox regression; Fisher Fisher exact test; Gam Reg Gamma Regression; GEE Generalised estimating equation; HR Hazard ratio; IIR Injury incidence rate; Imp Reg Imputation Regression; IR Injury rate; KG Kilogram; LBP Low back pain; LCGA Latent class growth analysis; Log Reg Logistic regression; M Meter; MANCOVA Multivariate analysis of covariance; MSK musculoskeletal; MTH Month; N Number; NSLBP Non-specific low back pain; OR Odds ratio; Ord Log Reg Ordinal logistic regression; PDS Pubertal Development Scale; PHV Peak height velocity; SNK Student–Newman–Keuls test; TMD Temporomandibular disorder.

Chapter Five

Short-term Clinical Course of Knee Pain in Children and Adolescents: A Feasibility Study Using Electronic Methods of Data Collection

“Failure is success in progress.”

- Albert Einstein

RESEARCH ARTICLE

Short-term Clinical Course of Knee Pain in Children and Adolescents: A Feasibility Study Using Electronic Methods of Data Collection

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Abstract

Background and Purpose. Musculoskeletal disorders, such as knee pain, are common in children and adolescents, but there is a lack of high quality research that evaluates the clinical course of these conditions. The objective of this study was to evaluate the feasibility of conducting a prospective study of children and adolescents with knee pain using electronic methods of data collection. **Methods.** Children and adolescents with knee pain that presented to primary care physiotherapy clinics were enrolled and followed-up on a weekly basis via short messaging service (SMS) until their knee pain had recovered (i.e. two consecutive weeks of no pain). Feasibility was assessed in terms of recruitment, retention and response rates to SMS and an online questionnaire. Baseline and 6-month follow-up measures included pain, disability, physical function, physical activity and health related quality of life. Kaplan–Meier survival analysis was used to estimate the median time to knee pain recovery. **Results.** Thirty participants (mean age 13.0 ± 2.2 years, 53% boys) were recruited over 26 months. The overall response rate to weekly SMS follow-up was 71.3% (809 received/1135 sent). One third of participants stopped responding to SMS prior to recovery, and these participants typically had a much lower response rate during the time they remained in the study. At 6-month follow-up, 80% of the cohort completed the final online questionnaire, and 29% of participants still reported current knee pain (≥1/10 VAS). The median time for knee pain recovery was 8 weeks (95% CI: 5, 10). **Conclusion.** Electronic data collection alone seems insufficient to track pain recovery in young people and may need to be supplemented with more traditional data collection methods. Researchers should consider further measures to address slow recruitment rates and high attrition when designing large prospective studies of children and adolescents in the future.

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Keywords

adolescence; cohort study; measurement; musculoskeletal; paediatrics

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Introduction

Musculoskeletal (MSK) conditions are a major public health issue and the leading cause of disability globally (Vos *et al.*, 2015). They pose a significant burden to primary health-care systems (Woolf and Pfleger, 2003), even during childhood and adolescence (Henschke *et al.*, 2014). Studies suggest MSK conditions become common during adolescence, for example, back pain prevalence increases from 1% at age 7 years to 12–40% at 12 years and increases to 39–71% by 15 years (Hill and Keating, 2009). This is important given MSK pain in adolescence predicts pain and disability in adult life (Hestbaek *et al.*, 2006; Kamaleri *et al.*, 2009a, 2009b). Hence, better understanding of MSK pain in young people has considerable promise in reducing the individual and societal burden of these conditions.

There are few suitably designed longitudinal studies that investigate the clinical course of MSK conditions in children and adolescents (Artus *et al.*, 2014). Prospective cohort studies to date have drawn upon population samples of school children, including those with, and without pain, and collected follow-up measures at wide time-intervals. (Jeffries *et al.*, 2007; Hill and Keating, 2009; McBeth and Jones, 2007) These studies do not report on the correct variables at an appropriate frequency in well-defined clinical samples to accurately delineate prognosis. Several large cohort studies (El-Metwally *et al.*, 2005; Hestbaek *et al.*, 2006; Rathleff *et al.*, 2013) only collect data at intervals of 1 year or more which means that variation in condition severity and impact that occurs within this time period is not captured. Furthermore, these studies capture information about how often a child experiences pain over a defined time period, this means that information about pain intensity, which is strongly related to the impact of the condition (Tiira *et al.*, 2012), is not recorded. Investigation of clinical course requires a sample of clinical patients that are followed-up at frequent time intervals with patient-relevant measures such as pain intensity and disability (Hayden *et al.*, 2010).

Large cohort studies are time-consuming, expensive, and it can be difficult to maintain good data quality because of attrition (Spector and Hochberg, 1994). The use of electronic data collection in health research is growing in popularity because it offers an efficient and flexible means of collecting information. Advantages over phone or in-person follow-up include reduced researcher and participant burden, which enables more frequent data collection from large samples. An example comes from a recent Danish study that collected data via short messaging service (SMS) to track individual patients' pain intensity every week in a large sample of adult participants with back pain, this enabled the identification of distinct patterns of back pain recovery over a 1-year follow-up period (Kongsted *et al.*, 2015). Another study followed MSK disorders in school children via weekly SMS answered by the parents (Wedderkopp *et al.*, 2012). It is not clear whether the follow-up rates reported by this study can be replicated when the child, rather than the parent, is asked to respond to SMSs about their symptoms.

To facilitate collection of robust prognostic and clinical course information on children and adolescents with MSK pain, the feasibility of electronic data collection methods in this group needs to be established. The aim of this study was to determine the feasibility of recruiting, retaining and following up a prospective cohort of young people with knee pain presenting to primary care, using electronic data collection methods (SMS and online questionnaire).

Methods

Study design, setting and participants

Ethical approval for this study was granted by the Human Research Ethics Committee of The University of Sydney, Australia (Protocol No.: 14519). Data were collected from May 2012 to June 2014. Participants were recruited from private physiotherapy clinics in Sydney, Australia.

Physiotherapists were approached to recruit participants to the study, gain consent, administer a baseline questionnaire and complete a baseline assessment within 2 days of the initial consultation. Thereafter physiotherapists provided clinical care as they saw fit, participation in the study had no influence on clinical management. When participants were discharged, physiotherapists completed either a paper-based or online follow-up questionnaire. Physiotherapists were reimbursed $AUD100 per enrolled participant to cover the time required to complete the study procedures (approximately 3 hours).

Children and adolescents (aged 8–18 years) were eligible to participate in this study if they presented with the primary complaint of pain or discomfort in the knee (region indicated on a body chart

diagram). Referral of knee pain beyond the knee did not preclude inclusion. All participants (and their parents/guardians) had to be able to speak and read English and provide written informed consent.

Commencing the week after enrolment, children and adolescents participating in the study were sent two SMS messages each week that asked about their knee pain. SMS follow-up was stopped when the patient had recovered, defined as two consecutive weeks reporting no pain. Six months after recruitment, participants were contacted by email and/or phone and asked to complete a web-based follow-up questionnaire. Participants were reimbursed with a $30 voucher recognizing the significant length of follow-up, the time taken to respond to the SMS and the mobile phone costs associated with participating in the trial.

Variables and measurements

Baseline

The baseline questionnaire completed by participants included socio-demographic characteristics such as age, gender and school year. Also included were a series of questionnaires consisting of measures of pain intensity (Quadruple Visual Analogue Scale — QVAS (Jensen *et al.*, 1996)), knee-specific (Lower Extremity Functional Scale — LEFS (Binkley *et al.*, 1999)) and general function (Functional Disability Index — FDI (Walker and Greene, 1991)), child health related quality of life (Child Health Questionnaire — CHQ-50 (Ruperto *et al.*, 2001)) and physical activity (Adolescent Physical Activity Recall Questionnaire — APARQ (Booth *et al.*, 2002; Gwynn *et al.*, 2010)).

At baseline, the Patient-Specific Functional Scale (PSFS) (Chatman *et al.*, 1997) was administered by physiotherapists. Physiotherapists and participants identified three important activities that the participants were unable to do, or had difficulty with as a result of their knee problem. The three activities were identified as relatively light, moderate and vigorous or sustained activities and recorded on a scale from zero (unable to perform activity) to 10 (able to perform activity at the same level as before this episode).

Follow-up

Participants were sent two SMS messages every week until their knee pain had resolved. One message contained two questions: "What is your knee pain RIGHT NOW?" and "Over the past week what was your AVERAGE knee pain?" The Numeric Pain Scale (Williamson and Hoggart, 2005) was used with 0 indicating no pain and 10 the worst possible pain. The other SMS question asked participants to rate their ability to complete the activities that they had nominated as having difficulty performing in the baseline PSFS questionnaire and read "How would you rate your ability to complete a) [activity 1], b) [activity 2], c) [activity 3]?" Response instructions were numeric on a scale from 0 (unable) to 10 (completely able). All SMS messages were sent and received via the SMSGlobal web messaging platform (https://www.smsglobal.com/). Incoming SMS responses were downloaded into a Microsoft Excel spreadsheet for analysis.

The six-month follow-up questionnaire was completed online by participants and included the following items: Pain intensity (QVAS), patient-specific, knee-specific and general function (PSFS, LEFS and FDI) and physical activity (APARQ).

Statistical methods

Descriptive statistics were used to characterize the cohort. Continuous outcome measures recorded at baseline and follow-up were summarized with means and standard deviations (SD); or medians and interquartile ranges when not normally distributed.

Response rate to SMS tracking was calculated by dividing the actual number of responses received by the total number of responses expected for each participant. Participants were censored if they still had pain the week before but stopped responding to the weekly SMS tracking for four consecutive weeks, time of censorship was listed as first week of non-response. SMS response rates were then calculated separately for participants who were uncensored and censored; the response rate of censored participants was calculated up to the week of censoring.

Using weekly pain intensity data Kaplan–Meier survival analysis was used to calculate median time to recovery from knee pain. Time of recovery was defined as the second consecutive week that a participant reported 0 out of 10, to the SMS question "What is your knee pain (intensity) RIGHT NOW". A survival plot was constructed to estimate the probability of recovery over the course of the study.

Descriptive statistics were generated using IBM SPSS (Chicago, IL, USA) version 22 and survival analysis was conducted in SAS (Cary, NC, USA) version 9.4.

Table 1. Baseline characteristics of participants ($n = 30$)

Year at school[†] mean (SD)	8 (2)
Duration of knee pain	
0–7 days	23.3%
1-4 weeks	30.0%
1-3 months	16.7%
>3 months	30.0%
Knee Pain (QVAS) mean (SD)	
Now	3.8 (2.5)
Average	4.2 (2.1)
Best	1.3 (1.6)
Worst	8.0 (1.4)
Knee Disability (PSFS) mean (SD)	
Light	4.6 (2.4)
Moderate	4.1 (2.4)
Vigorous/Sustained	4.3 (2.3)
FDI (scale 0–60) mean (SD)	15.2 (9.7)
LEFS (scale 0–80) mean (SD)	54.9 (14.7)
APARQ (min/week) median (IQR)	
Moderate Physical Activity	90 (4, 360)
Vigorous Physical Activity	364 (220, 668)
Moderate-Vigorous Physical Activity	563 (459, 990)

QVAS = Quadruple Visual Analogue Scale; PSFS = Patient Specific Functional Scale; FDI = Functional Disability Index; LEFS = Lower Extremity Functional Scale; APARQ = Adolescent Physical Activity Recall Questionnaire.

[†]In Sydney, Australia, school education is 13 years and divided into: Primary school, which runs from age 5–6 years to age 11–12 years (i.e. Kindergarten to Year 6) and Secondary school, which runs from age 12–13 years to age 17–18 years (i.e. Year 7 to 12).

Results

Thirty participants (53.3% boys) with a mean age (±SD) of 13.0 (±2.2) years were recruited over a period of 26 months. Forty-four physiotherapy clinics (including 108 physiotherapists) were contacted to recruit participants for this study; of these, only seven clinics (8 physiotherapists) actually recruited participants to the study. Baseline characteristics of participants are presented in Table 1.

Overall response rate to SMS tracking was 71.3%, rates were significantly lower in participants who were censored than those that were not (Table 2). During the SMS tracking period, 10 of the 30 participants (33.3%) stopped responding to the weekly SMS before meeting the recovery criterion (zero pain score for two consecutive weeks) and were therefore censored. There was no significant difference between the baseline pain and disability scores for censored versus uncensored participants. At six-month follow-up, 24 out of 30 participants (80%) completed all or part of the online questionnaire (Table 3). There was no consistent pattern of difference on the baseline scores between participants that completed the six-month follow-up and participants lost to follow-up (Additional Material: Table S1).

The median time for knee pain recovery was 8 weeks (95%CI: 5 to 10 weeks) (Figure 1) with 30% of participants having knee pain for longer than 3 months. At six-month follow-up, the percentage of participants who reported knee pain (≥1 on the QVAS-Now) at the time of response was 29.2%.

Discussion

This study explored the feasibility of conducting a longitudinal cohort study on the clinical course of knee pain in children and adolescents presenting to physiotherapy. We identified three major threats to study feasibility: (1) the slow rate of recruitment; (2) the high percentage of participants that stopped responding to SMS tracking prior to recovery (33.3%); and (3) high loss to follow-up at 6 months (20%).

Table 2. Mean response rate to SMS tracking from the total number of messages sent

	SMS 1. Pain		SMS 2. Disability (PSFS)			
	Now	Average	Activity 1	Activity 2	Activity 3	All items
All participants ($n = 30$)	74% (168/227)	71.8% (163/227)	75.8% (172/227)	67.8% (154/227)	67% (152/227)	71.3% (809/1135)
Uncensored participants ($n = 20$)	77.5% (117/151)	75.5% (114/151)	82.8% (125/151)	70.9% (107/151)	70.2% (106/151)	75.4% (569/755)
Censored participants ($n = 10$)	67.1% (51/76)	64.5% (49/76)	61.8% (47/76)	61.8% (47/76)	60.5% (46/76)	63.2% (240/380)

Response rate: %. In parenthesis: (total number of SMS received / total number of SMS sent).

PSFS = Patient Specific Functional Scale; SMS = short messaging service.

Table 3. Response rates and mean values at 6-month follow-up

Questionnaire	*N*	Response rate (%)	Mean score (SD)
Pain (QVAS)			
Now	24	80	0.7 (1.4)
Average	24	80	1.4 (1.3)
Best	24	80	0.2 (0.4)
Worst	24	80	4.0 (3.3)
Disability (PSFS)			
Light	23	76.7	8.4 (3.0)
Moderate	23	76.7	8.1 (2.9)
Vigorous/Sustained	12	40	8.3 (3.9)
FDI (scale 0–60)	23	76.7	3.4 (5.9)
LEFS (scale 0–80)	22	73.3	72.9 (12.3)
APARQ (min/week)			
Moderate Physical Activity	21	70	15 (0, 83)†*
Vigorous Physical Activity	21	70	323 (240, 573)†*
Moderate-Vigorous Physical Activity	21	70	435 (304, 743)†*

*median, (IQR).

QVAS = Quadruple Visual Analogue Scale; PSFS = Patient Specific Functional Scale; FDI = Functional Disability Index; LEFS = Lower Extremity Functional Scale; APARQ = Adolescent Physical Activity Recall Questionnaire; SD = standard deviation.

Poor patient recruitment and retention are two well-known threats to feasibility in clinical studies. In this study, recruitment relied on clinicians to screen and enrol young people. The length of time it took to recruit 30 participants (26 months) was a major challenge and represents a serious threat to the feasibility of conducting a large study on this population. Forty-four private physiotherapy clinics were approached to participate in this study; four of these declined on the basis that their patient base consisted of too few young people, and eight clinics did not respond to our requests for assistance. Of the remaining 32 clinics with which contact was made, only eight enrolled participants into the study. In order to be able to provide robust estimates of clinical course and identify prognostic factors with sufficient power, future studies on adolescent MSK pain would need to include approximately 10 times the number of participants as this pilot study. Fletcher *et al.*, (Fletcher *et al.*, 2012) found that the recruitment activity of clinicians in clinical studies can be improved by implementing qualitative methods at the study design phases to what are likely barriers to recruitment activity and how these may be overcome. This may be an important factor to consider in future studies to maximize clinician involvement.

Additionally the nature of the question used for SMS tracking might have adversely influenced the response rate in our study. The feasibility of SMS was recently assessed in a study of Australian children with haemophilia (Broderick *et al.*, 2012). The authors of this study used a yes/no response option and reported a follow-up rate of 86.8% to document bleeding episodes. In contrast, another study used SMS to collect data on eating and exercise behaviour in overweight children using response options on a 5-point Likert scale had a response rate of 67% (Bauer *et al.*, 2010). The response rates to the SMS questions in our study were quite low. A mean response rate of 71% represents a substantial threat

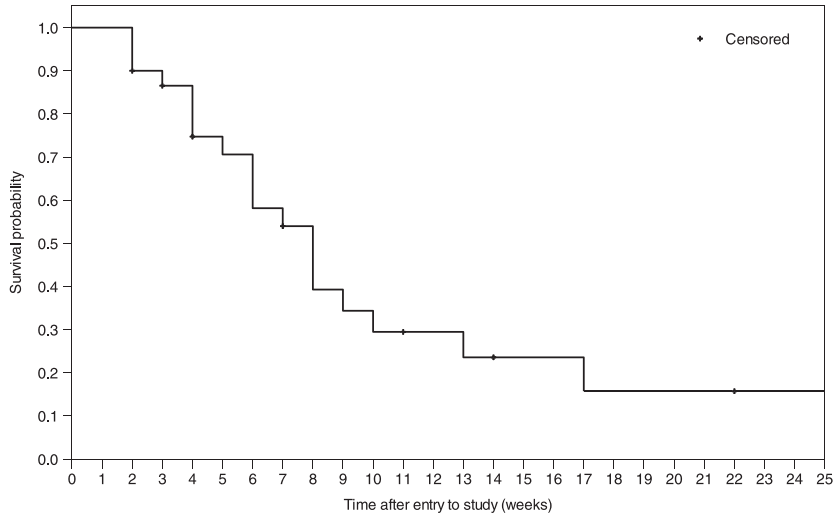

Figure 1. Kaplan–Meier survival plot for knee pain recovery in children and adolescents

to study validity, as it is likely that this amount of missing data would introduce bias into estimates of prognosis calculated from a larger study. These response rates to follow-up were lower than in a study of Danish children with musculoskeletal pain (Jespersen *et al.*, 2015), which can be most likely explained by the fact that data in the Danish study were provided by parents, not children themselves. Differences in nature of the question, population (clinical versus population) and cultural attitudes to medical research may also help explain this discrepancy (Kelly *et al.*, 2002).

Our rationale to explore the feasibility of electronic data collection methods was, in part, motivated by the desire to minimize both researcher and participant burden and project expense. SMS reminders were used in studies by Moller *et al.* and Jespersen *et al.* (Moller *et al.*, 2012; Jespersen *et al.*, 2015) to improve data capture rates and also to flag where additional participant support was needed. In these studies, SMS reports of pain or injury would prompt a follow-up telephone call from researchers to further investigate the nature of the problem. Thus, participants reporting pain would receive feedback, adding to the significance of their response. Participants in the study of Jespersen *et al.* also received a clinical examination following the telephone call, if indicated. The response rates to SMS tracking in these two studies was much higher than ours ranging from 85% to 96% suggesting that children and their families respond better when there is greater contact with study staff. The additional burden for researchers and greater project cost may be necessary if optimal response rates are to be obtained.

The third major threat to feasibility in this study was participant retention. Over 30% of participants stopped answering SMS questions prior to recovery, and 20% of participants did not complete the 6 months follow-up questionnaire. A comparable loss to follow-up rate is likely to introduce bias into estimates of prognosis calculated from a larger study in the same population. In our study, we reimbursed participants for their time and the cost of their mobile phone use only. Future research may be guided by literature that suggests an actual financial incentive (monetary) might boost retention rates; notwithstanding, there are complex ethical issues with incentivizing young people to participate in research that must be considered. A definite reward (as opposed to lotteries) has been demonstrated to improve retention in young people (Henderson *et al.*, 2010) and this appears to increase in proportion to the incentive value (Booker *et al.*, 2011). Alternate methods such as reminder telephone calls also appear to have a greater effect in younger aged cohorts. In this study we did not employ reminder correspondence during the final follow-up period, and ongoing SMS messages or mixed follow-up methods (such as telephone calls) could have helped improve the follow-up rate (Booker *et al.*, 2011).

A limitation of our study is that we did not capture information on the reason for participant attrition (at both SMS and six-month follow-up). While the potential for electronic methods of data collection is clear, the follow-up rates in our study were quite low. It is possible that the density of information we sought, or regularity of contact, was too onerous for some participants and negatively influenced response rates.

Conclusion

Musculoskeletal conditions commonly affect young people and can prompt them to seek help from primary care clinicians. Larger studies are needed to help clinicians identify children at risk of poor recovery and to also better inform management strategies. Finding physiotherapists that were willing and able to identify, and recruit, participants to the study was challenging. While the use of electronic data collection methods is potentially useful in clinical research that follows young people over time, the methods used in our study led to unacceptably high levels of missing data. Researchers embarking on research in the area should seek solutions to the problems of low recruitment rates and high loss to follow up when planning large prospective studies in the future.

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REFERENCES

Artus M, Van Der Windt D, Jordan KP, Croft PR. The clinical course of low back pain: a meta-analysis comparing outcomes in randomised clinical trials (RCTs) and observational studies. BMC Musculoskeletal Disorders 2014; 15: 68.

Bauer S, De Niet J, Timman R, Kordy H. Enhancement of care through self-monitoring and tailored feedback via text messaging and their use in the treatment of

childhood overweight. Patient Education and Counseling 2010; 79: 315–319.

Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): Scale development, measurement properties, and clinical application. Physical Therapy 1999; 79: 371–383.

Booker C, Harding S, Benzeval M. A systematic review of the effect of retention methods in population-based cohort studies. BMC Public Health 2011; 11: 249.

Booth ML, Okely AD, Chey T, Bauman A. The reliability and validity of the adolescent physical activity recall questionnaire. Medicine and Science in Sports and Exercise 2002; 34: 1986–1995.

Broderick CR, Herbert RD, Latimer J, Mathieu E, Van Doorn N, Curtin JA. Feasibility of short message service to document bleeding episodes in children with haemophilia. Haemophilia 2012; 18: 906–910.

Chatman AB, Hyams SP, Neel JM, Binkley JM, Stratford PW, Schomberg A, Stabler M. The Patient-Specific Functional Scale: measurement properties in patients with knee dysfunction. Physical Therapy 1997; 77: 820–829.

El-Metwally A, Salminen J, Auvinen A, Kautiainen H, Mikkelsson M. Lower limb pain in a preadolescent population: prognosis and risk factors for chronicity — a prospective 1- and 4- year follow-up study. Pediatrics 2005; 116: 673–681.

Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. BMJ Open 2012; 2.

Gwynn JD, Hardy LL, Wiggers JH, Smith WT, D'este CA, Turner N, Cochrane J, Barker DJ, Attia JR. The validation of a self-report measure and physical activity of Australian Aboriginal and Torres Strait Islander and non-Indigenous rural children. Australian and New Zealand Journal of Public Health 2010; 34(Suppl 1): S57–65.

Hayden JA, Dunn KM, Van Der Windt DA, Shaw WS. What is the prognosis of back pain? Best Practice & Research. Clinical Rheumatology 2010; 24: 167–179.

Henderson M, Wight D, Nixon C, Hart G. Retaining young people in a longitudinal sexual health survey: a trial of strategies to maintain participation. BMC Medical Research Methodology 2010; 10: 9.

Henschke N, Harrison C, Mckay D, Broderick C, Latimer J, Britt H, Maher CG. Musculoskeletal conditions in children and adolescents managed in Australian primary care. BMC Musculoskeletal Disorders 2014; 15.

Hestbaek L, Leboeuf-Yde C, Kyvik KO, Manniche C. The course of low back pain from adolescence to adulthood: eight-year follow-up of 9600 twins. Spine (Phila Pa 1976) 2006; 31: 468–72.

Hill JJ, Keating JL. A systematic review of the incidence and prevalence of low back pain in children. Physical Therapy Reviews 2009; 14: 272–284.

Jeffries LJ, Milanese SF, Grimmer-Somers KA. Epidemiology of adolescent spinal pain: a systematic overview of the research literature. Spine (Phila Pa 1976) 2007; 32: 2630–7.

Jensen MP, Turner LR, Turner JA, Romano JM. The use of multiple-item scales for pain intensity measurement in chronic pain patients. Pain 1996; 67: 35–40.

Jespersen E, Rexen CT, Franz C, Møller NC, Froberg K, Wedderkopp N. Musculoskeletal extremity injuries in a cohort of schoolchildren aged 6–12: A 2.5-year prospective study. Scandinavian Journal of Medicine and Science in Sports 2015; 25: 251–258.

Kamaleri Y, Natvig B, Ihlebaek CM, Benth JS, Bruusgaard D. Change in the number of musculoskeletal pain sites: a 14-year prospective study. Pain 2009a; 141: 25–30.

Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D. Does the number of musculoskeletal pain sites predict work disability? A 14-year prospective study. European Journal of Pain 2009b; 13: 426–430.

Kelly AM, Powell CV, Williams A. Parent visual analogue scale ratings of children's pain do not reliably reflect pain reported by child. Pediatric Emergency Care 2002; 18: 159–162.

Kongsted A, Kent P, Hestbaek L, Vach W. Patients with low back pain had distinct clinical course patterns that weretypically neither complete recovery nor constant pain. A latent classanalysis of longitudinal data. Spine Journal 2015.

McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. Best Practice & Research Clinical Rheumatology 2007; 21: 403–425.

Moller M, Attermann J, Myklebust G, Wedderkopp N. Injury risk in Danish youth and senior elite handball using a new SMS text messages approach. British Journal of Sports Medicine 2012; 46: 531–537.

Rathleff CR, Olesen JL, Roos EM, Rasmussen S, Rathleff MS. Half of 12-15-year-olds with knee pain still have pain after one year. Danish Medical Journal 2013; 60: A4725.

Ruperto N, Ravelli A, Pistorio A, Malattia C, Cavuto S, Gado-West L, Tortorelli A, Landgraf JM, Singh G, Martini A. Cross-cultural adaptation and psychometric evaluation of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ) in 32 countries. Review of the general methodology. Clinical and Experimental Rheumatology 2001; 19: S1–S9.

Spector TD, Hochberg MC. Methodological problems in the epidemiological study of osteoarthritis. Annals of the Rheumatic Diseases 1994; 53: 143–146.

Tiira AH, Paananen MV, Taimela SP, Zitting PJ, Järvelin MR, Karppinen JI. Determinants of adolescent health care use for low back pain. European Journal of Pain 2012; 16: 1467–1476.

Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, Charlson F, Davis A, Degenhardt L, Dicker D, Duan L, Erskine H, Feigin VL, Ferrari AJ, Fitzmaurice C, Fleming T, Graetz N, Guinovart C, Haagsma J, Hansen GM, Hanson SW, Heuton KR, Higashi H, Kassebaum N, Kyu H, Laurie E, Liang X, Lofgren K, Lozano R, Macintyre MF, Moradi-Lakeh M, Naghavi M, Nguyen G, Odell S, Ortblad K, Roberts DA, Roth GA, Sandar L, Serina PT, Stanaway JD, Steiner C, Thomas B, Vollset SE, Whiteford H, Wolock TM, Ye P, Zhou M, Āvila MA, Aasvang GM, Abbafati C, Ozgoren AA, Abd-Allah F, Aziz MIA, Abera SF, Aboyans V, Abraham JP, Abraham B, Abubakar I, Abu-Raddad LJ, Abu-Rmeileh NME, Aburto TC, Achoki T, Ackerman IN, Adelekan A, Ademi Z, Adou AK, Adsuar JC, Arnlov J, Agardh EE, Al Khabouri MJ, Alam SS, Alasfoor D, Albittar MI, Alegretti MA, Aleman AV, Alemu ZA, Alfonso-Cristancho R, Alhabib S, Ali R, Alla F, Allebeck P, Allen PJ, Almazroa MA, Alsharif U, Alvarez E, Alvis-Guzman N, Ameli O, Amini H, Ammar W, Anderson BO, Anderson HR, CaT A, Anwari P, Apfel H, Arsenijevic VSA, Artaman A, Asghar RJ, Assadi R, Atkins LS, Atkinson C et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 2015; 386: 743–800.

Walker LS, Greene JW. The functional disability inventory: Measuring a neglected dimension of child health status. Journal of Pediatric Psychology 1991; 16: 39–58.

Wedderkopp N, Jespersen E, Franz C, Klakk H, Heidemann M, Christiansen C, Moller N, Leboeuf-Yde C. Study protocol. The Childhood Health, Activity, and Motor Performance School Study Denmark (The CHAMPS-study DK). BMC Pediatrics 2012; 12: 128.

Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. Journal of Clinical Nursing 2005; 14: 798–804.

Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bulletin of the World Health Organization 2003; 81: 646–56.

Supporting information

Additional supporting information may be found in the online version of this paper at publisher's web site:

Table S1. Differences in baseline measures for children and adolescents based on follow-up attrition.

Appendix 1

Additional Material: Table S1. Differences in baseline measures for children and adolescents based on follow-up attrition.

	Baseline mean difference (95% confidence interval)			
	SMS tracking (Uncensored n=20 vs. Censored n=10)		**Follow-up at 6 months** (Responders n=24 vs. Drop out n=6)	
Age	1.5 (-0.3, 3.2), P=0.09		0.4 (-1.7, 2.5), P=0.72	
Gender				
Male	65% vs. 30%	X^2=3.3, P=0.12	58.3% vs. 33.3%	X^2=1.2, P=0.38
Female	35% vs. 70%		41.7% vs. 66.7%	
Year at school	1.2 (-0.5,2.8), P=0.15		0.04 (-1.9, 2.0), P=0.97	
Duration of pain				
0-7 days	25% vs. 20%		25% vs. 16.7%	
1-4 weeks	35% vs. 20%	X^2=2.2, P=0.54	29.2% vs.33.3%	X^2=0.2, P=0.98
1-3 months	10% vs. 30%		16.7% vs. 16.7%	
>3 months	30% vs. 30%		29.2% vs. 33.3%	
Pain (QVAS)				
Now	-0.2 (-2.2, 1.8), P=0.84		-1.1 (-3.5,1.2), P=0.33	
Average	-0.5 (-2.1, 1.2), P=0.56		-1.6 (-3.5, 0.2), P=0.08	
Best	-0.7 (-1.9, 0.6), P=0.3		-2.4 (-3.6, -1.2), P<0.05	
Worst	0.3 (-0.9, 1.4), P=0.65		-0.3 (-1.6, 1.1), P=0.7	
Disability (PSFS)				
Light	0.7 (-1.3, 2.6), P=0.5		0.2 (-2.1, 2.5), P=0.88	
Moderate	-0.4 (-2.3, 1.5), P=0.68		-0.7 (-2.9, 1.6), P=0.55	
Vigorous/Sustained	-1 (-2.8, 0.8), P=0.28		-1.1 (-3.3, 1.0), P=0.28	
FDI	3.8 (-4.0, 11.5), P=0.33		-2.6 (-11.8, 6.6), P=0.56	
LEFS	-1.7 (-13.5, 10.2), P=0.78		6.8 (-15.4, 28.9), P=0.48	
APARQ				
Moderate Physical Activity	172 (-178, 520), P=0.32		-107 (-538, 325), P=0.62	
Vigorous Physical Activity	-224 (-656, 207), P=0.30		134 (-401, 669), P=0.61	
Moderate-Vigorous Physical Activity	-53 (-595, 489), P=0.86		27 (-634, 689), P=0.93	
CHQ-50				
Physical functioning	-4.8 (-17.5, 7.9), P=0.44		-12.9 (-28.2,2.5), P=0.1	
Social role, emotional/behavioral	-5 (-17.5, 7.6), P=0.43		-6.9 (-22.7,8.9), P=0.38	
Social role, physical	2 (-13.8, 17.7), P=0.8		-1.5 (-21.3,18.3), P=0.88	
Bodily pain	4.9 (-9.6, 19.4), P=0.5		0.8 (-17.6,19.3), P=0.93	
Behavior	-2.1 (-10, 5.7), P=0.58		-5.8 (-15.4,3.8), P=0.23	
Mental health	-4.4 (-11.6, 2.9), P=0.23		-2.5 (-11.8,6.8), P=0.59	
Self-esteem	-3.6 (-14.6, 7.3), P=0.5		-8.9 (-22.3,4.4), P=0.18	
General health	1.9 (-9.4, 13.2), P=0.74		-6.2 (-20.2,7.9), P=0.38	
Parental impact, emotional	-6 (-20.1, 8.1), P=0.39		-16.8 (-33.5,-0.2), P=0.05	
Parental impact, time	0.4 (-12.3, 13.2), P=0.94		-3.7 (-19.7,12.3), P=0.64	
Family activities	-3.8 (-17.3, 9.6), P=0.56		-9.9 (-26.5,6.7), P=0.23	
Family cohesion	-1.3 (-15.5, 13), P=0.86		-10.7 (-28.1,6.8), P=0.22	

QVAS, Quadruple Visual Analogue Scale. PSFS, Patient Specific Functional Scale. FDI, Functional Disability Index. LEFS, Lower Extremity Functional Scale. APARQ, Adolescent Physical Activity Recall Questionnaire. CHQ-50, Child Health Questionnaire - 50.

Chapter Six

Accuracy of clinical tests in the diagnosis of anterior cruciate ligament injury: a systematic review

"Certainty is the enemy of change."

- Salvador Minuchin

CHIROPRACTIC & MANUAL THERAPIES

SYSTEMATIC REVIEW Open Access

Accuracy of clinical tests in the diagnosis of anterior cruciate ligament injury: a systematic review

Michael S Swain[1,2*], Nicholas Henschke[1,3], Steven J Kamper[1,4], Aron S Downie[1,2], Bart W Koes[5] and Chris G Maher[1]

Abstract

Background: Numerous clinical tests are used in the diagnosis of anterior cruciate ligament (ACL) injury but their accuracy is unclear. The purpose of this study is to evaluate the diagnostic accuracy of clinical tests for the diagnosis of ACL injury.

Methods: Study Design: Systematic review. The review protocol was registered through PROSPERO (CRD42012002069).
Electronic databases (PubMed, MEDLINE, EMBASE, CINAHL) were searched up to 19th of June 2013 to identify diagnostic studies comparing the accuracy of clinical tests for ACL injury to an acceptable reference standard (arthroscopy, arthrotomy, or MRI). Risk of bias was appraised using the QUADAS-2 checklist. Index test accuracy was evaluated using a descriptive analysis of paired likelihood ratios and displayed as forest plots.

Results: A total of 285 full-text articles were assessed for eligibility, from which 14 studies were included in this review. Included studies were deemed to be clinically and statistically heterogeneous, so a meta-analysis was not performed. Nine clinical tests from the history (popping sound at time of injury, giving way, effusion, pain, ability to continue activity) and four from physical examination (anterior draw test, Lachman's test, prone Lachman's test and pivot shift test) were investigated for diagnostic accuracy. Inspection of positive and negative likelihood ratios indicated that none of the individual tests provide useful diagnostic information in a clinical setting. Most studies were at risk of bias and reported imprecise estimates of diagnostic accuracy.

Conclusion: Despite being widely used and accepted in clinical practice, the results of individual history items or physical tests do not meaningfully change the probability of ACL injury. In contrast combinations of tests have higher diagnostic accuracy; however the most accurate combination of clinical tests remains an area for future research.

Clinical relevance: Clinicians should be aware of the limitations associated with the use of clinical tests for diagnosis of ACL injury.

Keywords: Anterior cruciate ligament, Diagnosis, Medical history taking, Physical examination, Diagnostic test accuracy

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Background

The anterior cruciate ligament (ACL) is an important stabilising structure of the knee and its disruption is associated with pain and activity limitation [1]. The annual incidence of ACL injury ranges from 0.01% to 0.05% [2], however it is higher in sporting groups and most frequently affects individuals during late adolescence and early adulthood [3–5]. The prevalence of ACL injury in adults presenting to primary care with acute knee pain is estimated to be 4% [6]. Many cases are initially missed [7] in primary care and these undiagnosed ACL injuries are of concern because of the risk of cartilage tear and premature knee osteoarthritis [8].

Clinical diagnosis of ACL injury is based upon history and physical examination findings with suspected cases confirmed by MRI or arthroscopy [9]. Numerous clinical tests and findings have been proposed to aid the diagnosis of ACL injury. A popping sound, swelling and instability following high impact sport trauma along with a positive Lachman's, anterior draw or pivot shift test is the most common method of clinical diagnosis [9]. However, there are over 25 specific physical tests and numerous features from the clinical history that have been proposed for detection of ACL injury [10]. At present the diagnostic accuracy of these tests is unclear.

Most existing reviews evaluating the accuracy of tests to diagnose ACL injury [6,11–14] are now over a decade old and contain methodological limitations such as inclusion of inappropriate studies and pooling of estimates from heterogeneous studies. Since these reviews were published there has been much progress in the diagnostic field with regard to study appraisal and synthesis [15]. There is now a greater appreciation of how design features may lead to biased estimates of diagnostic test accuracy and when meta-analysis is justified. In addition it is likely that more recent primary research studies have been conducted in the area of ACL diagnosis.

The objective of this systematic review was to report the diagnostic accuracy of clinical tests for the diagnosis of ACL injury and describe the quality of research evaluating these tests.

Methods

A systematic review protocol [16] was registered at the International Prospective Register of Systematic Reviews - PROSPERO 2012:CRD42012002069.

Identification of selected studies

Electronic databases (PubMed, MEDLINE, EMBASE, and CINAHL) were searched for eligible diagnostic studies from the earliest year possible up to 19th of June 2013. The search strategy was developed for PubMed and modified for use in other databases (Additional file 1: Table S1). The reference lists of all included publications and relevant systematic reviews were checked and forward citation searches performed.

Eligibility criteria

Diagnostic studies were eligible if they compared the accuracy of history taking or physical examination to an acceptable reference standard (arthroscopy, arthrotomy, or MRI) in the identification of ACL injury. Both prospective and retrospective studies were eligible for inclusion. We did not include case control studies as they substantially overestimate diagnostic accuracy compared with studies that use a clinical population [17].

The focus of this review was on studies that evaluated patients presenting to a care provider for diagnosis of knee pain or dysfunction, where the diagnostic accuracy of individual, or combinations of, history features or physical assessment procedures was evaluated. Studies in which a substantial proportion of recruited patients had already been diagnosed with ACL injury were excluded to minimise verification bias [17].

Included studies had to report sufficient data on diagnostic tests to enable construction of a 2 × 2 table so estimates of diagnostic accuracy (such as sensitivity and specificity) could be calculated. Studies that evaluated the accuracy of an unspecified combination of history and physical examination, such as clinical diagnosis or global clinician judgment were excluded as they do not allow for replication, validation and generalization of the study results [18].

If studies had been reported in abstracts or conference proceedings, the related full publications were retrieved if available, but only full articles published in peer-reviewed journals were included. Studies published in all languages were considered eligible and translations were sought where necessary.

Study selection

Two authors (MS and NH) independently screened all titles and abstracts identified in the searches with respect to the inclusion and exclusion criteria. Full text copies of potentially relevant articles were retrieved and final inclusion or exclusion was determined. Disagreements regarding inclusion were resolved by consensus, including a third review author (SK) where necessary.

Data extraction

Three review authors (MS, NH, SK) independently extracted information from the included studies. Data were extracted into a specifically designed spreadsheet and included details on the study design, setting, enrolment procedures, number of participants, patient demographics, and time since initial ACL injury. Details of the type of index test and the type of reference standard were also extracted and the proportion of participants with ACL injuries was calculated for each included study.

Diagnostic two-by-two tables (true positive, false positive, true negative and false negative) were either extracted from the publications or reconstructed using information from other reported parameters (sensitivity, specificity, or predictive values). Uninterpretable index test outcomes, such as an equivocal finding were dealt with as a negative index test finding. The authors of one study [19] were contacted and provided additional information.

Quality assessment

The quality of each included study was assessed by two review authors (MS, NH) using the QUality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist [20]. The QUADAS-2 checklist consists of four domains relating to patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of applicability. The review authors classified each item as "yes" (adequately addressed), "no" (inadequately addressed), or "unclear" (inadequate detail presented to allow a judgment to be made). Disagreements were resolved by consensus and consulting with a third (SK) review author where necessary.

Synthesis of results

The two-by-two tables were used to calculate index test summary statistics: sensitivity, specificity, likelihood ratios along with their 95% confidence intervals using MetaDiSc 1.4. Index test accuracy was presented as forest plots of likelihood ratios, as likelihood ratios provide the best way for clinicians to use diagnostic data to establish clinical diagnoses in patient care [21]. Categorisation of likelihood ratios was adopted from Jaeschke et al. [18] where positive likelihood ratios (+LR) <5 and a negative likelihood ratios (−LR) >0.2 were considered small, +LR 5–10 and −LR 0.1-0.2 were moderate, and + LR>10 and −LR <0.1 were considered large, with respect to changing the pre to post-test probability.

Both clinical and statistical heterogeneity as well as methodological quality were evaluated to determine the appropriateness of meta-analysis. Assessment of clinical heterogeneity involved comparison of the study populations, settings, performance of index tests and reference standards among included studies. Assessment of statistical heterogeneity involved visual inspection of forest plots and performance of the chi-square (χ^2) test and calculation of the inconsistency index (I^2) which quantifies the proportion of variation across the included studies that is due to heterogeneity rather than chance [22].

Results

Study selection

The initial database searches retrieved 21,691 citations of which 10,796 citations remained after duplicates were removed (Figure 1). Screening of the titles and abstracts identified 285 potentially relevant articles that were retrieved in full text format. Forwards and backwards citation tracking identified 12 potentially relevant articles which were also retrieved. Fourteen articles were finally included, of which 11 were published in English [19,23–32] and three in German [33–35]. Additional file 2: Table S2 lists the reasons for excluding 28 articles that were included in one or more of the previous five systematic reviews.

Description of included studies

Of the 14 included articles, 10 had a prospective study design [19,23,24,28–30,32–35], two used a retrospective design [26,27] and for two studies [25,31] the design was unclear (Table 1).

Only one study [19] evaluated the diagnostic accuracy of clinical tests in primary care. The other 13 studies evaluated the accuracy of clinical tests in secondary contact settings, defined here as either a referral to an orthopaedic department or presentation to an accident and emergency department. In three studies the reference standard was MRI [19,24,27], eight studies applied arthroscopy [23,26,29–32,34,35] and three studies applied either arthroscopy or arthrotomy [25,28,33]. Only five studies [25–27,29,30] reported in detail the method of index test application with slight variations between them in the way the index tests was performed.

Nine studies [19,23,26,28,30–32,34,35] assessed diagnostic accuracy for partial or complete ACL injuries, however only four of these [19,23,30,32] provided sufficient information to determine if the index test result pertained to a partial or complete disruption of the ACL. Injury severity (partial or complete ACL disruption) was unclear and treated as partial *and* complete injuries in the remaining studies. Nine studies [19,24–26,28,30,31,33,35] described ACL injuries with concomitant injury to other knee structures, while comorbid knee injuries were unclear or not reported in the remaining five studies [23,27,29,32,34].

There was variability between participants in the included studies with respect to sample size (50–350), average age (25–40 years), proportion of males (52%-100%) and time since ACL injury (one day to longer than one year). The prevalence of verified partial *and* complete ACL injury ranged from 21%-81%.

Quality assessment

The QUADAS-2 ratings of risk of bias and study applicability are shown in Table 2. Only one study [19] adequately addressed all risk of bias domains. For the 14 studies, risk of bias was high or unclear with regard to patient selection for 10 studies, for the index text four studies, for the reference standard nine studies and for flow and timing eight studies.

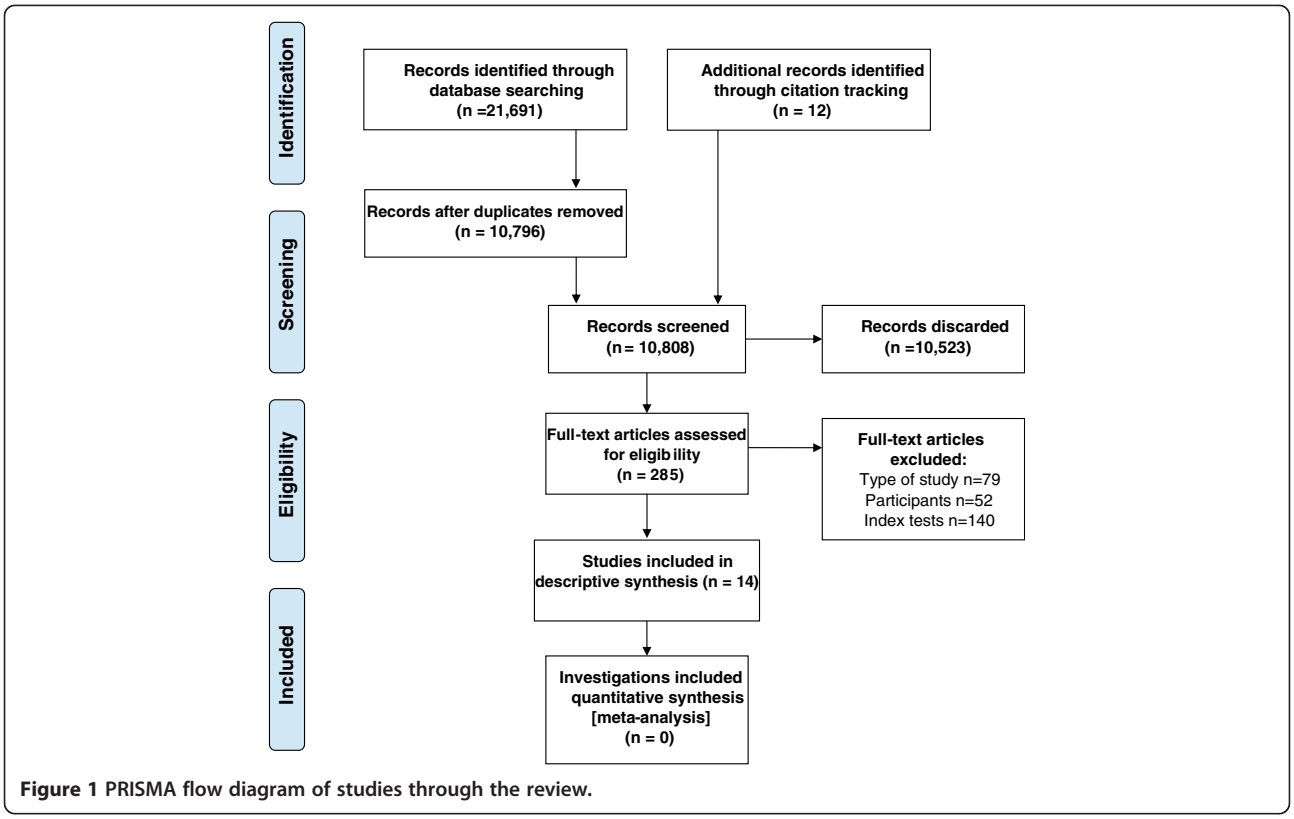

Figure 1 PRISMA flow diagram of studies through the review.

Only one study [19] clearly stated that the reference standard was assessed without knowledge of the results of the index test, while in 12 studies this was unclear [23–26,28–35]. In one study the reference standard was not applied independently of clinical tests [27]. Six studies [24,27,28,32,34,35] included all enrolled participants in the analysis. Across the remaining eight studies [19,23,25,26,29–31,33] the number of participants left out of the analyses ranged from 1%-71% of those originally included.

Diagnostic accuracy of clinical tests

A total of nine clinical index tests were identified by this review. Five tests were items from the clinical history (popping sound at time of injury, giving way, effusion, pain, ability to continue activity) and four index tests were applied as part of physical assessment (the anterior draw test, Lachman's test, prone Lachman's test, the pivot shift). Three of the tests were also performed under anaesthesia (anterior draw test, Lachman's test, pivot shift test). Diagnostic accuracy statistics for all index tests are presented as supplemental material (Additional file 3: Table S3). The anterior draw, Lachman and pivot shift tests were each evaluated in subgroups where the tests were applied in secondary contact settings to identified partial *and* complete ACL injury. The chi-square test ranged from $\chi^2 = 50.66$, 6df, $P < 0.001$ to $\chi^2 = 6.55$, 4df, $P = 0.16$ and the inconsistency indexes were typically high (>75%) ranging from 99.2% to 38.9%. The three physical tests plotted on the ROC plane as well the subgroups sensitivity and specificity forest plots are presented as supplementary information (Additional file 4: Figure S1, Additional file 5: Figure S2). The variability in patient spectrum and performance of index tests among the included studies resulted in important clinical and statistical heterogeneity. In addition, only a small number of studies evaluate specific clinical tests, with all but one study at high risk of bias, so a decision was made not to perform a meta-analysis. The diagnostic accuracy of individual clinical tests for ACL injury along with thresholds for defining clinical usefulness (i.e. small, moderate and large change in post-test probability) are illustrated in Figure 2. The number of studies that evaluated each individual test ranged from two studies for clinical history items to nine studies for Lachman's test.

Only two studies [19,30], from different settings (primary and secondary care), investigated test accuracy for clinical history items. Clinical history items had low value in correctly diagnosing ACL injury (+LR range 0.93-2.54, –LR range 0.15-1.18) (Figure 2).

Six studies [19,23,24,27,31,34] reported the accuracy of the anterior draw test in diagnosing ACL injury. Small, moderate and large +LR (range 1.94-87.88) were observed for the anterior draw test across studies. The

Table 1 Characteristics of included studies

First author, year	Design	Setting	Participants	Partial *and* complete ACL tear prevalence % (n)	Complete ACL tear prevalence % (n)	Reference standard(s)
Beldame, 2011 [23]	Prospective	University hospital, France.	*112 patient/knees with an indication for knee arthroscopy.	37.5% (42)	28.5% (32)	Arthroscopy
Boeree, 1991 [24]	Prospective	Orthopaedic clinic, UK.	203 patient/knees referred from GPs or the A&E.	29.1% (51)	nr	MRI
Decker, 1988 [33]	Prospective	Hospital, Germany.	†108 patient/knees suspected to have knee ligament injury.	61.1% (66)	nr	Arthroscopy/ Surgery
Harilainen, 1987 [25]	Unclear	Emergency department, Finland.	†350 patient/knees with acute knee injury.	41.7% (146)	nr	Arthroscopy/ Arthrotomy
Katz, 1986 [26]	Retrospective	Community hospital, USA.	85 participant/knees with knee injuries presenting for arthroscopy.	25.9% (22)	nr	Arthroscopy
Lee, 1988 [27]	Retrospective	Orthopaedic department of a hospital, USA.	79 magnetic resonance studies of the knee were reviewed.	29.1% (22)	nr	MRI
Lucie, 1984 [28]	Prospective	Orthopaedic clinic, USA.	50 patient/knees with acute traumatic knee haemarthrosis.	76.0% (38)	nr	Arthroscopy/ Arthrotomy
Mulligan, 2011 [29]	Prospective	Orthopaedic surgery and sports medicine service, USA.	*†52 patient/knees with a complaint of knee pain referred from emergency department.	44.2% (23)	nr	Arthroscopy
Noyes, 1980 [30]	Prospective	Orthopaedic/Sports medicine knee clinic, USA.	*85 injured knees (83 patients) that had traumatic haemarthrosis.	71.8% (61)	43.5% (37)	Arthroscopy
Richter, 1996 [34]	Prospective	Hospital, Germany.	74 patient/knees with effusion of the knee following trauma.	78.4% (58)	64.9% (48)	Arthroscopy
Schwartz, 1997 [35]	Prospective	Hospital, Germany.	58 patient/knees with acute knee injury.	81.0% (47)	65.5% (38)	Arthroscopy
Tonino, 1986 [31]	Unclear	Hospital, Netherlands.	*66 patient/knees with acute symptoms of a ligamentous lesion of the knee after trauma.	45.5% (30)	nr	Arthroscopy
Wagemakers, 2010 [19]	Prospective	GP clinics, Netherlands.	*134 patient/knees with new knee symptoms.	20.9% (28)	12.7% (17)	MRI
Wong, 1999 [32]	Prospective	Orthopaedic department of a hospital, Hong Kong.	91 patient/knees with an acute knee haemarthrosis.	nr	56.0% (51)	Arthroscopy

nr: not reported.
*Not all participants evaluated by index test(s).
†Not all participants evaluated by reference standard.

large +LR estimates all had wide confidence intervals and were reported in studies with high risk of bias. All −LRs (range 0.23-0.74) for the anterior draw test were within the small threshold.

Nine studies [19,23–25,27,31,32,34,35] investigated the accuracy of Lachman's test in diagnosing ACL injury. Small, moderate and large LRs (+LR range 1.39-40.81, −LR range 0.02-0.52) were reported for Lachman's test across the studies. Studies that report moderate or large LRs tended to be at risk of bias and had wide confidence intervals. One study [29] investigated the prone Lachman's test and reported small and imprecise LRs (+LR 3.50, −LR 0.38).

Five studies [23,24,30,31,34], all at risk of bias, evaluated the accuracy of the pivot shift test. Small, moderate and large +LRs (range 4.37-16.42) and small −LRs (range 0.38-0.84) were reported for the pivot shift test in all studies. Accuracy estimates with moderate and large +LRs tended to lack precision.

Five studies at high risk of bias [26,28,30,31,33] investigated physical tests when examination was performed under anaesthesia (EUA) (Additional file 6: Figure S3). The anterior draw test, Lachman's test and pivot shift test appear to provide improved diagnostic accuracy when examination is performed under anaesthesia. While LRs are moderate-large the confidence intervals around the +LR estimates are wide.

Only one study, from the primary care setting with low risk of bias, provided data on the effect of combining clinical tests [19]. Specifically, this included two or three positive history tests (from a list of popping sensation, giving way, effusion, immediate pain at trauma and continuation of activity impossible) as well as a positive anterior draw or Lachman's test (Figure 3). The addition of a positive anterior draw test to the combinations of two positive history tests increase the +LR (4.81) close to moderate diagnostic threshold. The addition of a third

Table 2 Risk of bias and applicability concerns summary based on the QUADAS-2 checklist

	Risk of bias				Applicability concerns concerns		
First author, year	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Beldame, 2011 [23]	?	+	+	-	+	+	+
Boeree, 1991 [24]	-	?	+	+	+	+	+
Decker, 1988 [33]	?	+	?	-	+	+	+
Harilainen, 1987 [25]	+	?	?	-	+	+	+
Katz, 1986 [26]	-	+	?	+	+	+	+
Lee, 1988 [27]	-	+	?	-	+	+	+
Lucie, 1984 [28]	-	+	?	-	+	+	+
Mulligan, 2011 [29]	+	+	?	?	+	+	+
Noyes, 1980 [30]	-	?	+	-	?	+	+
Richter, 1996 [34]	-	+	?	+	+	+	+
Schwartz, 1997 [35]	-	+	+	+	+	+	+
Tonino, 1986 [31]	-	+	?	?	+	+	+
Wagemakers, 2010 [19]	+	+	+	+	+	+	+
Wong, 1999 [32]	+	?	?	+	+	+	+

Judgements on risk of bias and applicability concerns: – = high risk; ? = unclear risk; + = low risk.

history test produced a large but imprecise +LR (35.64) but reduced the –LR (0.82).

Discussion

This systematic review included 14 studies that evaluated the diagnostic accuracy of clinical tests for ACL injury. Just one study, which was the only study performed in primary care, had a low risk of bias and showed that results of individual tests produce only small changes in the probability of ACL injury. The same study investigated the diagnostic accuracy of combining history items with physical tests and reported improved accuracy when doing so. The other studies, performed in secondary contact settings, had moderate to high risk of bias and reported quite diverse and imprecise estimates of diagnostic accuracy. Based upon these findings, clinical tests in combination, but not individually, may assist the diagnosis of ACL injury.

The key strengths of the review include a pre-specified and registered review protocol, the use of inclusion criteria to ensure that the study settings reflected clinical practice and the evaluation of study quality using the QUADAS-2 checklist. This review also reported likelihood ratios as they are the preferred approach to report estimates of diagnostic accuracy [21]. The limitations of the study were that sparse data were available on most clinical tests and that we were unable to perform a meta-analysis due to heterogeneity in the estimates of diagnostic accuracy, risk of bias and clinical characteristics. The heterogeneity among studies is well illustrated by the results for Lachman's test, where reported +LRs ranged from 1.5 to 102, risk of bias varied and ACL injury prevalence in the included studies ranged from 21% to 81%.

The clinical tests reviewed are those most commonly used for the diagnosis of ACL injury in clinical practice. Our findings suggest that a clinician cannot rely on a single clinical test in isolation, particularly one from the clinical history, to identify patients with ACL injury. Due to the fact that diagnostic decisions regarding ACL injury are not made on the basis of a single test, studies should ideally focus on test performance in combination. The best estimates of diagnostic accuracy come from Wagemakers et al. [19] whose data suggest that there may be some potential in combining clinical tests, specifically the anterior draw test with two or three of the following five history findings: popping sensation, giving way, effusion, immediate pain at trauma and inability to continue activity. Notwithstanding, these findings must be interpreted with caution as a major drawback of Wagemakers et al's study was its low power to sufficiently analyse multiple combined tests. An important direction for future research is identification of the optimal combination of currently available clinical tests to accurately diagnose ACL injury. While the literature regarding the accuracy of currently used tests is of variable quality, those identified in this body of literature (and included in this review) are the logical candidates to investigate using more robust methods. Such studies are well suited to primary care settings (limiting referral bias), but sample sizes will need to be substantially larger than studies to date in order to investigate multiple sequencing of index tests.

In contrast to our findings, previous systematic reviews have concluded that individual clinical tests can be used to accurately diagnose ACL injury [11,14]. The

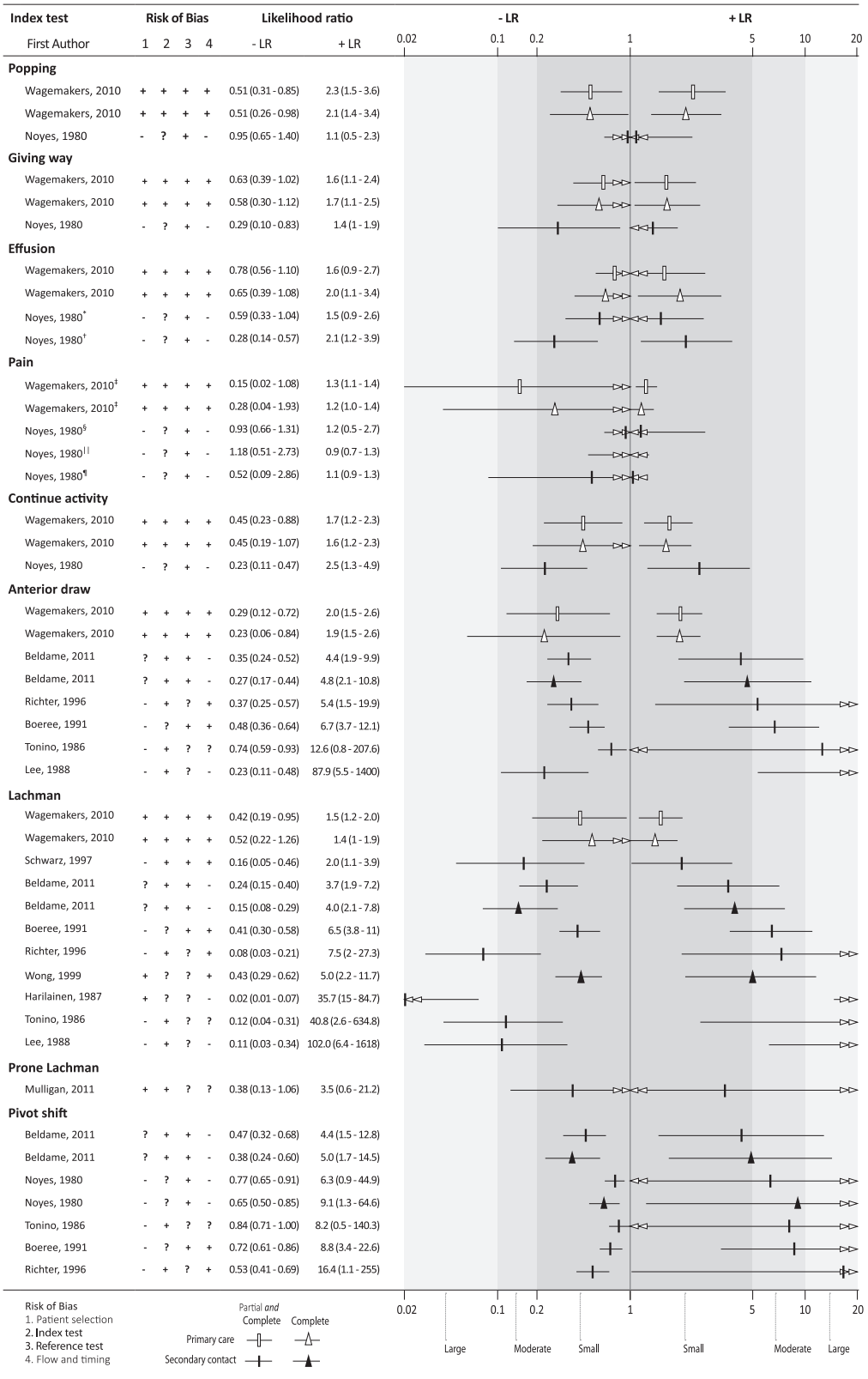

Figure 2 (See legend on next page.)

(See figure on previous page.)
Figure 2 Diagnostic accuracy of clinical examination for ACL injury. Legend: Risk of bias judgements: (–) = high risk; (?) = unclear risk; (+) = low risk. LR thresholds: +LR <5 and -LR >0.2 = small; +LR 5–10 and; –LR 0.1–0.2 = moderate and +LR >10 and –LR <1 = large. Studies that reported estimates for complete ACL injury as well as partial *and* complete ACL injury estimates have been plotted together to provide a comparison of test performance. Different symbols are used for the estimates for complete versus partial and complete ACL injury and for primary care versus secondary contact settings. *joint effusion 2 hours; †joint effusion 12 hours; ‡immediate pain at trauma; §pain none to slight; ‖pain moderate to severe; ¶guarded or painful ROM 24 hours after injury. Guide for interpretation: Greater distance between the –LR and +LR symbols for the test indicates better diagnostic performance.

difference in conclusions is primarily because we only included studies evaluating a clinical sample with diagnostic uncertainty. Other reviews have included case–control studies, a study design which has been shown to inflate estimates of diagnostic accuracy [36]. Our decision to interpret test accuracy via clinically usefully thresholds of likelihood ratios also distinguishes this from previous reviews. A final point of difference concerns our decision not to pool accuracy estimates, which we believe this is the only appropriate course given the risk of bias and heterogeneity evident in the included studies.

Although we applied a critical approach to study selection we still identified several methodological issues that affect internal validity and may result in overestimation of diagnostic test accuracy [17,37]. The spectrum of patients in the included studies varied because of different methods in patient sampling. Most obviously, the characteristics of the samples varied due to the differences in study inclusion and exclusion criteria. Two recent prospective cohort studies illustrate this: Wagemakers et al. [19] included participants with new knee symptoms and excluded participants who were suspected of knee fracture; whereas Beldame et al. [23] included participants with indication for knee arthroscopy, meaning the sample was subject to referral filter bias [37]. The paucity of diagnostic studies for ACL injury conducted in primary care also suggests caution should be taken when generalising these findings to this setting.

In some instances the index tests were not applied to all participants prior to the application of the reference test, or the reference test was performed without a clinical test. There was under reporting of reasons for patient exclusion and withdrawals. Reporting was deficient in most primary studies which limited our appraisal of study quality. This is perhaps most evident with respect to risk of bias domains associated with blinding of the index tests and reference standards. Where multiple index tests were applied concurrently it is unclear the extent to which knowledge of prior testing (test review bias) overestimated the accuracy of index tests. Similarly, there was concern that the invasive nature of knee arthroscopy or surgery as a reference test may have affected the flow of participants through some studies. In these

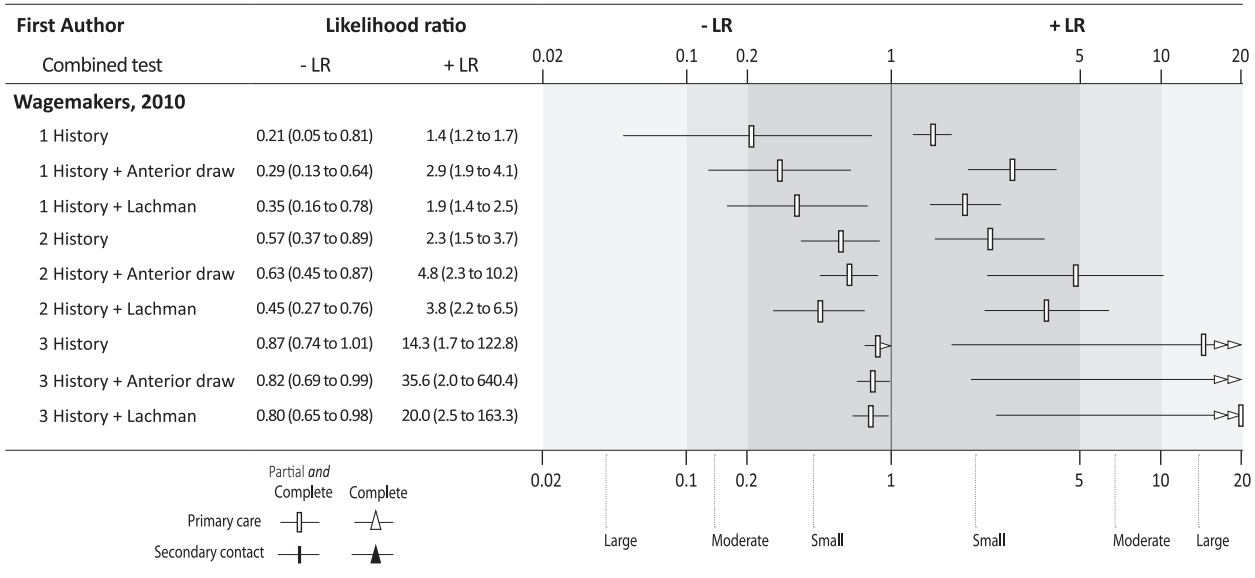

Figure 3 Diagnostic accuracy of composite index tests for partial *and* complete ACL injury in primary care. Legend: Thresholds: +LR <5 and -LR >0.2 = small; +LR 5–10 and; –LR 0.1–0.2 = moderate and +LR >10 and -LR <1 = large. Guide for interpretation: Greater distance between the –LR and +LR symbols for the test indicates better diagnostic performance.

instances a patient with a negative index test may not have received a reference test creating partial verification bias.

Conclusion

This systematic review of clinical tests for ACL injury incorporates the most recent knowledge of diagnostic test accuracy methods. The findings highlight the lack of clinical test accuracy data to support the use of history and physical examination to diagnose ACL injury. Most diagnostic studies on this topic contain methodological flaws which can overestimate the diagnostic accuracy of clinical tests. The available high quality evidence suggests that tests are not useful on their own but combinations may prove to be more useful.

Additional files

Additional file 1: Table S1. PubMed search strategy.

Additional file 2: Table S2. Excluded articles from previous systematic reviews.

Additional file 3: Table S3. Summary statistics for Index tests in the diagnosis of ACL injury.

Additional file 4: Figure S1. Anterior draw, Lachman and pivot shift tests plotted on the ROC plane. Legend: Green: Primary care study setting. Red: Secondary contact study setting.

Additional file 5: Figure S2. Subgroup sensitivity and specificity forest plots. Legend: Anterior draw, Lachman and pivot shift test sensitivity and specificity for partial *and* complete ACL injury in secondary contact settings.

Additional file 6: Figure S3. Diagnostic accuracy of index test EUA in the diagnosis of partial and complete ACL injury. Legend: Risk of bias judgements: (−) = high risk; (?) = unclear risk; (+) = low risk. LR thresholds: +LR <5 and −LR >0.2 = small; +LR 5–10 and; −LR 0.1–0.2 = moderate and +LR>10 and −LR <1 = large. Studies that reported estimates for complete ACL injury as well as partial and complete ACL injury estimates have been plotted together to provide a comparison of test performance. Different symbols are used for the estimates for complete versus partial and complete ACL injury and for primary care versus secondary contact settings. Guide for interpretation: Greater distance between the −LR and +LR symbols for the test indicates better diagnostic performance.

Abbreviations

ACL: Anterior cruciate ligament; QUADAS: QUality assessment of diagnostic accuracy studies; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; EUA: Examination under anaesthesia.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conception and design: MSS, NH, SJK, BWK, CGM. Analysis and interpretation of the data: MSS, NH, SJK, ASD, BWK, CGM. Drafting of the article: MSS, NH, SJK, ASD, CGM. Critical revision of the article for important intellectual content: MSS, NH, SJK, ASD, BWK, CGM. Final approval of the article: MSS, NH, SJK, ASD, BWK, CGM. Statistical expertise: NH, SJK, CGM. Administrative, technical, or logistic support: MSS, NH, SJK, CGM. Collection and assembly of data: MSS, NH, SJK, ASD. All authors read and approved the final manuscript.

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References

1. Lerat JL, Moyen BL, Cladiere F, Besse JL, Abidi H: **Knee instability after injury to the anterior cruciate ligament. Quantification of the Lachman test.** *J Bone Joint Surg Br* 2000, **82:**42–47.
2. Moses B, Orchard J, Orchard J: **Systematic review: annual incidence of ACL injury and surgery in various populations.** *Res Sports Med* 2012, **20:**157–179.
3. Gianotti SM, Marshall SW, Hume PA, Bunt L: **Incidence of anterior cruciate ligament injury and other knee ligament injuries: a national population-based study.** *J Sci Med Sport* 2009, **12:**622–627.
4. Janssen KW, Orchard JW, Driscoll TR, van Mechelen W: **High incidence and costs for anterior cruciate ligament reconstructions performed in Australia from 2003–2004 to 2007–2008: time for an anterior cruciate ligament register by Scandinavian model?** *Scand J Med Sci Sports* 2012, **22:**495–501.
5. Shea KG, Grimm NL, Ewing CK, Aoki SK: **Youth sports anterior cruciate ligament and knee injury epidemiology: who is getting injured? In what sports? When?** *Clin Sports Med* 2011, **30:**691–706.
6. Jackson JL, O'Malley PG, Kroenke K: **Evaluation of acute knee pain in primary care.** *Ann Intern Med* 2003, **139:**575–588.
7. Bollen SR, Scott BW: **Rupture of the anterior cruciate ligament–a quiet epidemic?** *Injury* 1996, **27:**407–409.
8. Louboutin H, Debarge R, Richou J, Selmi TA, Donell ST, Neyret P, Dubrana F: **Osteoarthritis in patients with anterior cruciate ligament rupture: a review of risk factors.** *Knee* 2009, **16:**239–244.
9. Cimino F, Volk BS, Setter D: **Anterior cruciate ligament injury: diagnosis, management, and prevention.** *Am Fam Physician* 2010, **82:**917–922.
10. Magee DJ: *Orthopedic physical assessment 5th ed.* Saunders Elsevier: St. Louis, Mo; 2008.
11. Benjaminse A, Gokeler A, van der Schans CP: **Clinical diagnosis of an anterior cruciate ligament rupture: a meta-analysis.** *J Orthop Sports Phys Ther* 2006, **36:**267–288.
12. Scholten RJ, Opstelten W, van der Plas CG, Bijl D, Deville WL, Bouter LM: **Accuracy of physical diagnostic tests for assessing ruptures of the anterior cruciate ligament: a meta-analysis.** *J Fam Pract* 2003, **52:**689–694.
13. Solomon DH, Simel DL, Bates DW, Katz JN, Schaffer JL: **Does this patient have a torn meniscus or ligament of the knee? Value of the physical examination.** *JAMA* 2001, **286:**1610–1620.
14. van Eck CF, van den Bekerom MPJ, Fu FH, Poolman RW, Kerkhoffs GMMJ: **Methods to diagnose acute anterior cruciate ligament rupture: a meta-analysis of physical examinations with and without anaesthesia.** *Knee Surg Sports Traumatol Arthrosc* 2013, **21:**1898–1903.
15. Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM: **Cochrane Diagnostic Test Accuracy Working G: Systematic reviews of diagnostic test accuracy.** *Ann Intern Med* 2008, **149:**889–897.
16. Swain M, Henschke N, Maher C, Keuerleber J: Diagnostic accuracy of history and physical examination to diagnose knee anterior cruciate ligament injury. PROSPERO 2012:CRD42012002069 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002069 (accessed 20th August 2013).
17. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JHP, Bossuyt PMM: **Epmerical evidence of design-related bias in studies of diagostic tests.** *JAMA* 1999, **282:**1061–1066.
18. Jaeschke R, Guyatt GH, Sackett DL: **Users' guides to the medical literature. III. How to use an article about a diagnostic test B. What are the results and will they help me in caring for my patients?** *JAMA* 1994, **271:**703–707.
19. Wagemakers HP, Luijsterburg PA, Boks SS, Heintjes EM, Berger MY, Verhaar JA, Koes BW, Bierma-Zeinstra SM: **Diagnostic accuracy of history taking and physical examination for assessing anterior cruciate ligament lesions of the knee in primary care.** *Arch Phys Med Rehabil* 2010, **91:**1452–1459.
20. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM, Group Q: **QUADAS-2: a revised tool**

for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011, **155:**529–536.
21. Grimes DA, Schulz KF: **Refining clinical diagnosis with likelihood ratios.** *Lancet* 2005, **365:**1500–1505.
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG: **Measuring inconsistency in meta-analyses.** *BMJ* 2003, **327:**557–560.
23. Beldame J, Bertiaux S, Roussignol X, Lefebvre B, Adam JM, Mouilhade F, Dujardin F: **Laxity measurements using stress radiography to assess anterior cruciate ligament tears.** *Orthop Traumatol Surg Res* 2011, **97:**34–43.
24. Boeree NR, Ackroyd CE: **Assessment of the menisci and cruciate ligaments: an audit of clinical practice.** *Injury* 1991, **22:**291–294.
25. Harilainen A: **Evaluation of knee instability in acute ligamentous injuries.** *Ann Chir Gynaecol* 1987, **76:**269–273.
26. Katz JW, Fingeroth RJ: **The diagnostic accuracy of ruptures of the anterior cruciate ligament comparing the Lachman test, the anterior drawer sign, and the pivot shift test in acute and chronic knee injuries.** *Am J Sports Med* 1986, **14:**88–91.
27. Lee JK, Yao L, Phelps CT, Wirth CR, Czajka J, Lozman J: **Anterior cruciate ligament tears: MR imaging compared with arthroscopy and clinical tests.** *Radiology* 1988, **166:**861–864.
28. Lucie RS, Wiedel JD, Messner DG: **The acute pivot shift: clinical correlation.** *Am J Sports Med* 1984, **12:**189–191.
29. Mulligan EP, Harwell JL, Robertson WJ: **Reliability and diagnostic accuracy of the lachman test performed in a prone position.** *J Orthop Sports Phys Ther* 2011, **41:**749–757.
30. Noyes FR, Bassett RW, Grood ES, Butler DL: **Arthroscopy in acute traumatic hemarthrosis of the knee. Incidence of anterior cruciate tears and other injuries.** *J Bone Joint Surg Am* 1980, **62:**687–695.
31. Tonino AJ, Huy J, Schaafsma J: **The diagnostic accuracy of knee testing in the acutely injured knee. Initial examination versus examination under anaesthesia with arthroscopy.** *Acta Orthop Belg* 1986, **52:**479–487.
32. Wong JWK, Chien EP, Yip DKH, Tang WM, Chin ACW, Peh WCG: **Is MRI necessary to confirm an acute ACL rupture?** *Hong Kong J Sports Med Sports Sci* 1999, **8:**1–5.
33. Decker R, Ruf W: **[The diagnostic certainty of various methods of evaluating recent trauma to knee ligaments].** *Unfallchirurgie* 1988, **14:**204–210. German.
34. Richter J, David A, Pape HG, Ostermann PA, Muhr G: **[Diagnosis of acute rupture of the anterior cruciate ligament. Value of ultrasonic in addition to clinical examination].** *Unfallchirurg* 1996, **99:**124–129. German.
35. Schwarz W, Hagelstein J, Minholz R, Schierlinger M, Danz B, Gerngross H: **[Manual ultrasound of the knee joint. A general practice method for diagnosis of fresh rupture of the anterior cruciate ligament].** *Unfallchirurg* 1997, **100:**280–285. German.
36. Rutjes AWS, Reitsma JB, Vandenbroucke JP, Glas AS, Bossuyt PMM: **Case–control and two-gate designs in diagnostic accuracy studies.** *Clin Chem* 2005, **51:**1335–1341.
37. Leeflang MMG, Bossuyt PMM, Irwig L: **Diagnostic test accuracy may vary with prevalence: implications for evidence-based diagnosis.** *J Clin Epidemiol* 2009, **62:**5–12.

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Appendix 1

Table S1. PubMed search strategy

1. Index test:

"Medical History Taking"[mesh] OR history[tw] OR Pain[mesh] OR pain[tw] OR complaint*[tw] OR dysfunction*[tw] OR disabil*[tw] OR “Physical Examination” [mesh] OR "physical examination"[tw] OR "function test"[tw] OR "physical test"[tw] OR ((clinical[tw] OR clinically[tw]) AND (diagnosis[tw] OR sign[tw] OR signs[tw] OR significance[tw] OR symptom*[tw] OR parameter*[tw] OR assessment[tw] OR finding*[tw] OR evaluat*[tw] OR indication*[tw] OR examination*[tw])) OR “Joint instability”[mesh] OR “give way”[tw] OR pop[tw] OR “lachman test”[tw] OR “anterior drawer test”[tw] OR “pivot shift test”[tw]

2. Target condition:

“Anterior Cruciate Ligament”[mesh] OR “ACL”[tw] OR “anterior cruciate”[tw] OR “Cruciate”[tw]

3. Exclusion criteria:

(Animals[mesh] NOT (Animals[mesh] AND Humans[mesh])) NOT "case report"[ti]

4. Search combination

1 AND 2 NOT 3

Appendix 2

Table S2: Excluded articles from previous systematic reviews

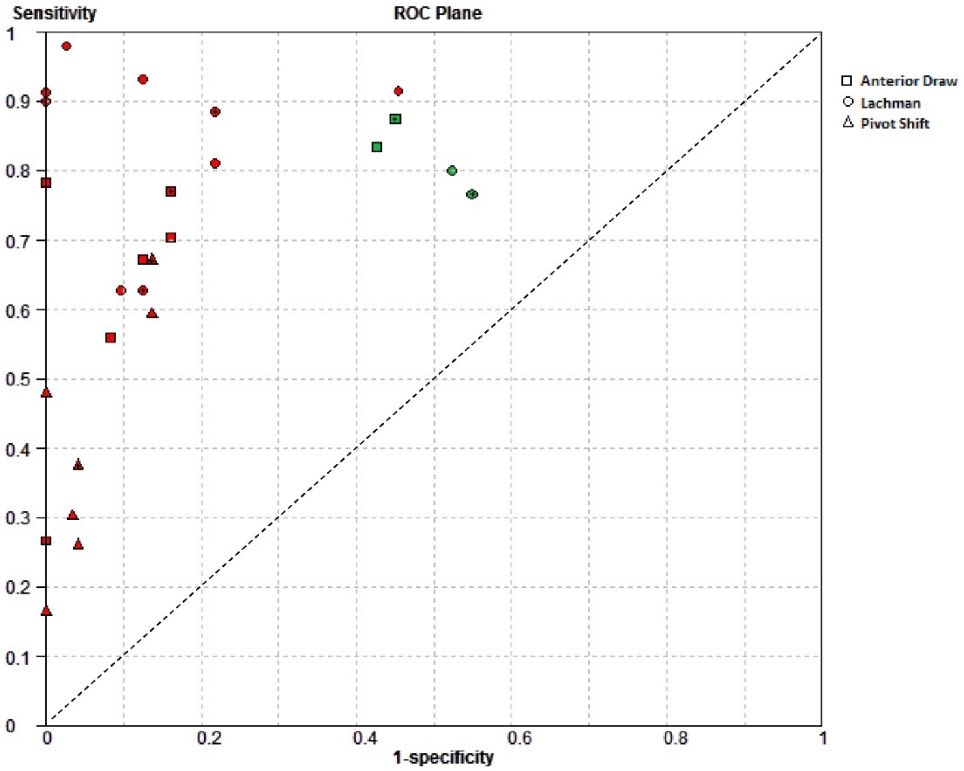
Previously included study	Review included	Reason for exclusion
al-Duri 1992	Scholten, 2003	Study: Insufficient data to construct 2 × 2; Participants: diagnosed ACL injuries
Anderson 1989	Scholten, 2003 Benjaminse, 2006 van Eck, 2012	Participants: Patients were suspected to have cruciate ligament tears
Bomberg 1990	Benjaminse, 2006 van Eck, 2012	Participants: Only included patients with ACL injury in analysis; Insufficient data to reconstruct 2 x 2 table
Braunstein 1982	Solomon, 2001 Jackson, 2003 Scholten, 2003 Benjaminse, 2006	Participants: Comparison made with surgically proven cases
Cooperman 1990	Scholten, 2003 Benjaminse, 2006	Participants: Over 1/3 of the patients had an ACL injury as determined by arthroscopy/arthrotomy on entering the study. Reference test: No other participants (other
Dahlstedt 1989	Solomon, 2001 Benjaminse, 2006 Van Eck, 2012	Study: Insufficient data to reconstruct 2 x 2; Participants: Patients included were those with arthroscopically verified complete anterior cruciate ligament rupture
Dehaven 1980	Solomon, 2001 Benjaminse, 2006 Van Eck, 2012	Study: Insufficient data to reproduce 2 x 2
Donaldson 1985	Solomon, 2001 Jackson, 2003 Benjaminse, 2012 Van Eck, 2012	Study: Insufficient data to reconstruct 2 x 2 table; Participants: Included only patients found to have ACL tears
Fowler 1989	Solomon, 2001	Index test: No specific clinical test(s) used in the diagnosis of ACL injury
Gurtler 1987	Solomon, 2001	Participants: Were patients with arthroscopically documented complete ACL tears; Study: insufficient data
Hardaker 1990	Scholten, 2003 Benjaminse, 2006 Van Eck, 2012	Insufficient data: Only the proportion of positive index test data was presented
Hughston 1976	Solomon, 2001 Jackson, 2003 Benjaminse, 2006 Van Eck, 2012	Participants: Had medial-compartment or cruciate ligament tears – insufficient diagnostic uncertainty
Jonsson 1982	Solomon, 2001 Jackson, 2003 Benjaminse, 2006 Van Eck, 2012	Study: Insufficient data to reconstruct 2 x 2 table
Kim 1995	Benjaminse, 2006	Study: Insufficient data; Patients with arthroscopically proven ACL injury
Learmonth 1991	Benjaminse, 2006 Evan Eck, 2012	Participants: All patients with a normal Lachman test were discharged, leaving only data for those with positive tests
Liu 1995	Solomon, 2001 Jackson, 2003 Benjaminse, 2006 Van Eck, 2012	Study: Insufficient data to reconstruct 2 x 2 table
Mitsou 1988	Solomon, 2001 Benjaminse, 2006 Van Eck, 2012	Study: Insufficient data to reconstruct 2 x 2 table; Participants: Included only patients found to have ACL tears
O'Shea 1996	Solomon, 2001	Index test: General examination
Otter 1994	Benjaminse, 2006	Study: non-peer reviewed
Rose 1996	Solomon, 2001	Participants: Clinically diagnosed ACL tear; Index tests: General examination
Rubinstein 1994	Scholten, 2003 Benjaminse, 2006	Participants: Participants with known diagnoses
Sandberg 1986	Scholten, 2003 Benjaminse, 2006 Van Eck, 2012	Participants: High level of diagnostic certainty
Simonsen 1984	Solomon, 2001	Index test: General examination
Steinbruck 1988	Schlten, 2003 Benjaminse, 2006	Study design: Insufficient data to recreate 2x2 tables
Strand 1995	Van Eck, 2012	Participants: Found by having arthroscopically proven ACL rupture
Torg 1976	Jackson, 2003 Scholten, 2003 Benjaminse, 2006	Study design: Insufficient data to recreate 2x2 tables
Warren 1978	Benjaminse, 2006	Participants: Patients had sustained ACL injury
Wirth 1985	Van Eck, 2012	Participants: Patients had proven rupture of the ACL

Table S3. Summary statistics for Index tests in the diagnosis of ACL injury

Index test	First Author, Year	ACL injury type	TP	FP	FN	TN	Sensitivity% (95%CI)	Specificity% (95%CI)	+LR(95%CI)	-LR(95%CI)	DOR(95%CI)
History: Primary Care											
Popping sensation	Wagemakers, 2010	Partial *and* complete	17	27	10	72	0.63 (0.42 to 0.81)	0.73 (0.63 to 0.81)	2.31 (1.50 to 3.56)	0.51 (0.31 to 0.85)	4.53 (1.85 to 11.12)
Popping sensation	Wagemakers, 2010	Complete	11	33	6	76	0.65 (0.38 to 0.86)	0.70 (0.60 to 0.78)	2.14 (1.36 to 3.36)	0.51 (0.26 to 0.98)	4.22 (1.44 to 12.38)
Giving way	Wagemakers, 2010	Partial *and* complete	17	38	11	64	0.61 (0.41 to 0.79)	0.63 (0.53 to 0.72)	1.63 (1.10 to 2.41)	0.63 (0.39 to 1.02)	2.60 (1.10 to 6.14)
Giving way	Wagemakers, 2010	Complete	11	44	6	69	0.65 (0.38 to 0.86)	0.61 (0.51 to 0.70)	1.66 (1.09 to 2.53)	0.58 (0.30 to 1.12)	2.88 (0.99 to 8.33)
Effusion	Wagemakers, 2010	Partial *and* complete	12	27	16	73	0.43 (0.25 to 0.63)	0.73 (0.63 to 0.81)	1.58 (0.93 to 2.71)	0.78 (0.56 to 1.10)	2.03 (0.85 to 4.84)
Effusion	Wagemakers, 2010	Complete	9	30	8	81	0.53 (0.28 to 0.77)	0.73 (0.64 to 0.81)	1.96 (1.14 to 3.37)	0.65 (0.39 to 1.08)	3.04 (1.07 to 8.60)
Continuation of activity impossible	Wagemakers, 2010	Partial *and* complete	21	44	7	55	0.75 (0.55 to 0.89)	0.56 (0.45 to 0.66)	1.69 (1.24 to 2.29)	0.45 (0.23 to 0.88)	3.75 (1.46 to 9.63)
Continuation of activity impossible	Wagemakers, 2010	Complete	13	52	4	58	0.77 (0.50 to 0.93)	0.53 (0.43 to 0.62)	1.62 (1.16 to 2.25)	0.45 (0.19 to 1.07)	3.63 (1.11 to 11.82)
Immediate pain at trauma	Wagemakers, 2010	Partial *and* complete	27	75	1	23	0.96 (0.82 to 1.00)	0.24 (0.16 to 0.33)	1.26 (1.11 to 1.44)	0.15 (0.02 to 1.08)	8.28 (1.07 to 64.31)
Immediate pain at trauma	Wagemakers, 2010	Complete	16	86	1	23	0.94 (0.71 to 1.00)	0.21 (0.14 to 0.30)	1.19 (1.02 to 1.39)	0.28 (0.04 to 1.93)	4.28 (0.54 to 33.98)
History: Secondary Contact											
Popping sensation	Noyes, 1980	Partial *and* complete	19	6	33	12	0.37 (0.24 to 0.51)	0.67 (0.41 to 0.87)	1.10 (0.52 to 2.31)	0.95 (0.65 to 1.40)	1.15 (0.37 to 3.57)
Pain none to slight	Noyes, 1980	Partial *and* complete	17	5	35	13	0.33 (0.20 to 0.47)	0.72 (0.47 to 0.90)	1.18 (0.51 to 2.73)	0.93 (0.66 to 1.31)	1.26 (0.39 to 4.12)
Pain moderate to severe	Noyes, 1980	Partial *and* complete	35	13	17	5	0.67 (0.53 to 0.80)	0.28 (0.10 to 0.54)	0.93 (0.66 to 1.31)	1.18 (0.51 to 2.73)	0.79 (0.24 to 2.59)
Limb collapse, patient fell to ground	Noyes, 1980	Partial *and* complete	47	12	5	6	0.90 (0.79 to 0.97)	0.33 (0.13 to 0.59)	1.36 (0.97 to 1.90)	0.29 (0.10 to 0.83)	4.7 (1.22 to 18.05)
Guarded or painful ROM (24hr after injury)	Noyes, 1980	Partial *and* complete	49	16	3	2	0.94 (0.84 to 0.99)	0.11 (0.01 to 0.35)	1.06 (0.89 to 1.27)	0.52 (0.09 to 2.86)	2.04 (0.31 to 13.33)
Inability to resumed sport immediately after injury	Noyes, 1980	Partial *and* complete	44	6	8	12	0.85 (0.72 to 0.93)	0.67 (0.41 to 0.87)	2.54 (1.31 to 4.93)	0.23 (0.11 to 0.47)	11.00 (3.20 to 37.86)
Joint effusion 2hr	Noyes, 1980	Partial *and* complete	35	8	17	10	0.67 (0.53 to 0.80)	0.56 (0.31 to 0.79)	1.51 (0.87 to 2.63)	0.59 (0.33 to 1.04)	2.57 (0.86 to 7.70)
Joint effusion 12hr	Noyes, 1980	Partial *and* complete	43	7	9	11	0.83 (0.70 to 0.92)	0.61 (0.36 to 0.83)	2.13 (1.18 to 3.85)	0.28 (0.14 to 0.57)	7.51 (2.29 to 24.66)
Physical Test: Primary Care											
Anterior draw	Wagemakers, 2010	Partial *and* complete	20	44	4	59	0.83 (0.63 to 0.95)	0.57 (0.47 to 0.67)	1.95 (1.47 to 2.60)	0.29 (0.12 to 0.72)	6.71 (2.14 to 21.01)
Anterior draw	Wagemakers, 2010	Complete	14	50	2	61	0.86 (0.62 to 0.98)	0.55 (0.45 to 0.64)	1.94 (1.47 to 2.56)	0.23 (0.06 to 0.84)	8.54 (1.85 to 39.36)
Lachman	Wagemakers, 2010	Partial *and* complete	20	54	5	49	0.80 (0.59 to 0.93)	0.48 (0.38 to 0.58)	1.53 (1.17 to 2.00)	0.42 (0.19 to 0.95)	3.63 (1.27 to 10.41)
Lachman	Wagemakers, 2010	Complete	13	61	4	50	0.77 (0.50 to 0.93)	0.45 (0.36 to 0.55)	1.39 (1.02 to 1.90)	0.52 (0.22 to 1.26)	2.66 (0.82 to 8.68)
Physical Test: Secondary Contact											
Anterior draw	Beldame, 2011	Partial *and* complete	50	5	21	26	0.70 (0.58 to 0.81)	0.84 (0.66 to 0.95)	4.37 (1.93 to 9.88)	0.35 (0.24 to 0.52)	12.38 (4.19 to 36.62)
Anterior draw	Boeree, 1991	Partial *and* complete	33	12	26	132	0.56 (0.42 to 0.69)	0.92 (0.86 to 0.96)	6.71 (3.73 to 12.07)	0.48 (0.36 to 0.64)	13.96 (6.38 to 30.55)
Anterior draw	Lee, 1988	Partial *and* complete	18	0	5	56	0.78 (0.56 to 0.93)	1.00 (0.94 to 1.00)	87.88 (5.52 to 1399.9)	0.23 (0.11 to 0.48)	380.09 (20.05 to 7206.20)
Anterior draw	Richter, 1996	Partial *and* complete	39	2	19	14	0.67 (0.54 to 0.79)	0.88 (0.62 to 0.98)	5.38 (1.45 to 19.91)	0.37 (0.25 to 0.57)	14.37 (2.96 to 69.75)
Anterior draw	Tonino, 1986	Partial *and* complete	8	0	22	22	0.27 (0.12 to 0.46)	1.00 (0.85 to 1.00)	12.61 (0.77 to 207.56)	0.74 (0.59 to 0.93)	17.00 (0.93 to 312.51)
Anterior draw	Beldame, 2011	Complete	47	5	14	26	0.77 (0.65 to 0.87)	0.84 (0.66 to 0.95)	4.78 (2.12 to 10.79)	0.27 (0.17 to 0.44)	17.46 (5.65 to 53.93)
Lachman	Boeree, 1991	Partial *and* complete	37	14	22	130	0.63 (0.49 to 0.75)	0.90 (0.84 to 0.95)	6.45 (3.78 to 11.02)	0.41 (0.30 to 0.58)	15.62 (7.28 to 33.50)
Lachman	Harilainen, 1987	Partial *and* complete	143	5	3	177	0.98 (0.94 to 1.00)	0.97 (0.94 to 0.99)	35.65 (15.02 to 84.65)	0.02 (0.01 to 0.07)	1687.4 (396.52 to 7180.80)
Lachman	Lee, 1988	Partial *and* complete	21	0	2	56	0.91 (0.72 to 0.99)	1.00 (0.94 to 1.00)	102.13 (6.44 to 1618.40)	0.11 (0.03 to 0.34)	971.8 (44.81 to 21075.6)
Lachman	Richter, 1996	Partial *and* complete	54	2	4	14	0.93 (0.83 to 0.98)	0.88 (0.62 to 0.98)	7.45 (2.03 to 27.28)	0.08 (0.03 to 0.21)	94.5 (15.68 to 569.57)
Lachman	Schwarz, 1997	Partial *and* complete	43	5	4	6	0.92 (0.80 to 0.98)	0.55 (0.23 to 0.83)	2.01 (1.05 to 3.87)	0.16 (0.05 to 0.46)	12.90 (4.26 to 39.09)
Lachman	Tonino, 1986	Partial *and* complete	27	0	3	22	0.90 (0.74 to 0.98)	1.00 (0.85 to 1.00)	40.81 (2.62 to 634.75)	0.12 (0.04 to 0.31)	353.57 (17.34 to 7209.90)
Lachman	Beldame, 2011	Partial *and* complete	64	7	15	25	0.81 (0.71 to 0.89)	0.78 (0.60 to 0.91)	3.70 (1.91 to 7.19)	0.24 (0.15 to 0.40)	15.24 (5.55 to 41.81)
Lachman	Beldame, 2011	Complete	61	7	8	25	0.88 (0.78 to 0.95)	0.78 (0.60 to 0.91)	4.04 (2.09 to 7.82)	0.15 (0.08 to 0.29)	27.23 (8.92 to 83.14)
Lachman	Wong, 1999	Complete	32	5	19	35	0.63 (0.48 to 0.76)	0.88 (0.73 to 0.96)	5.02 (2.15 to 11.71)	0.43 (0.29 to 0.62)	11.79 (3.94 to 35.26)
Prone Lachman	Mulligan, 2011	Partial *and* complete	7	1	3	4	0.70 (0.35 to 0.93)	0.80 (0.28 to 1.00)	3.50 (0.58 to 21.16)	0.38 (0.13 to 1.06)	9.33 (0.71 to 122.57)
Pivot shift	Beldame, 2011	Partial *and* complete	31	3	21	19	0.60 (0.45 to 0.73)	0.86 (0.65 to 0.97)	4.37 (1.49 to 12.81)	0.47 (0.32 to 0.68)	9.35 (2.45 to 35.62)
Pivot shift	Boeree, 1991	Partial *and* complete	18	5	41	139	0.31 (0.19 to 0.44)	0.97 (0.92 to 0.99)	8.79 (3.42 to 22.57)	0.72 (0.61 to 0.86)	12.21 (4.27 to 34.89)
Pivot shift	Richter, 1996	Partial *and* complete	28	0	30	16	0.48 (0.35 to 0.62)	1.00 (0.79 to 1.00)	16.42 (1.06 to 255.24)	0.53 (0.41 to 0.69)	30.84 (1.77 to 538.16)
Pivot shift	Tonino, 1986	Partial *and* complete	5	0	25	22	0.17 (0.06 to 0.35)	1.00 (0.85 to 1.00)	8.16 (0.48 to 140.30)	0.84 (0.71 to 1.00)	9.71 (0.51 to 185.45)
Pivot shift	Noyes, 1980	Partial *and* complete	16	1	45	23	0.26 (0.16 to 0.39)	0.96 (0.79 to 1.00)	6.30 (0.88 to 44.88)	0.77 (0.65 to 0.91)	8.18 (1.02 to 65.58)

Pivot shift	Noyes, 1980	Complete	14	1	23	23	0.38 (0.23 to 0.55)	0.96 (0.79 to 1.00)	9.08 (1.28 to 64.64)	0.65 (0.50 to 0.85)	14.00 (1.70 to 115.42)
Pivot shift	Beldame, 2011	Complete	29	3	14	19	0.67 (0.52 to 0.81)	0.86 (0.65 to 0.97)	4.95 (1.69 to 14.45)	0.38 (0.24 to 0.60)	13.12 (3.32 to 51.87)
Examination Under Anaesthesia : Secondary Contact											
Anterior draw	Katz, 1986	Partial *and* complete	9	3	13	60	0.41 (0.21 to 0.64)	0.95 (0.87 to 0.99)	8.59 (2.55 to 28.90)	0.62 (0.44 to 0.88)	13.85 (3.29 to 58.30)
Anterior draw	Tonino, 1986	Partial *and* complete	17	0	13	22	0.57 (0.37 to 0.75)	1.00 (0.85 to 1.00)	25.97 (1.65 to 409.84)	0.45 (0.30 to 0.67)	58.33 (3.24 to 1050.60)
Lachman	Katz, 1986	Partial *and* complete	18	2	4	61	0.82 (0.60 to 0.95)	0.97 (0.89 to 1.00)	25.77 (6.50 to 102.23)	0.19 (0.08 to 0.46)	137.25 (23.22 to 811.38)
Lachman	Tonino, 1986	Partial *and* complete	28	0	2	22	0.93 (0.78 to 0.99)	1.00 (0.85 to 1.00)	42.29 (2.72 to 657.25)	0.08 (0.03 to 0.27)	513 (23.43 to 11232.3)
Lachman	Decker, 1988	Partial *and* complete	60	5	6	14	0.91 (0.81 to 0.97)	0.74 (0.49 to 0.91)	3.46 (1.62 to 7.36)	0.12 (0.55 to 0.28)	28.00 (7.47 to 105.00)
Lachman	Wong, 1999	Complete	45	4	6	36	0.88 (0.76 to 0.96)	0.90 (0.76 to 0.97)	8.82 (3.46 to 22.48)	0.13 (0.06 to 0.28)	67.5 (17.69 to 257.51)
Pivot shift	Katz, 1986	Partial *and* complete	18	1	4	62	0.82 (0.60 to 0.95)	0.98 (0.92 to 1.00)	51.55 (7.30 to 363.86)	0.19 (0.08 to 0.45)	279 (29.31 to 2655.70)
Pivot shift	Lucie, 1984	Partial *and* complete	38	0	7	5	0.84 (0.71 to 0.94)	1.00 (0.48 to 1.00)	10.04 (0.71 to 143.14)	0.18 (0.09 to 0.36)	56.47 (2.81 to 1132.90)
Pivot shift	Tonino, 1986	Partial *and* complete	15	0	15	22	0.50 (0.31 to 0.69)	1.00 (0.85 to 1.00)	23.00 (1.45 to 364.86)	0.51 (0.36 to 0.73)	45.00 (2.50 to 809.32)
Pivot shift	Decker, 1988	Partial *and* complete	57	0	9	19	0.86 (0.76 to 0.94)	1.00 (0.82 to 0.96)	34.33 (2.22 to 530.94)	0.15 (0.08 to 0.26)	236.05 (13.12 to 4246.70)
Pivot shift	Wong, 1999	Complete	42	0	9	40	0.82 (0.69 to 0.92)	1.00 (0.91 to 1.00)	67.02 (4.25 to 1056.60)	0.19 (0.10 to 0.33)	362.37 (20.42 to 6430.90)
Pivot shift	Noyes, 1980	Partial *and* complete	47	3	13	21	0.78 (0.66 to 0.88)	0.88 (0.68 to 0.97)	6.27 (2.16 to 18.21)	0.25 (0.15 to 0.41)	25.31 (6.52 to 98.28)
Pivot shift	Noyes, 1980	Complete	32	3	4	21	0.89 (0.74 to 0.97)	0.88 (0.68 to 0.97)	7.11 (2.45 to 20.62)	0.13 (0.05 to 0.32)	56.00 (11.36 to 275.97)
Composite Test: Primary Care											
1 History	Wagemakers, 2010	Partial *and* complete	26	67	2	35	0.93 (0.77 to 0.99)	0.34 (0.25 to 0.44)	1.41 (1.19 to 1.68)	0.21 (0.05 to 0.81)	6.79 (1.52 to 30.29)
1 History	Wagemakers, 2010	Complete	15	78	2	35	0.88 (0.64 to 0.99)	0.31 (0.23 to 0.40)	1.28 (1.03 to 1.58)	0.38 (0.10 to 1.44)	3.36 (0.73 to 15.52)
1 History + Anterior draw	Wagemakers, 2010	Partial *and* complete	19	28	5	72	0.79 (0.58 to 0.93)	0.72 (0.62 to 0.81)	2.83 (1.94 to 4.12)	0.29 (0.13 to 0.64)	9.77 (3.33 to 28.70)
1 History + Anterior draw	Wagemakers, 2010	Complete	13	34	3	74	0.81 (0.54 to 0.96)	0.69 (0.59 to 0.77)	2.58 (1.79 to 3.72)	0.27 (0.10 to 0.77)	9.43 (2.52 to 35.29)
1 History + Lachman	Wagemakers, 2010	Partial *and* complete	20	43	5	58	0.80 (0.59 to 0.93)	0.57 (0.47 to 0.67)	1.88 (1.39 to 2.54)	0.35 (0.16 to 0.78)	5.40 (1.88 to 15.52)
1 History + Lachman	Wagemakers, 2010	Complete	13	50	4	59	0.76 (0.50 to 0.93)	0.54 (0.44 to 0.64)	1.67 (1.19 to 2.33)	0.44 (0.18 to 1.04)	3.84 (1.18 to 12.51)
2 History	Wagemakers, 2010	Partial *and* complete	16	25	12	76	0.57 (0.37 to 0.76)	0.75 (0.66 to 0.83)	2.31 (1.45 to 3.68)	0.57 (0.37 to 0.89)	4.05 (1.69 to 9.72)
2 History	Wagemakers, 2010	Complete	13	28	4	84	0.77 (0.50 to 0.93)	0.75 (0.66 to 0.83)	3.06 (2.02 to 4.63)	0.31 (0.13 to 0.74)	9.75 (2.94 to 32.36)
2 History + Anterior draw	Wagemakers, 2010	Partial *and* complete	12	9	16	92	0.43 (0.25 to 0.63)	0.91 (0.84 to 0.96)	4.81 (2.26 to 10.24)	0.63 (0.45 to 0.87)	7.67 (2.78 to 21.14)
2 History + Anterior draw	Wagemakers, 2010	Complete	11	10	6	102	0.65 (0.38 to 0.86)	0.91 (0.84 to 0.96)	7.25 (3.64 to 14.42)	0.39 (0.20 to 0.74)	18.70 (5.7 to 61.34)
2 History + Lachman	Wagemakers, 2010	Partial *and* complete	15	16	9	80	0.63 (0.41 to 0.81)	0.83 (0.74 to 0.90)	3.75 (2.18 to 6.46)	0.45 (0.27 to 0.76)	8.33 (3.11 to 22.32)
2 History + Lachman	Wagemakers, 2010	Complete	10	21	7	82	0.59 (0.33 to 0.82)	0.80 (0.71 to 0.87)	2.89 (1.66 to 5.01)	0.52 (0.29 to 0.92)	5.58 (1.90 to 16.40)
3 History	Wagemakers, 2010	Partial *and* complete	4	1	24	99	0.14 (0.04 to 0.33)	0.99 (0.94 to 1.00)	14.29 (1.66 to 122.75)	0.87 (0.74 to 1.01)	16.50 (1.76 to 154.41)
3 History	Wagemakers, 2010	Complete	3	2	14	109	0.18 (0.04 to 0.43)	0.98 (0.94 to 1.00)	9.79 (1.76 to 54.41)	0.84 (0.67 to 1.05)	11.68 (1.79 to 76.06)
3 History + Anterior draw	Wagemakers, 2010	Partial *and* complete	4	0	20	98	0.17 (0.05 to 0.37)	1.00 (0.96 to 1.00)	35.64 (1.98 to 640.40)	0.82 (0.69 to 0.99)	43.24 (2.24 to 834.72)
3 History + Anterior draw	Wagemakers, 2010	Complete	3	1	13	105	0.19 (0.04 to 0.46)	0.99 (0.95 to 1.00)	19.88 (2.20 to 179.60)	0.82 (0.65 to 1.04)	24.23 (2.35 to 250.39)
3 History + Lachman	Wagemakers, 2010	Partial *and* complete	5	1	19	95	0.21 (0.07 to 0.42)	0.99 (0.94 to 1.00)	20.00 (2.45 to 163.31)	0.80 (0.65 to 0.98)	25.00 (2.76 to 226.26)
3 History + Lachman	Wagemakers, 2010	Complete	3	3	14	100	0.18 (0.04 to 0.43)	0.97 (0.92 to 0.99)	6.06 (1.33 to 27.59)	0.85 (0.68 to 1.06)	7.14 (1.31 to 38.91)

Appendix 4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ROC Plane
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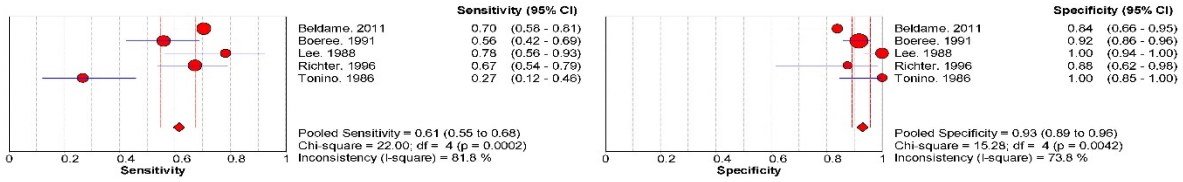
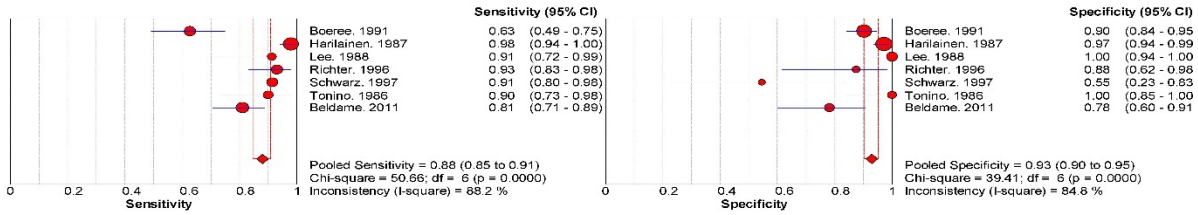
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Anterior Draw
Lachman
Pivot Shift

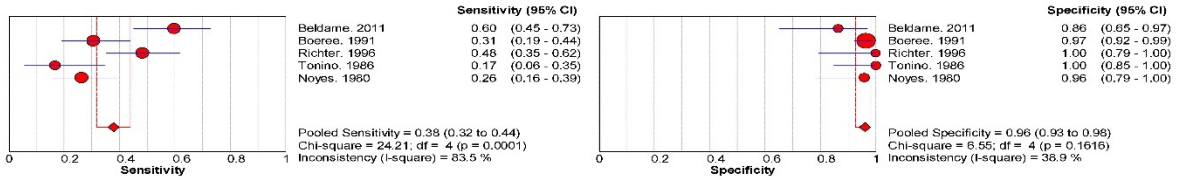
Anterior Draw



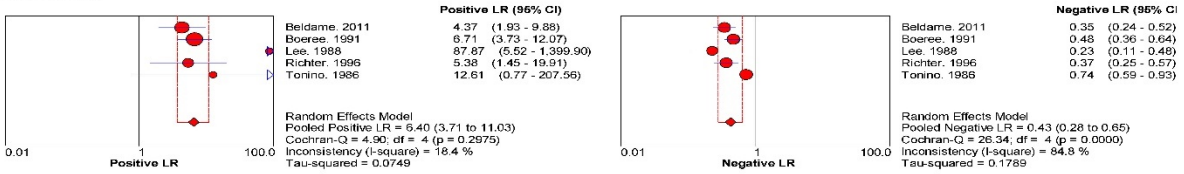
Lachman



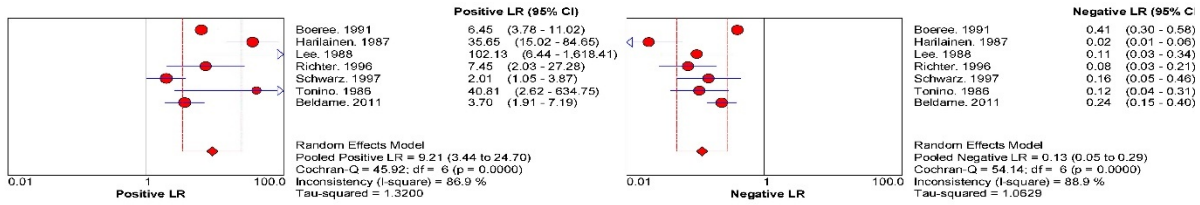
Pivot Shift



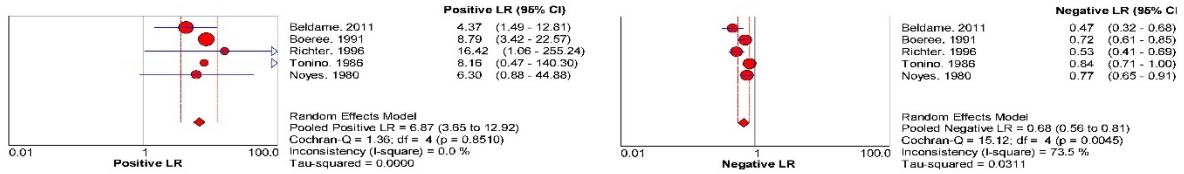
Anterior Draw

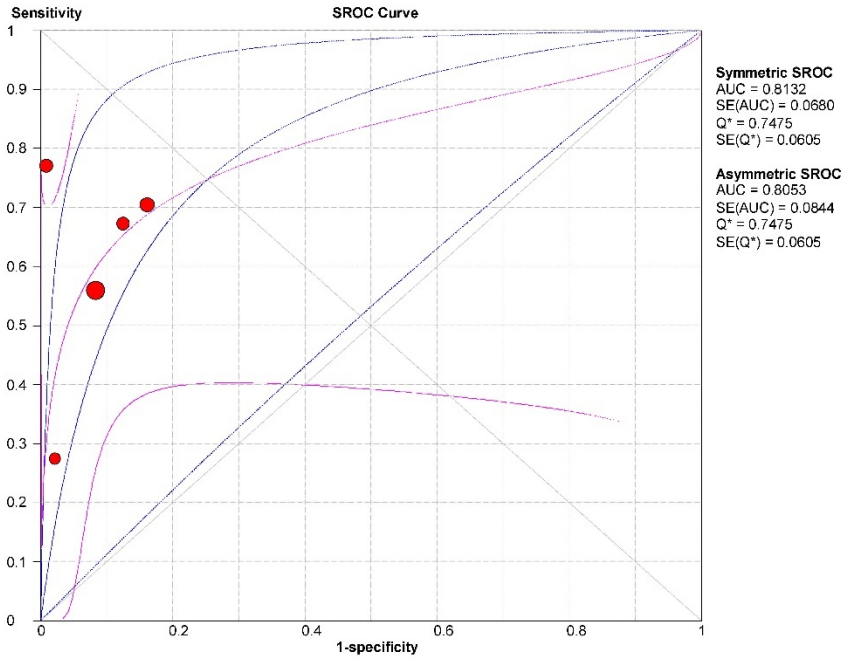


Lachman



Pivot Shift

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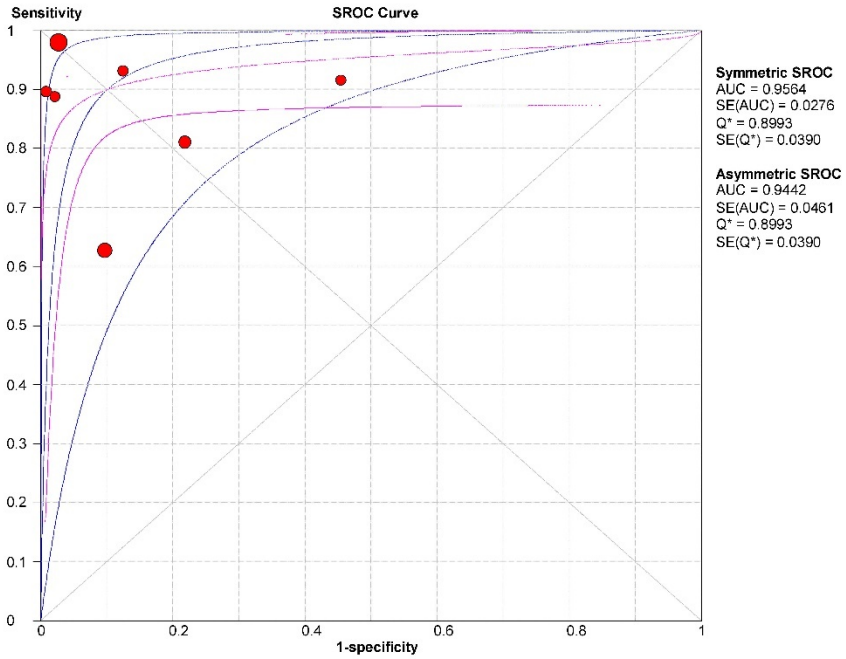
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Symmetric SROC
AUC = 0.8132
SE(AUC) = 0.0680
Q* = 0.7475
SE(Q*) = 0.0605
Asymmetric SROC
AUC = 0.8053
SE(AUC) = 0.0844
Q* = 0.7475
SE(Q*) = 0.0605


Sensitivity
SROC Curve
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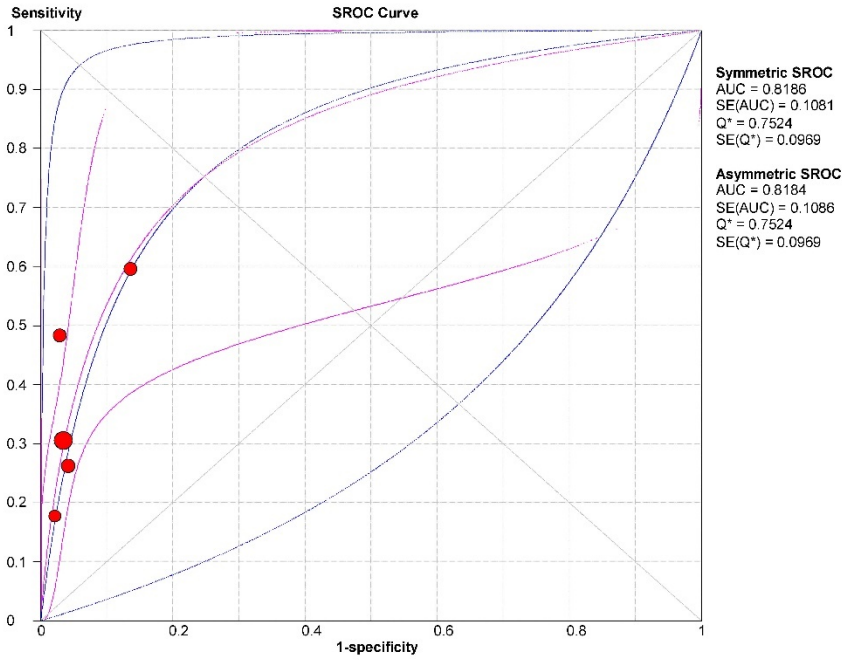
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Symmetric SROC
AUC = 0.9564
SE(AUC) = 0.0276
Q* = 0.8993
SE(Q*) = 0.0390
Asymmetric SROC
AUC = 0.9442
SE(AUC) = 0.0461
Q* = 0.8993
SE(Q*) = 0.0390


Sensitivity
SROC Curve
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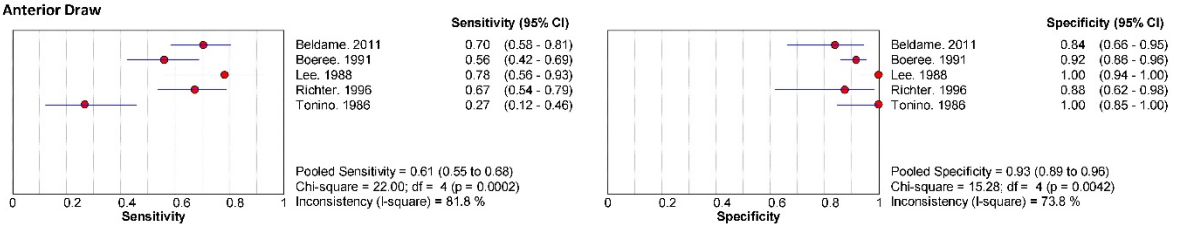
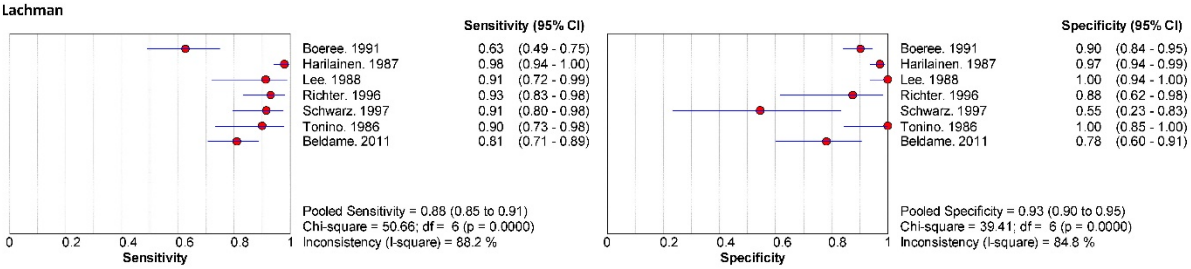
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.2
0.4
0.6
0.8
1
1-specificity
Symmetric SROC
AUC = 0.8186
SE(AUC) = 0.1081
Q* = 0.7524
SE(Q*) = 0.0969
Asymmetric SROC
AUC = 0.8184
SE(AUC) = 0.1086
Q* = 0.7524
SE(Q*) = 0.0969

Appendix 5

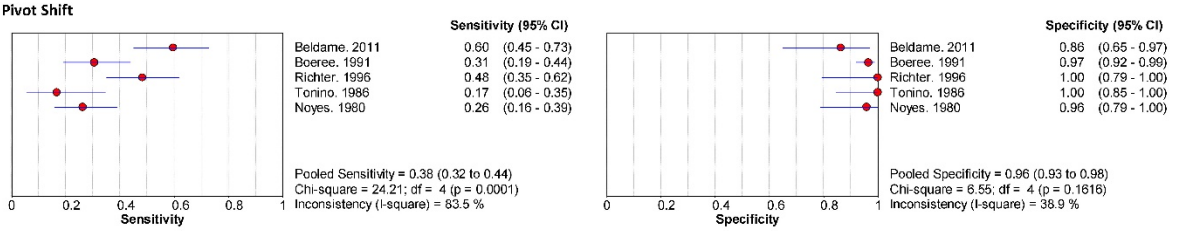
Anterior Draw



Lachman

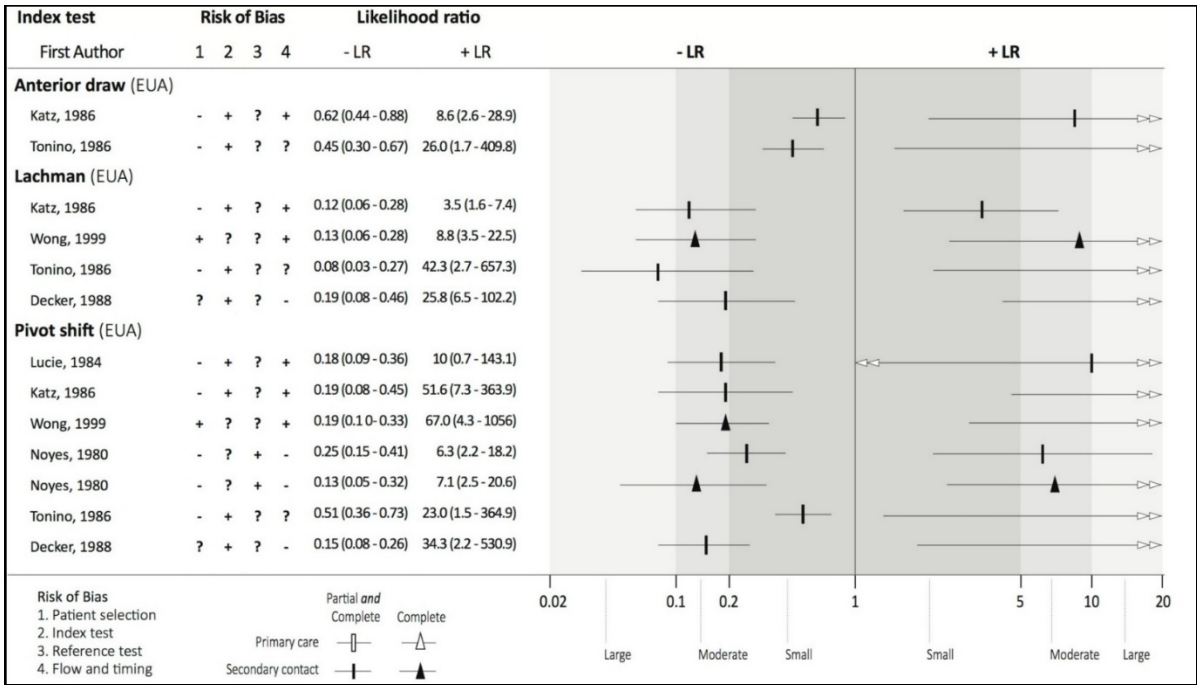


Pivot Shift



Appendix 6

Figure S1. Diagnostic accuracy of index test EUA in the diagnosis of partial *and* complete ACL injury



Legend: EUA: Examination Under Anaesthesia. Risk of bias judgements: (-) = high risk; (?) = unclear risk; (+) = low risk. LR thresholds: +LR <5 and -LR >0.2 = small; +LR 5–10 and; -LR 0.1–0.2 = moderate and +LR >10 and -LR <1 = large. Studies that reported estimates for complete ACL injury as well as partial *and* complete ACL injury estimates have been plotted together to provide a comparison of test performance. Different symbols are used for the estimates for complete versus partial and complete ACL injury and for primary care versus secondary contact settings. Guide for interpretation: Greater distance between the –LR and +LR symbols for the test indicates better diagnostic performance.

Chapter Seven

Conclusions

“Human progress is neither automatic nor inevitable. Every step toward the goals requires sacrifice, suffering, and struggle; the tireless exertions and passionate concern of dedicated individuals.”

- Martin Luther King

7.1 Overview of main findings

This thesis provides original contributions to the epidemiology of pain and injury in adolescents and young adults. The work contains important advances to the field, specifically: precise estimates of the prevalence of back pain (and headache and stomach ache) in adolescents across 28 countries in Europe and North America (Chapter 2); estimates of the association and potential impact of back pain (and headache and stomach ache) on adolescents reaching recommended physical activity levels (Chapter 3); a synthesis of evidence regarding whether pubertal development is an aetiological factor for musculoskeletal (MSK) disorders (Chapter 4); the feasibility of conducting a longitudinal cohort study to investigate MSK pain in Australian adolescents, with insights to the clinical course of knee pain (Chapter 5), and; the diagnostic accuracy of clinical tests for anterior cruciate ligament (ACL) injuries, a common and impactful knee disorder in adolescents and young adults (Chapter 6).[1]

The first aim of the thesis was to investigate the frequency and co-occurrence of common pain types (back pain, headache and stomach ache) in adolescents. Data from a large multinational study[2] showed approximately one in three adolescents experience back pain (37%), and one in two headache (54.1%), or stomach ache (49.8%) monthly or more often. Coexistence of back pain with other pains is more common than in isolation. Collectively, three-quarters (74.4%) of adolescents experienced one of the three pain types at least once per month in the last 6-months. Back pain, headache, and stomach ache were more commonly experienced among girls than boys, and among older adolescents.

The second aim was to investigate whether pain was associated with adolescents not reaching the recommended level of moderate-to-vigorous physical activity (MVPA). Data from over 200,000 adolescents in 28 countries[2] showed that only 18.7% of young people met MVPA recommendations. In no country was it common for adolescents to meet MVPA guidelines (range: 12.8% to 41.7%). Girls and older adolescents less frequently met MVPA recommendations. Adolescents who experienced pain were generally less likely to meet The World Health Organisation's (WHO) targets for MVPA.[3] The magnitude of this relationship was small (odds ratios ranged from 0.7 to 0.9) and varied by sex, age and the pain type. The unadjusted risk differences for adolescents with pain not meeting MVPA guidelines were up to 4.6% for boys and 4.3% for girls, compared to those without pain.

The third aim was to evaluate if there is an aetiological association between growth, maturation and MSK disorders in adolescents. The systematic review in Chapter 4 included 56 studies that evaluated the link between adolescent growth/maturity and MSK disorders (pain, injury, and fracture). Included studies reported 208 associations (101 associations for MSK pain, 32 for head/chest pain, 50 for sports and dance injury, 2 for stress fracture and 23 for fracture). Ninety-nine (48%) associations were cross-sectional or retrospective and cannot inform causal mechanisms. In general, the available evidence does not support an aetiological association between pubertal development and MSK disorders. The relationship between growth and maturation, and back pain was unclear despite a weak association between advanced maturation status and more frequent back pain (OR range 1.1 to 1.9). Much uncertainty remains; available evidence reports inconsistent associations, is methodologically heterogeneous, and is at high risk of bias.

The fourth aim was to investigate the feasibility of conducting a prospective clinical course study of knee pain in adolescents using electronic data collection. The study revealed major potential threats to feasibility, namely; slow recruitment in private clinics (1.2 patients per month across 8 clinics), high non-response to short message service (response rate: 71.3%) and considerable loss to follow-up at 6-months (20%, 6/30 participants). When adolescents with MSK pain were recruited in Australian primary-care (private physiotherapy clinics), electronic follow-up measures alone seemed insufficient to track (weekly) the clinical course of pain over a 6-month period. Although the purpose of the study was to estimate feasibility and caution is needed when interpreting clinical outcome data, only 50% of respondents reported no pain (0/10 numeric rating scale) at 8-weeks follow-up.

The final aim was to investigate the accuracy of clinical tests for the diagnosis of ACL injury, a common and impactful knee condition that peaks in adolescence and young adulthood.[1] The prevalence of ACL injury presenting for care in the 14 included studies ranged from 20.9% to 81.0%. Clinical tests included; history questions (popping sound at time of injury, giving way, effusion, pain, ability to continue activity), physical tests (anterior draw, Lachman's, prone Lachman's, pivot shift) and combinations thereof. Clinical history items used in isolation had low value in diagnosing ACL injury (positive likelihood ratio (+LR) range 0.9 to 2.5, negative likelihood ratio (−LR) range 0.2 to 1.2). Accuracy of physical examination tests varied, e.g. estimates for Lachman's test ranged from +LR 1.4 to 102.1, −LR 0.02 to 0.5. Clinical tests with moderate or large likelihood ratios (moderate to high accuracy) tended to lack precision. For example, 3 positive history items in

combination with a positive anterior draw test resulted in a large +LR of 35.6, but a wide confidence interval; 2.0 to 640.4. Only one study was conducted in primary care,[4] and this was the only study at low risk of bias. All other studies were conducted in secondary contact settings and had moderate to high risk of bias. Available high-quality evidence showed that clinical tests in combination, but not individually, may assist in the accurate diagnosis of ACL injury.

7.2 Implications and future research directions

The findings of this thesis have implications for epidemiological pain research, public health policy, and clinical practice.

Firstly, the extent of pain experienced by adolescents represents a potentially substantial public health problem. Chapter 2 dispels the myth that pain in school-aged children is rare,[5] and draws much needed attention to the global problem of pain in adolescents. Pain should not only be considered an issue of middle or older age. The fact that girls and older adolescents experience pain most often aids targeting of public health strategies. Prevention efforts and resources need to be prioritised to address the adolescent age-frame, for example, school-based campaigns that focus on primary or secondary prevention. Given the high prevalence of back pain in adolescents there is a need to update clinical practice guidelines to include evidence-based management advice for younger patients. Current back pain guidelines target adults and are mostly silent on the management of adolescents.[6] Previous guidelines have considered younger age (e.g. onset <20 years) as a sign of potentially serious disease,[7-9] but this feature would yield substantial false positives.

Given the paucity of pain research in young people compared to adults,[10] greater efforts need to be directed at the study of pain in children and adolescents. There is need for emphasis on identifying episodes of pain in adolescents that have important consequences for the child, for example, impact on participation and quality of life. Given the large multinational design of the study in Chapter 2, pain measures were limited to brief single items that provide limited information on severity and impact of the pain. Future research requires more sophisticated measures that better capture the physical and mental health domains affected by pain. Chapter 2 highlights the tendency for pain conditions to coexist in adolescents, which indicates the need for research to better understand the severity, mechanisms and risk factors of coexisting pains in adolescence. Similarly, differences in pain prevalence by sex and age were identified, but mechanisms to explain these differences are not well understood.

Chapter 3 was the first large study to find that pain is associated with lower odds of adolescents meeting minimum MVPA recommendations, suggesting pain is potentially a barrier to achievement of physical activity guidelines. Pain may play a role in the burden of adolescent physical inactivity. This notion has potential to direct interventions that target adolescent pain with the aim of improving physical activity levels. However, this conclusion needs to be balanced against the strength of association found in Chapter 3. With the presence of pain in adolescents contributing an absolute risk of <5%, differences in MVPA between adolescents with and without pain were small. Caution in advocating public health strategies that target adolescent pain to improve physical activity levels is necessary at this point.

Clinicians should be aware of the potential impact pain can have on the physical activity levels of some adolescents seeking care. The WHO physical activity guideline[3] provides a simple framework to assess adolescent physical activity levels, as well as establish functional goals. Given the potential health implications of physical inactivity in adolescence and across the lifespan, clinicians should prioritise strategies to improve physical activity in adolescents they treat who are affected by pain.

The relationship between adolescent pain and physical activity is still not well understood. Typically, large studies like Chapter 3 report correlations rather than establish causal effects. Longitudinal studies are needed to investigate the effects of pain, including the impact on physical activity. Unlike cross-sectional research, longitudinal studies allow the temporal sequence of events to be established, which is necessary to draw causal inferences. Future research also needs to account for important confounders to more accurately understand the effects of pain on adolescent health behaviours like physical activity.

Chapter 4 is the first comprehensive review to synthesise research on the association between pubertal development and MSK disorders. It casts doubt on a meaningful aetiological link between biological maturation, growth, and MSK disorders in adolescents. In doing so it questions the common clinical belief that adolescents are more likely to incur MSK disorders during periods of rapid growth.[11] [12] In clinical practice, young people and their parents seek to understand the cause of these painful conditions. Contemporary clinical recommendations for the management of adolescent MSK conditions involve explaining the factors associated

with pain.[13] The findings of this study suggest that clinicians should avoid implicating maturation and growth as the cause of MSK conditions in young people until robust evidence becomes available.

Several methodological shortcomings were identified in studies that evaluated whether biological growth and maturation are aetiologically linked to MSK disorders. Many of the concerns identified apply to the study of risk factors for MSK disorders in adolescence generally. There is currently only limited evidence to inform risk factors for MSK pains[14] and additional high-quality research is required. Seldom do aetiological studies satisfy the Bradford-Hill criteria[15] and adequately account for key considerations such as confounding and establishing a temporal sequence.[16] Future research needs to address these issues in their design and better account for emergent factors such as health comorbidities and contemporary social context of adolescence and young adulthood.

Clinical management of knee pain in adolescents and young adults is challenged by the lack of robust evidence on clinical course.[14 16] Estimates of prognosis and prognostic factors are currently based on either non-clinical or anecdotal evidence. Chapter 5 takes an initial step in addressing the urgent need for prognostic studies on the clinical course of knee disorders in young people. School-based studies suggest that less than 10% of school children with lower extremity pain experience chronic pain.[17] In Chapter 5, 30% of adolescents reported chronic knee pain, which suggests substantial differences between estimates from studies of non-clinical and clinical samples. The ability to reliably inform clinical management of MSK disorders in young people requires appropriately designed, feasible clinical studies.

Future research must enrol and follow large clinical cohorts of young people with MSK disorders. While electronic methods of communication (text messaging, mobile phone applications, email) hold promise to reduce the financial and logistical burden to researchers, participants and parents, traditional methods of follow-up such as telephone contact may still be necessary to minimise loss to follow-up. Alternately, new methods may yet provide opportunity for researchers such as communication through social media platforms as well as applications that leverage engagement through gamification. As illustrated in Chapter 5, participant follow-up via electronic communications has potential advantages over traditional follow-up methods. For example, the ability to respond frequently, in real-time to collect information on multiple dimensions of health. Future research that leverages the immediacy of electronic communications to limit recall bias may gain deeper insights into adolescent MSK symptoms, affect, and behaviours.

Finally, clinicians that manage adolescents and young adults' knee disorders need to be aware of limitations of clinical tests for the diagnosis of ACL injuries. Clinicians should make diagnostic decisions on the basis of a combination of clinical test findings, particularly in primary practice settings. For example, combining information from three positive history items (such as popping, giving way, and activity discontinuation) and either a positive Lachman test or positive anterior draw test provides a clinician with compelling diagnostic evidence of ACL injury.[4]

Diagnosis of ACL injury in young people can be challenging because of poor recall, laxity, and an increased likelihood of different knee injuries associated with an

immature musculoskeletal system.[18] Research is needed to identify the best combination of tests for diagnosis. Given studies in Chapter 6 included participants ranging from 6 to 72 years (mean age 28-years), there is a need for diagnostic test accuracy research that focuses specifically on adolescents and young adults, where ACL injuries are most common.[1] Accurate clinical diagnoses are also important for epidemiological understanding of MSK conditions in young people. At present clinical research that aims to understand specific conditions commonly use diagnostic classification standards such as the WHO International Classification of Disease (ICD),[19] or the Orchard Sports Injury Classification System (OSICS).[20] While future clinical studies are needed to understand the course and management of specific pain and injury diagnoses in young people, researchers should first consider the accuracy of diagnostic tests they employ.

In conclusion, the findings of this thesis provide important new knowledge regarding the epidemiology of pain and injury in adolescents and young adults. Pain and MSK conditions are common in adolescents and may impact their ability to meet physical activity recommendations. Commonly held beliefs about risks of biological growth and maturation seem doubtful, and limited research resources in the adolescent MSK field may be better directed elsewhere. Prospective clinical research is needed to inform clinical management of pain and injuries in young people. In particular, electronic methods of adolescent follow-up provide a promising method of short term follow-up, but should be augmented with traditional follow-up methods. In focusing clinical, public health and research efforts on specific MSK conditions, stakeholders need to be cognisant of the limitations of clinical diagnosis. Hence, the findings

presented in this thesis are relevant to clinicians, policy makers and researchers who work with pain and injury in adolescents and young adults.

7.3 References

1. Zbrojkiewicz D, Vertullo C, Grayson JE. Increasing rates of anterior cruciate ligament reconstruction in young Australians, 2000-2015. *Med J Aust* 2018;208:354-58.
2. Roberts C, Freeman J, Samdal O, et al. The Health Behaviour in School-aged Children (HBSC) study: methodological developments and current tensions. *Int J Public Health* 2009;54:140-50.
3. World Health Organization. Global Recommendations on Physical Activity for Health. 2010 https://www.ncbi.nlm.nih.gov/books/NBK305057/ (Accessed 3 Aug 2018).
4. Wagemakers HP, Luijsterburg PA, Boks SS, et al. Diagnostic Accuracy of History Taking and Physical Examination for Assessing Anterior Cruciate Ligament Lesions of the Knee in Primary Care. *Arch Phys Med Rehabil* 2010;91:1452-59.
5. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet* 2017;389:736-47.
6. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the american college of physicians. *Ann Intern Med* 2017;166:514-30.
7. Airaksinen O, Brox JI, Cedraschi C, et al. Chapter 4 European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006;15:s192-s300.

8. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: A joint clinical practice guideline from the american college of physicians and the american pain society. *Ann Intern Med* 2007;147:478-91.
9. van Tulder M, Becker A, Bekkering T, et al. Chapter 3. European guidelines for the management of acute nonspecific low back pain in primary care. *Eur Spine J* 2006;15 Suppl 2:S169-91.
10. Michaleff ZA, Kamper SJ, Maher CG, et al. Low back pain in children and adolescents: a systematic review and meta-analysis evaluating the effectiveness of conservative interventions. *Eur Spine J* 2014;23:2046-58.
11. DiFiori JP, Benjamin HJ, Brenner JS, et al. Overuse injuries and burnout in youth sports: a position statement from the American Medical Society for Sports Medicine. *Br J Sports Med* 2014;48:287-88.
12. Uziel Y, Hashkes PJ. Growing pains in children. *Pediatr Rheumatol* 2007;5:5.
13. O'Sullivan P, Smith A, Beales D, et al. Understanding Adolescent Low Back Pain From a Multidimensional Perspective: Implications for Management. *J Orthop Sports Phys Ther* 2017;47:741-51.
14. Huguet A, Tougas ME, Hayden J, et al. Systematic review with meta-analysis of childhood and adolescent risk and prognostic factors for musculoskeletal pain. *Pain* 2016;157:2640-56.
15. Fedak KM, Bernal A, Capshaw ZA, et al. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol* 2015;12:14.
16. Kamper SJ, Yamato TP, Williams CM. The prevalence, risk factors, prognosis and treatment for back pain in children and adolescents: An overview of systematic reviews. *Best Pract Res Clin Rheumatol* 2016;30:1021-36.

17. Fuglkjær S, Hartvigsen J, Wedderkopp N, et al. Musculoskeletal extremity pain in Danish school children – how often and for how long? The CHAMPS study-DK. *BMC Musculoskelet Disord* 2017;18:492.

18. Ardern CL, Ekås G, Grindem H, et al. 2018 International Olympic Committee consensus statement on prevention, diagnosis and management of paediatric anterior cruciate ligament (ACL) injuries. *Knee Surg Sports Traumatol Arthrosc* 2018;26:989-1010.

19. What does ICD-11 mean for child health professionals? *Lancet Child Adolesc Health* 2018;2:543.

20. Rae K, Orchard J. The Orchard Sports Injury Classification System (OSICS) version 10. *Clin J Sport Med* 2007;17:201-4.

Appendix A

PROSPERO International prospective register of systematic reviews

The relationship between growth, maturity, and musculoskeletal conditions in adolescents: a systematic review

The relationship between growth, maturity, and musculoskeletal conditions in adolescents: a systematic review

Michael Swain, Steve Kamper, Chris Maher, Carolyn Broderick, Damien McKay, Nicholas Henschke

Citation

Michael Swain, Steve Kamper, Chris Maher, Carolyn Broderick, Damien McKay, Nicholas Henschke. The relationship between growth, maturity, and musculoskeletal conditions in adolescents: a systematic review. PROSPERO 2014 CRD42014014333 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42014014333

Review question

Is there an association between physical growth and maturation (as determined by biological markers of maturation) and musculoskeletal conditions in young people?

Searches

Electronic databases that will be searched include: PubMed, EMBASE and CINAHL. Bibliographies of relevant journal publications and forward citation tracking using the Scopus citation database will be performed. Databases will be searched from inception to date of search.
The search strategy was developed for PubMed and modified for use in other databases:
Search terms
((((((((((sports) OR athletic) OR soft tissue) OR overuse) OR musculoskeletal) OR back) OR lower extremity) OR upper extremity) OR neck))
AND
(((pain) OR injury) OR fracture))
AND
((((((((((((((((bone age) OR skeletal age) OR body size) OR peak height velocity) OR height velocity) OR growth spurt) OR maturation) OR skeletal maturity) OR biologic maturity) OR sexual maturity) OR Tanner stage) OR Tanner staging) OR puberty) OR somatic growth) OR pubertal development) OR pubertal spurt) OR sex factor) OR risk factor) OR anthropometr*))
AND
((child*) OR adolescen*)

Types of study to be included

Only peer-reviewed journal publications of primary observational research will be included. All languages.

Condition or domain being studied

Musculoskeletal disorders (including MSK injury)

Participants/population

Inclusion Criteria of Population (P): Adolescents (chronological age range: 10-19 years of age). Male and Female.

Intervention(s), exposure(s)

Inclusion Criteria for Exposure (I): At least one quantitative measure of biological maturity or growth (e.g. peak height velocity, Tanner staging, bone age).
Exclusion Criteria for Exposure (I): (1) Insufficient measures of growth (i.e. do not account for temporal change e.g. height, weight, BMI without time as a denominator). (2) Unreliable measures of stage of maturation (e.g. chronological age).
Inclusion Criteria for Outcome (O): Estimates of the prevalence or incidence of MSK disorders.
Exclusion Criteria for Outcome (O): Case-series (frequency) of only MSK disorders.

Comparator(s)/control
Inclusion Criteria for comparator (C): The study must provide a measure of the association (e.g. OR, RR) between measures of biological maturity or growth and MSK conditions.

Primary outcome(s)
Studies must estimate the incidence or prevalence of at least one MSK condition (including pain and injury), stratified by a measure of growth or maturation as a risk factor.

Secondary outcome(s)
None

Data extraction (selection and coding)
One review author will extract data using a standardised form. A second review author will check extracted data against the included study. Extracted data will include the following:
• Satisfaction of inclusion criteria.
• Study characteristics
• Population characteristics; participant source or setting, age and gender distribution
• MSK condition characteristics; Frequency and duration of symptoms, pain and disability measures, body location/diagnosis
• Maturity or growth measurement; type, categories
• Measures of association; for example proportional differences, incidence comparison or ratios of the two. Measures of precision e.g. 95% confidence intervals and adjustment for confounders will be extracted where available.
The two researchers will discuss their findings and compare results. Discrepancies will be resolved by way of comparing data extraction findings for studies that are under scrutiny, and justification for areas of discrepancy. It is anticipated that a consensus will be reached on any areas of discrepancy. Where required a third author will mediate. Authors of included studies will be contacted to provide further data where further information is needed.

Risk of bias (quality) assessment
Steering questions in The Quality in Prognosis Studies (QUIPS) tool will be modified to assess the quality of included studies. The tool will rate individual studies according to the potential risk of bias associated with six domains:
(1) study participation,
(2) study attrition,
(3) etiological factor measurement,
(4) outcome measurement,
(5) confounding measurement and account, and
(6) analysis.
The QUIPS tool was designed for use in prognostic factor studies to comprehensively assess risk of bias based on epidemiological principles, which are applicable to risk factors. The level of risk of bias associated with each domain can be rated as 'low', 'moderate' and 'high' based on the responses that reviewers give to each item. Pairs of independent reviewers will assess the methodological quality. Discrepancies will be resolved by consensus and with a third author if necessary.

Strategy for data synthesis
It is anticipated that standard statistical measures for outcomes (e.g. Rate Ratios) for individual studies will be extracted, and if possible results will be combined in a Meta-Analysis.

Analysis of subgroups or subsets
Items for maturation and growth will be analysed separately
Population of athletes will be analysed separately

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English

Country

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Stage of review

Review_Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Adolescent; Humans; Musculoskeletal Diseases

Date of registration in PROSPERO

17 October 2014

Date of publication of this version

17 October 2014

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

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

17 October 2014

Appendix B

PROSPERO International prospective register of systematic reviews

Diagnostic accuracy of history and physical examination to diagnose knee anterior cruciate ligament injury

Diagnostic accuracy of history and physical examination to diagnose knee anterior cruciate ligament injury

Michael Swain, Nick Henschke, Chris Maher, Julia Keuerleber

Citation

Michael Swain, Nick Henschke, Chris Maher, Julia Keuerleber. Diagnostic accuracy of history and physical examination to diagnose knee anterior cruciate ligament injury. PROSPERO 2012 CRD42012002069 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42012002069

Review question

The objective of this review is to evaluate the diagnostic accuracy of clinical assessment (patient history and physical examination methods) for the diagnosis of ACL injury
The secondary objective of this review is to assess the influence of sources of heterogeneity on the diagnostic accuracy of clinical assessment, in particular the study design (e.g. consecutive series or case-control and consistency of applied reference standards and blinding), the health care setting (e.g. primary or secondary care), and aspects of study methods as reflected in the items of the QUality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist

Searches

Relevant computerised databases will be searched for eligible diagnostic studies from the earliest year possible, including MEDLINE, PubMed, EMBASE, and CINAHL The strategy uses several combinations of searches related to the patient population, history taking, physical examination, and the target condition. The reference lists of all included publications will be checked, as well as a forward citation search for additional studies.

Types of study to be included

Primary diagnostic studies will be considered if they compare the results of history taking and physical examination for the identification of ACL injury, to those of an acceptable reference standard namely (arthroscopy, arthrotomy and MRI). The primary focus of the review will be studies enrolling a consecutive series of clinical patients with diagnostic uncertainty where these tests would typically be used. Studies also need to present sufficient data to allow construction of a 2 x 2 table to allow estimates of diagnostic accuracy (such as sensitivity and specificity) to be derived. Case-control studies will also be considered, but because the case-control design is associated with overestimation of diagnostic accuracy, the influence of study design on the outcomes will be investigated. If studies have been reported in abstracts or conference proceedings, the full publications will be retrieved where possible. Studies published in all languages will be retrieved and included in this review. If necessary, appropriate translation of potentially eligible articles will be sought.

Condition or domain being studied

The anterior cruciate ligament (ACL) is an important stabilising structure of the knee. It prevents anterior translation and torsional movements of the tibia on the femur. Disruption of the ACL creates knee instability and dysfunction which is a risk factor for knee meniscus lesion, articular cartilage lesion and subsequent osteoarthritis. Injuries to the ACL occur on a spectrum from partial tear to complete rupture. Partial tears have traditionally been defined by the proportion of ACL disruption. ACL injuries may occur in isolation or combined with secondary knee structures such meniscus, articular cartilage/bone, and/or the collateral ligaments.

Participants/population

Studies will be included if they evaluate patients presenting to a care provider for diagnosis of knee pain.

Studies in which a substantial proportion of recruited patients (>10%) have already been diagnosed with ACL injury that is likely to be causing their knee pain or dysfunction will be excluded. This proportion was chosen based on a consensus among the author team, in an attempt to minimise verification bias. The potential influence of the setting (whether patients present to primary, secondary or tertiary care settings) on diagnostic performance will be investigated.

Intervention(s), exposure(s)

Index tests: Studies evaluating any aspects of the history taking or physical examination of knee pain or dysfunction in patients will be eligible for inclusion. This includes all information regarding the demographic characteristics (e.g. age, gender), clinical and medical history (e.g. mode or features of onset, symptoms of knee giving away), and physical examination results (e.g. palpation, muscle strength testing, orthopaedic testing). Studies will be included where the diagnostic accuracy of individual history features or physical assessment procedures are evaluated in isolation, or as part of a combination. In the case of a combination of clinical assessment findings, the study should clearly describe which tests are included in the combination, and how studies in which only a "clinical diagnosis" or "global clinician judgment" (some unknown combination of history and physical examination) are compared with a reference standard will be excluded from this review. An undefined clinical judgment represents an individual clinician's diagnostic ability (which cannot be taught to other clinicians), rather than providing data on clearly defined patient characteristics.

Comparator(s)/control

Reference standards: Studies will be included if clinical assessment procedures are compared to magnetic resonance imaging (MRI), arthroscopy or arthrotomy to confirm the presence of ACL injury.

Primary outcome(s)

Diagnostic outcomes (true positive, false positive, true negative, and false negative numbers). They may be reconstructed using information from other relevant parameters (sensitivity, specificity, or predictive values)

Timing and effect measures

Test characteristics will include the type of index test; methods of execution; experience and expertise of the assessors; type of reference standard; and where relevant cut-off points for diagnosing ACL lesion (e.g. quantitative observation/imaging measures). Interpretations of "positive" results may vary across studies and some studies may present the diagnostic performance of an index test at several different cut-off points. Data regarding the most commonly used cut-off points used by studies in the review will be extracted.

Secondary outcome(s)

None.

Data extraction (selection and coding)

Two review authors (MS and J) will independently apply the selection criteria to all citations (titles and abstracts) identified by the search strategy described above. Consensus meetings will be organised to discuss any disagreement regarding selection. Final selection will be based on a review of full publications, which will be retrieved for all studies that either meet the selection criteria, or for which there will be uncertainty regarding selection. The other review authors will be consulted in cases of persisting disagreement. Prior to performing the search, the selection criteria and the QUADAS-2 criteria will be piloted on selected diagnostic studies to ensure consistency of interpretation among the reviewers.Two review authors (MS and NH) will independently extract the data to ensure adequate reliability of collected data. For each study, aspects of study design, characteristics of the population, index test and reference standard will be presented in tables.

Risk of bias (quality) assessment

The quality of each study will be assessed by at least two review authors using the QUality Assessment of Diagnostic Accuracy Studies (QUADAS-2) list (Whiting 2011). The Cochrane Diagnostic Test Accuracy Working Group recommends these items. The QUADAS-2 tool consists of 4 domains that refer to internal validity (for example: blind assessment of index and reference test, or avoidance of verification bias).

The review authors will classify each item as "yes" (adequately addressed); "no" (inadequately addressed); or "unclear" (inadequate detail presented to allow a judgment to be made). Guidelines for the assessment of each item will be made available to the review authors. Disagreements will be resolved by discussion and if necessary, by consulting a third review author.
The four domains of the QUADAS-2 will be considered individually for each study, without the application of weights or the use of a summary score to select studies with certain levels of quality in the analysis. The influence of negative or unclear classification of important items will be explored using sensitivity analyses or meta-regression analyses (see below). The following items will be considered for these analyses:
(1) spectrum variation/selective sample;
(2) adequate reference standard;
(3) verification bias;
(5) same reference standard;
(6) blinded interpretation of index test and reference standard; and
(7) explanation of withdrawals.

Strategy for data synthesis

Indices of diagnostic performance will be extracted or derived from data presented in each primary study for each clinical assessment procedure or combination of clinical assessment procedures. Diagnostic two-by-two tables will be generated, from which sensitivities and specificities for each index test with 95% confidence intervals will be calculated and presented in forest plots. In addition, a Receiver Operating Characteristic (ROC) plot of sensitivity versus 1-specificity will be used to display the data.
For pooling of results of sensitivity and specificity we will use a bivariate analysis, which preserves the two-dimensional nature of the data, accounts for between-study variability by using a random effects approach, and allows for the possibility of a negative correlation that may exist between sensitivity and specificity across studies. If studies show sufficient clinical homogeneity (e.g. same index test, similar definition of ACL injury) we will present summary estimates with a 95% confidence ellipse (i.e. a bivariate confidence interval) in ROC space. We will use pooled estimates of sensitivity and specificity to calculate the positive and negative likelihood ratios for each index test.
All meta-analyses will be carried out using STATA and SAS statistical software.

Analysis of subgroups or subsets

We will investigate the potential influence of differences in the type of reference standard (e.g. arthroscopy, MRI), study setting (primary/secondary/tertiary care), and study design (positive/negative/unclear scores on domains of the QUADAS-2 checklist) through sensitivity analyses.

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Australia

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Review_Ongoing

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Subject index terms
Anterior Cruciate Ligament; Humans; Knee Injuries; Medical History Taking; Physical Examination; Predictive Value of Tests

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

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions
25 April 2012

List of Special Names

Adolescence: The phase of life between 10 and 19 years of age, inclusive.

Adolescent: A person between 10 and 19 years of age, inclusive.

Child: A person 19 years old or younger.

Puberty: (as per the U.S. National Library of Medicine) A period in the human life in which the development of the hypothalamic-pituitary-gonadal system takes place and reaches full maturity. The onset of synchronized endocrine events in puberty lead to the capacity for reproduction, development of secondary sex characteristics, and other changes seen in adolescent development.

School-aged child: A child who is old enough to go to school.

Young adult: A person between 19 and 24 years of age, inclusive.

Young people: People between 10 and 24 years of age, inclusive.