School of Physiotherapy and Exercise Science

Cross Sectional and Longitudinal Investigation
of Pain Sensitivity in Early Adulthood

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council Statement on Ethical Conduct in Human Research (2007) – updated in March 2014. Ethics approval for the Raine Study Cohort 22 year follow up was obtained for a period of five years from the University of Western Australia (UWA) on February 20, 2012 (ref: RA/4/1/5202). Reciprocal approval was obtained from Curtin University Human Research Ethics Committee (ref: HR23/2013).

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Abstract

There is substantial burden of persistent musculoskeletal pain worldwide with low back pain, neck pain and 'other musculoskeletal disorders' being leading global causes of disability in 2017. There is substantial burden on society in terms of cost of management and of productivity loss, decreased quality of life and functional restriction. Many people with persistent musculoskeletal pain do not receive appropriate care. In this context, there are calls for musculoskeletal conditions to be recognised as a global public health priority.

The global burden of persistent musculoskeletal pain reflects many interacting factors including a lack of adherence to contemporary evidence-based practice and a predominantly biomedical approach to management. An overwhelming number of studies reveal a poor correlation between pathology measured by imaging techniques and severity of pain for those with persistent musculoskeletal pain. Conversely, there is substantial literature describing changes in nociceptive processing of various noxious and non-noxious stimuli, typically reflecting heightened pain sensitivity, in clinical populations with persistent or recurrent musculoskeletal pain disorders. Collectively, these studies suggest that factors other than pathology are important in the experience of pain and highlight that changes in nociceptive processing are an important mechanism in persistent clinical pain disorders.

Currently there is a lack of large population-based studies to assist our understanding of pain mechanisms specifically in young adults. This requires better pain sensitivity reference values for people without pain and a better understanding of the relationship between pain sensitivity and the pain experience. This relationship may be especially important for young adults who are at a critical life transition stage where trajectories of musculoskeletal pain become established and can continue into later adulthood.

Therefore, the aims of this doctoral thesis are:

1. to establish the intrarater and interrater reliability of pressure pain threshold testing using five research assistants from the Raine Study and pain-free non-Raine Study young adults;

2. using cross-sectional Gen 2-22 year data from the Raine Study cohort (referring to the follow-up of Gen2 (the Raine study participants recruited into the study at birth) participants when they were 22 years old);

   i) to establish reference data from healthy, pain free individuals

   ii) to characterise the relationship between pain sensitivity and pain disorders, which will include correlates of demographics, physical measures, sleep patterns, psychological status, physical activity and health related quality of life;

   iii) to explore the relationship between pain sensitivity and physical activity or sedentary behaviour considering the presence of single-site and multisite pain;

3. A longitudinal study investigating whether a range of early life stressors are associated with pain sensitivity at young adulthood (22 years of age) in Gen2 participants of the Raine Study.

Study 1: Pressure pain threshold testing reliability in young adults

The first study of this thesis aimed to assess the intrarater and interrater reliability, including systematic bias, of pressure pain threshold testing by the same method (handheld algometer) and at the same body sites (lumbar spine, tibialis anterior, neck and dorsal wrist) as in the used for the Gen2-22 year follow-up of the Raine Study.

Methods: Five research assistants (RAs) each tested 20 pain free subjects at the wrist, leg, cervical and lumbar spine. Intraclass correlation coefficient (ICC), standard error of measurement (SEM) and systematic bias were calculated.

Results: Both intrarater reliability (ICC = 0.81–0.99) and interrater reliability (ICC = 0.92–0.95) were excellent and intrarater SEM ranged from 79 to 100 kPa. There was systematic bias detected at three sites with no single rater tending to consistently rate higher or lower than others across all sites.

Conclusions: The excellent ICCs observed in this study support the utility of using multiple RAs in large cohort studies using standardised protocols, with the caveat that an absence of any confounding of study estimates by rater is checked, due to systematic rater bias identified in this study.

Study 2: Pressure and cold pain threshold reference values in young adults

The second study in this thesis aimed to (i) provide sex-specific reference values of pressure and cold pain thresholds in young pain-free adults; (ii) examine the association of potential correlates of pain sensitivity with pain threshold values.

Methods: This study investigated sex specific pressure and cold pain threshold estimates for young pain free adults aged 21–24 years. A cross-sectional design was utilised using participants (n = 617) from The Raine Study Gen2-22 year follow-up. The association of body site, sex, height, weight, smoking, health related quality of life, psychological measures and activity with pain threshold values was examined. Pressure pain threshold (lumbar spine, tibialis anterior, neck and dorsal wrist) and cold pain threshold (dorsal wrist) were assessed using standardised quantitative sensory testing protocols.

Results: Reference values for pressure pain threshold (four body sites) stratified by sex and site, and cold pain threshold (dorsal wrist) stratified by sex are provided. Statistically significant, independent correlates of increased pressure pain sensitivity measures were site (neck, dorsal wrist), sex (female), higher waist-hip ratio and poorer mental health. Statistically significant, independent correlates of increased cold pain sensitivity measures were sex (female), poorer mental health and smoking.

Conclusions: These data provide the most comprehensive and robust sex specific reference values for pressure pain threshold specific to four body sites and cold pain threshold at the dorsal wrist for young adults aged 21–24 years. Establishing normative values in this young age group is important given that the transition from adolescence to adulthood is a critical temporal period during which trajectories for persistent pain can be established.

Study 3: Pressure and cold pain sensitivity associations with musculoskeletal pain experience in young adults

The third study in this thesis aimed to investigate the cross-sectional associations between musculoskeletal pain experience and measures of pressure and cold pain sensitivity.

Methods: A cross-sectional design was utilised using participants (n = 917) from The Raine Study at the 22-year follow-up, who were eligible for analysis if they provided data pertaining to musculoskeletal pain status at the Raine Study Gen2-22 year follow-up and had data for at least 1 valid pain sensitivity test. Standardized protocols were used to assess pressure pain threshold (4 sites: lumbar spine, tibialis anterior, upper trapezius, and wrist) and cold pain threshold (wrist). Four pain experience groups ("No pain" [n =562, 61.3%], "Low" [n =84, 9.2%], "Medium" [n =147, 16.0%], "High" [n=124, 13.5%]) were determined by latent class analysis using parameters of pain chronicity, frequency, intensity, and number of pain areas. Variables considered as confounders included sex, age, ethnicity, waist-hip ratio, psychological symptoms, sleep quality, physical activity, sedentary behavior, smoking, and income.

Results: There were no associations between pain experience and pressure pain sensitivity after adjusting for confounders. The "Medium" and "High" pain experience groups demonstrated heightened cold pain sensitivity compared with the "No pain" group (p=0.023), adjusted for sex and smoking.

Conclusions: This study provides the most extensive investigation of the relationship between musculoskeletal pain experience and pressure and cold pain sensitivity in young adults. Heightened cold pain sensitivity in those classified as "Medium" and "High" pain experience may suggest altered nociceptive processing and has implications for clinical management.

Study 4: Pressure and cold pain sensitivity associations with physical activity or sedentary behaviour in young adults

The fourth study of this thesis aimed to explore the relationships of physical activity (PA) and sedentary behaviour (SB) with pain sensitivity measured by pressure pain thresholds and cold pain thresholds, considering the presence of single-site and multisite pain and controlling for potential confounders.

Methods: A cross-sectional design was utilised using participants from The Raine Study (n= 714) provided data at age 22-years. PA and SB were measured via accelerometry over a 7-day period. Pain sensitivity was measured using pressure pain threshold (4 sites) and cold pain threshold (wrist). Participants were grouped by number of pain areas into "No pain areas" (n = 438), "Single-site pain" (n = 113) and "Multisite pain" (n = 163) groups. The association of PA and SB variables with pain sensitivity was tested separately within each pain group by multivariable regression, adjusting for potential confounders.

Results: For those with "Single-site pain", higher levels (>13 min/day) of moderate-vigorous PA in ≥10 min bouts was associated with more pressure pain sensitivity (p = 0.035). Those with "Multisite pain" displayed increased cold pain sensitivity with greater amounts of vigorous PA (p = 0.011). Those with "No pain areas" displayed increased cold pain sensitivity with decreasing breaks from sedentary time (p = 0.046).

Conclusions: This study was a comprehensive investigation of a community-based sample of young adults with "No pain areas", "Single-site pain" and "Multisite pain" and suggests some associations of measures of PA and SB with pain sensitivity.

Study 5: The association of pressure and cold pain sensitivity and pain experience in young adults with early life stressors

The aim of the fifth and final study of this thesis was to evaluate a range of early life stressors (prenatal and first three years) for association with pressure and cold pain sensitivity in Raine participants at age 22, and to investigate if pain experience at age 22 moderated any associations.

Methods: A longitudinal design was utilised using participants (n=1065) from the Raine Study to assess the association between a wide range of early life stressors, including antenatally, and pressure and cold pain sensitivity at young adulthood. For the cold pain threshold analysis, participants were classified into two groups (low sensitivity, n=727 and high sensitivity, n=323) according to their cold pain sensitivity. Pressure pain threshold was analysed as a continuous variable. Additionally, the interaction between early life stress, pain sensitivity and pain experience (based on selected items from the Örebro Musculoskeletal Pain Questionnaire) at age 22 years was examined. Analysis was done using both a complete case and multiple imputation approach, adjusting for contemporaneous 22 year correlates, with comparable results in each model.

Results: More problematic behaviour at age two was associated with less pressure pain sensitivity at 22 years (13.7kPa, 95%CI: 1.0 to 27.0, p=0.037), with no interaction between problematic behaviour and pain experience at 22 years. For those reporting a moderate/high pain experience at 22 years, poor family functioning increased the odds ratio for high cold pain sensitivity (3.0, 95%CI: 1.6 to 5.6), but for those reporting no/low pain experience it did not (OR:1.2, 95%CI: 0.8 to 1.8).

Conclusions: This study provides the most comprehensive investigation of the relationship between early life stress and pressure and cold pain sensitivity in young adults supporting early life as a critical period of development influencing future nociceptive processing.

Overall conclusions:

The body of work presented in this doctoral thesis significantly contributes to the understanding of pressure and cold pain sensitivity in young adults. The work confirmed that: (1) the measurement of pressure pain threshold is reliable in large cohort studies; (2) the reference data reported is a valuable resource important for the understanding of 'normal' pain sensitivity in young adults; (3) measurement of cold pain sensitivity may help the understanding of pain mechanisms in young adults with a "medium" or "high" pain experience; and (4) early life stress related to poor family functioning and problematic behaviour is associated with future pain sensitivity. Together the findings of this thesis support the value of pain sensitivity measurement in musculoskeletal pain disorders to assist the understanding of pain mechanisms underlying the pain experience. Improving the understanding of the association of pain sensitivity with musculoskeletal pain disorders and how pain sensitivity develops offers opportunities to address and reduce the global impact of pain.

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List of Abbreviations

BMI	body mass index
CEO	common extensor origin
CI	confidence interval
CNS	central nervous system
COMT	catecholamine-0-methyltransferase
CPM	conditioned pain modulation
CPM	counts per minute
CPT	cold pain threshold
ECRB	extensor carpi radialis brevis
EIH	exercise induced hypoalgesia
ELS	early life stress
fMRI	functional magnetic resonance imaging
FMS	fibromyalgia syndrome
GCH1	GTP cyclohydrolase
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
IASP	The International Association for the Study of Pain
IPAQ	International Physical Activity Questionnaire
LBP	low back pain
LPL	lipoprotein lipase
MVC	maximum voluntary contraction
MVPA	moderate-vigorous physical activity
NDI	Neck Disability Index
NRS	numeric rating scale
OA	osteoarthritis
OPRM1	μ-opioid receptor gene
OR	odds ratio
PA	physical activity
PNS	peripheral nervous system
PPT	pressure pain threshold
PRTEE	Patient-rated Tennis Elbow Evaluation

PTSD	post-traumatic stress disorder
QST	quantitative sensory testing
RH	radial head
SB	sedentary behaviour
SMD	standardized mean difference
TS	temporal summation
WAD	whiplash associated disorder
WHR	waist-hip ratio
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
YLDs	Years Lived with Disability

List of Publications Arising from this Thesis

Chapter 3

Waller R, Straker L, O'Sullivan P, Sterling M, Smith A. "Reliability of pressure pain threshold testing in healthy pain free young adults. "Scandinavian Journal of Pain 2015, 9: 38-41

Chapter 4

Waller R, Smith A, O'Sullivan P, Slater H, Sterling M, McVeigh, Straker L,. "Pressure and cold pain threshold reference values in a large, young adult, pain-free population." Scandinavian Journal of Pain 2016, 13: 114-122

Chapter 5

Waller R, Smith A, Sullivan P, Slater H, Sterling M, Straker L. "Associations between musculoskeletal pain experience and pressure and cold pain sensitivity: A community based cross-sectional study of young adults in the Raine Study." Clinical Journal of Pain 2019; 35: 56-64

Chapter 6

Waller R, Smith A, Slater H, O'Sullivan P, Beales D, McVeigh J, Straker L. "Associations of physical activity or sedentary behaviour with pain sensitivity in young adults of the Raine Study." Scandinavian Journal of Pain, 2019: in-press doi:10.1515/sjpain-2019-0038

Chapter 7

Waller R, Smith A, Sullivan P, Slater H, Sterling M, Straker L. "The association of early life stressors with pain sensitivity and pain experience at 22 years." Pain 2019: in-press, doi: 10.1097/j.pain.0000000000001704

Statement of Contributors

Candidate

The candidate, Robert Waller, was responsible for all aspects of the research presented in this thesis, including conception, design, data collection, data analysis, and original manuscript writing and subsequent editing for the publications entitled:

Waller R, Straker L, O'Sullivan P, Sterling M, Smith A. "Reliability of pressure pain threshold testing in healthy pain free young adults." Scandinavian Journal of Pain 2015, 9: 38-41

Waller R, Smith A, O'Sullivan P, Slater H, Sterling M, McVeigh, Straker L. "Pressure and cold pain threshold reference values in a large, young adult, pain-free population." Scandinavian Journal of Pain 2016, 13: 114-122

Waller R, Smith A, Sullivan P, Slater H, Sterling M, Straker L. "Associations between musculoskeletal pain experience and pressure and cold pain sensitivity: A community based cross-sectional study of young adults in the Raine Study." Clinical Journal of Pain 2019; 35: 56-64

Waller R, Smith A, Slater H, O'Sullivan P, Beales D,McVeigh J, Straker L. "Associations of physical activity or sedentary behaviour with pain sensitivity in young adults of the Raine Study." Scandinavian Journal of Pain, 2019: in-press doi:10.1515/sjpain-2019-0038

Waller R, Smith A, Sullivan P, Slater H, Sterling M, Straker L. "The association of early life stressors with pain sensitivity and pain experience at 22 years." Pain 2019: in-press, doi: 10.1097/j.pain.0000000000001704

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Conferences, Co-authored Publications and Prizes

Invited conference speaker

- 2018 Australian Physiotherapy Association WA Symposium. presentation "What's associated with pain sensitivity in young adults?"

Oral presentations

- 2013 Raine Study Annual Scientific Meeting. "Reliability of pressure pain threshold testing in healthy pain free young adults"
- 2016 Australian Pain Society 36th Annual Scientific Meeting, Perth. 13-16 March. "Reference values for pressure and cold pain thresholds in a large cohort of young pain free adults."
- 2017 Raine Study Annual Scientific Meeting. "Associations between musculoskeletal pain and pressure and cold pain sensitivity: A community based cross-sectional study of young adults in the Raine Study"
- 2017 Australian Pain Society 36th Annual Scientific Meeting, Adelaide. 9-12 April. "Are physical activity and sedentary behaviour associated with pain senstivity in community-based young adults?." Waller R, Smith A, O'Sullivan P, Slater H, Sterling M, Beales D, J McVeigh, Straker L.
- 2019 Australian Pain Society 39th Annual Scientific Meeting, Gold Coast 7-10 April. "Associations of early life factors with pressure and cold pain sensitivity at 22 years in a population based cohort"

Co-authored publications

Baker B, Kessler K, Kaiser B, Waller R, Ingle M, Brambilla S, Viscardi E, Richards K, O'Sullivan P, Goucke R, Smith A, Yao F, Lin I. "Non-traumatic musculoskeletal pain in Western Australian hospital emergency departments: A clinical audit of the prevalence, management practices and evidence-to-practice gaps." Emergency Medicine Australasia. 2019; 0(0)

Lin I, Rankin A, Wiles L, Waller R, Goucke R, Nagree Y, Gibberd M, Straker L, Maher CG, O'Sullivan PB. Infographic. "11 best practice recommendations for care in musculoskeletal pain." Br J Sports Med. 2019:bjsports-2019-100821

Lin I, Wiles L, Waller R, Goucke R, Nagree Y, Gibberd M, Straker L, Maher C, O'Sullivan P. "What does best practice care for musculoskeletal pain look like? Eleven consistent recommendations from high-quality clinical practice guidelines: systematic review." British Journal of Sports Medicine 2019 in press

Rebbeck T, Moloney N, Azoory R, Hübscher M, Waller R, Gibbons R, Beales D. "Are measures of pain sensitivity associated with pain and disability at 12-month follow up in chronic neck pain?" Musculoskeletal Care 2018; 16(4):415-424

Lin, Ivan. Wiles, Lousie. Waller, Robert. Goucke, Roger. Nagree, Yusuf. Gibberd, Michael. Straker, Leon. Maher, Chris. O'Sullivan, Peter. "The overall quality of clinical practice guidelines for musculoskeletal pain is poor: a systematic review." British Journal of Sports Medicine 2018 52: 337-343

Rebbeck T, Moloney N, Azoory R, Hübscher M, Waller R, Gibbons R, Beales D. "Clinical ratings of pain sensitivity correlate with quantitative measures in people with chronic neck pain and healthy controls: Cross-sectional study." Physical Therapy 2015, 95 (11): 1536-1546

O'Sullivan, R. Waller, R et all. Sensory Characteristics of Chronic Non-specific Low Back Pain: A Subgroup Investigation, Manual Therapy 2014; 19: 311-318

Prizes

- 2017 Raine Study Annual Scientific Meeting: Raine Medical Research foundation prize for Best Oral Presentation by an early career researcher and student

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Chapter 1　　Introduction

1.1　　The problem of pain

There is a substantial burden of persistent musculoskeletal pain worldwide with low back pain, neck pain and 'other musculoskeletal disorders' representing three of the top 11 global causes of disability in 2017 (James, Abate et al. 2018). Persistent pain refers to ongoing or chronic pain and is defined as any pain lasting more than 12 weeks (Treede, Rief et al. 2015). In Australia, there is a substantial burden on society, including children and adolescents, with one in five suffering from persistent pain in their lifetime (Blyth, March et al. 2001). Additionally, the national cost of musculoskeletal conditions of back pain, osteoarthritis (OA), osteoporosis and rheumatoid arthritis in Australia was conservatively estimated at $55.1 billion in 2012, with costs predicted to escalate over the coming decade (Arthritis and Osteoporosis 2013). For those with persistent musculoskeletal pain, decreased quality of life and functional restriction, including a reduced capacity for employment, is common (Hoftun, Romundstad et al. 2011, Hay, Abajobir et al. 2017). Comorbidity is also common with, 2.4 million people in Australia with persistent pain reported to have a co-existing physical and mental health condition (Blyth and Huckel Schneider 2018). Additionally, up to 80% of people with persistent pain are not receiving management that could improve their quality of life (National Pain Strategy 2011). In the context of this rapidly escalating burden, there are calls for musculoskeletal conditions to be recognised as a global public health priority (Woolf, Erwin et al. 2012, Briggs, Cross et al. 2016, Rice, Smith et al. 2016, Buchbinder, van Tulder et al. 2018).

Musculoskeletal pain is a common reason for seeking medical care (Hasselström, Liu-Palmgren et al. 2002). A continuous national cross-sectional survey of Australian general practice using a subset of 197 general practitioners and 5,793 patients reported the prevalence of chronic pain was 19.2% (95% CI: 17.4-21.0, n=1,113) (Henderson, Harrison et al. 2013). The two most common causal conditions reported were OA (48.1%) and back pain (29.4%). The money spent medically managing pain has increased substantially without an improvement in disability and pain outcomes (Deyo, Mirza et al. 2009, 2010, Artus, van der Windt et al. 2010, Institute of Medicine Committee on Advancing Pain Research and Education 2011, James, Abate et al. 2018, 2019). It is proposed this failure reflects many interacting factors including a lack of adherence to

contemporary evidence-based practice guidelines (Williams, Maher et al. 2010, O' Sullivan and Lin 2014, Allen, Choong et al. 2016, Briggs, Chan et al. 2016, Dziedzic, French et al. 2016, Lin, Wiles et al. 2018) and the overuse of the biomedical approach to management of musculoskeletal pain disorders (Deyo, Mirza et al. 2009, Foster, Anema et al. 2018, O'Sullivan, Caneiro et al. 2018). Additional challenges are that for many pain treatments known to produce benefits, only some work for some of the people, some of the time (Cruz-Almeida and Fillingim 2014). A large number of studies reveal a poor correlation between pathology measured by imaging techniques and severity of pain for peripheral (Frost, Andersen et al. 1999, Moosmayer, Smith et al. 2009, Arendt-Nielsen, Nie et al. 2010, Girish, Lobo et al. 2011) and spinal (Hancock, Maher et al. 2007, Wassenaar, van Rijn et al. 2012, Brinjikji, Luetmer et al. 2015) musculoskeletal pain disorders. This makes sense in the context of many changes in structure seen on imaging also being highly prevalent in people without pain. For example, changes in structure seen on imaging have been shown to be highly prevalent in people without pain in the neck (Nakashima, Yukawa et al. 2015), lumbar spine (Brinjikji, Luetmer et al. 2015), shoulder (Girish, Lobo et al. 2011), hip (Frank, Harris et al. 2015) and knee (Culvenor, Øiestad et al. 2018). Many studies show a weak relationship between pain and severity of joint disease in OA, and pathology on imaging is as common in asymptomatic controls as those with symptoms (Dieppe and Lohmander 2005, Arendt-Nielsen 2017), highlighting that aspects other than structure are important to the experience of pain. Further highlighting this discordance, in an Australian study of 1172 patients presenting to primary care with acute low back pain, only 11 cases had a specific pathological cause for their pain (Henschke, Maher Christopher et al. 2009).

Conversely, there is substantial literature describing changes in nociceptive processing of various noxious and non-noxious stimuli, typically reflecting heightened pain sensitivity, in clinical populations with persistent or recurrent musculoskeletal pain disorders including knee OA (Suokas, Walsh et al. 2012), low back pain (O'Sullivan, Waller et al. 2014, Rabey, Slater et al. 2015), whiplash associated disorders (Van Oosterwijck, Nijs et al. 2013), elbow pain (Slater, Arendt-Nielsen et al. 2005) and widespread pain conditions such as fibromyalgia (Gracely, Petzke et al. 2002, Desmeules, Cedraschi et al. 2003, Gerhardt, Eich et al. 2016, King, Jastrowski Mano et al. 2017). Additionally, increased pressure and cold pain sensitivity have been identified in people with multisite musculoskeletal pain disorders when compared to people with localised musculoskeletal

pain disorders (Blumenstiel, Gerhardt et al. 2011, Gerhardt, Eich et al. 2016). Collectively, these studies suggest that factors other than pathology are important in the experience of pain and highlight that changes in nociceptive processing are an important mechanism in persistent clinical pain states (Johnston, Jimmieson et al. 2008, Chien and Sterling 2010, Arendt-Nielsen and Graven-Nielsen 2011, Woolf 2011).

At the clinical level, there are related evidence-to-practice gaps in the current health system that in part reflect a focus on the application of a biomedical model to the assessment and management of musculoskeletal pain (Speerin, Slater et al. 2014, O'Sullivan, Caneiro et al. 2018). There are calls to apply contemporary evidence to the practice of musculoskeletal pain care, to support the delivery of 'right care', reducing low value care and increasing high value care (Speerin, Slater et al. 2014, Briggs, Chan et al. 2016, Slater and Briggs 2017). This is particularly relevant in young adults (18-35 years) as they transition to adulthood. In the 20-24 age group, four in five with chronic pain reported interference with daily activities due to pain, the highest proportion of any age group (Blyth, March et al. 2001). Global burden of disease data from 2017 comparing Years Lived with Disability (YLDs) across 5-year age ranges shows a rapid increase in YLDs from 'low back and neck pain', and 'other musculoskeletal conditions' from late adolescence into young adulthood (Figure 1.1). At this critical life transition stage trajectories of musculoskeletal pain can become established and can continue into later adulthood, with potentially negative impact on quality of life and lost productivity (Leboeuf-Yde and Kyvik 1998, Hoftun, Romundstad et al. 2011, O'Sullivan, Beales et al. 2012, Slater, Jordan et al. 2016, Coenen, Smith et al. 2018).

Against this background of clinical challenges, there is a need to better understand the complex mechanisms and factors that can contribute to the development and persistence of musculoskeletal pain in young people. A better understanding of such mechanisms and factors can help to characterise specific clinical phenotypes (including identifying biological, psychological and social factors, and interactions) with the aim of informing more targeted patient-centred approaches to care and helping to reduce the global burden of musculoskeletal pain.
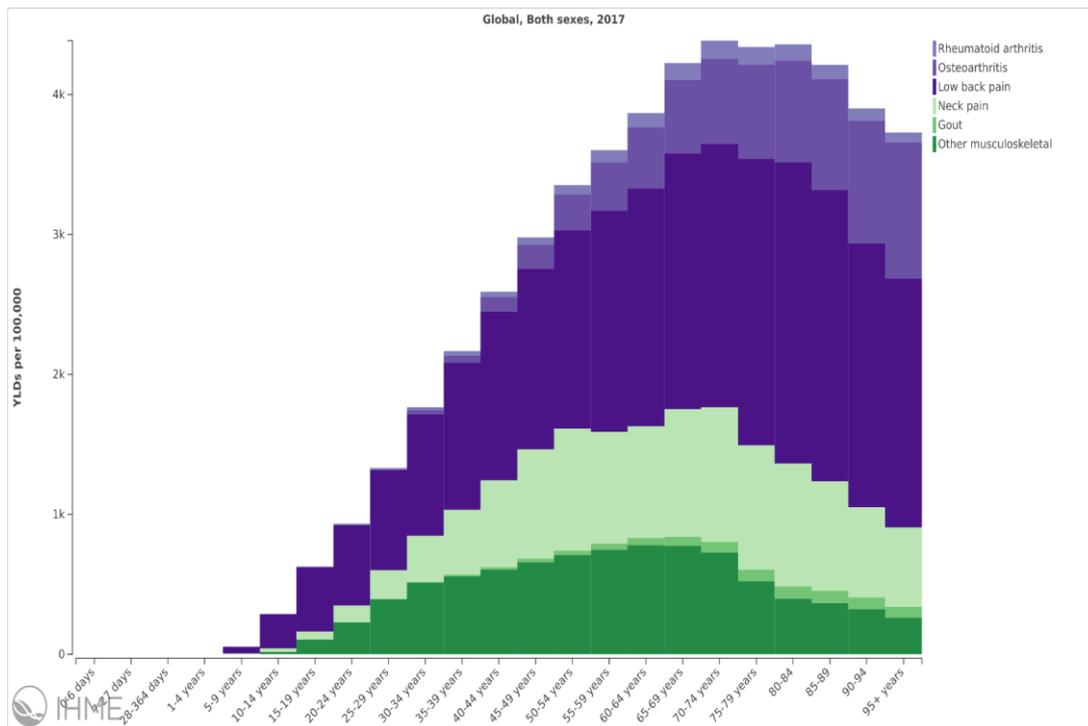
Figure 1.1 Years Lived with Disability (YLDs) globally for musculoskeletal conditions 2017 by age group.

Accessed https://vizhub.healthdata.org/gbd-compare/ 11th September 2019.

1.2 Pain definition

The International Association for the Study of Pain (IASP) currently defines pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' (IASP 2019). In 2016, an update to the definition of pain was proposed as follows: 'pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components' (Williams and Craig 2016). This proposed definitional change may better reflect the multidimensional factors that influences a pain experience and explain individual and temporal variation. On August 7, 2019, the IASP's proposed new definition of pain was released for comment as follows: 'An aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury' (Pain 2019). The proposed accompanying notes section acknowledges the subjective experience of pain 'that is influenced to varying degrees by biological, psychological, and social factors'. The pain experience is completely unique to the individual and is 'sculpted by a mosaic of factors unique to the person, which renders the pain experience completely individualized' (Fillingim 2017).

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The IASP recommends three clinical pain descriptors to characterise clinical pain (IASP 2019). The first is pain that acts as an early warning, protective system so if we touch something potentially damaging, such as heat or cold, we have an immediate withdrawal response. This is called nociceptive pain and demands immediate attention as it signals impending or actual tissue damage (Woolf 2010, IASP 2019). Nociceptive pain is defined as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors" (IASP 2019). A nociceptor is "a high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli" (IASP 2019). Nociception refers to the "neural process of encoding noxious stimuli" (IASP 2019). "Nociception includes mechanisms by which noxious stimuli are detected, encoded, transferred, and unconsciously treated by the nervous system" (Yezierski and Hansson 2018). The physiological process of nociception should be distinguished from the subjective experience of pain (Yezierski and Hansson 2018). Pain is now widely considered an emergent conscious experience (Moseley and Butler 2015) highlighting the difference between pain and nociception. Nociception can be present without pain and pain can occur without nociception.

The second type of pain is neuropathic pain, described as "pain caused by a lesion or disease of the somatosensory nervous system" (IASP 2012). Neuropathic pain is used as a clinical description of pain and is not a diagnosis, however it requires a demonstrable lesion or a disease that satisfies established neurological diagnostic criteria (IASP 2019). It is appropriate to use the term lesion when diagnostic investigations (e.g. imaging, biopsies, lab tests) reveal an abnormality or following obvious trauma (IASP 2019). If the underlying cause of the lesion is known (e.g. stroke, diabetes mellitus, genetic abnormality) then it is appropriate to use the term disease (IASP 2019).

The third type of pain is nociplastic pain and is recommended by the IASP to describe persistent pain arising from "altered nociception, despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors, or evidence for disease or lesion of the somatosensory system causing the pain" (IASP 2019). This type of pain typically persists past normal healing time lacking the acute warning function of nociception (Treede, Rief et al. 2015). The term nociplastic pain was accepted by the IASP in November 2017 as another mechanistic descriptor for the clinical classification of chronic pain that persists beyond three months following a

recommendation from the Presidential Terminology Task Force (Kosek, Cohen et al. 2016). Nociplastic pain can be present in conditions such as chronic low back pain, fibromyalgia syndrome (FMS) or irritable bowel syndrome where there is no identifiable tissue damage or inflammation (Clauw 2014). Nociplastic pain as a descriptor is particularly relevant to the introduction of the new International Classification of Diseases (ICD) of the World Health Organization category 'chronic pain'. The ICD-11 category for chronic pain is divided into 7 groups that represent the most common clinically relevant disorders: (1) chronic primary pain, (2) chronic cancer pain, (3) chronic post-traumatic and post-surgical pain, (4) chronic neuropathic pain, (5) chronic headache and orofacial pain, (6) chronic visceral pain, and (7) chronic musculoskeletal pain (Treede, Rief et al. 2015). Nociplastic pain can be considered within the context of chronic primary pain described as 'pain in one or more anatomic regions that persists or recurs for longer than three months and is associated with significant emotional distress or significant functional disability and that cannot be better explained by another chronic pain condition' (Treede, Rief et al. 2015). Clinically, a pain experience may be a variable mix of nociceptive, neuropathic and nociplastic pain types.

Pain as a human experience, therefore represents complex neurobiological and behavioural responses to actual or perceived threat of tissue damage to the body or the ability to function. In this context, a recent description of pain by Moseley and Butler is relevant: "any credible evidence that the body is in danger and protective behaviour would be helpful, will increase the likelihood and intensity of pain and any credible evidence that the body is safe will decrease the likelihood of pain" (Moseley and Butler 2015). This explanation may help to make sense where tissue damage and/or pathology is not well aligned to pain. A pain experience is always multidimensional and a biopsychosocial model is now widely accepted as a more contemporary understanding of pain (Gatchel, Peng et al. 2007), although not yet universally adopted (Pincus, Kent et al. 2013, Foster, Anema et al. 2018). There is enormous variation in people's response to their pain experience which is influenced by different combinations of pathoanatomical changes, lifestyle, psychological status, life experiences and genetics (Nielsen, Stubhaug et al. 2008, Denk, McMahon et al. 2014). Within the same condition, pain could be rated across the entire pain scale from no pain to the worst pain imaginable (Nielsen, Staud et al. 2009). These large individual differences in the pain experience remain even in experimental pain that is precisely controlled (Chen, Dworkin et al. 1989). Current

evidence also suggests that some of the variation in the pain experience is a reflection in part of individual differences in pain sensitivity to the application of noxious stimuli (Nielsen, Staud et al. 2009).

1.3   Pain sensitivity

Whereas pain is measured subjectively and refers to an unpleasant sensory and emotional experience, pain sensitivity refers to the responsiveness of the somatosensory nervous system. Pain sensitivity can be measured by quantitative sensory testing (QST) which involves application of a measurable stimulus and a subjective interpretation of the stimulus by the person tested (Backonja, Attal et al. 2013). Pain sensitivity can be influenced by any part of the nociceptive processing apparatus, from the peripheral nociceptive receptors to nociceptive regulating mechanisms in the brainstem and spinal cord, through to the influences of environmental factors, genetics, functioning of the endocrine and immune systems, emotions and cognitive processing of nociception in the brain cortex (Nielsen, Stubhaug et al. 2008, Nielsen, Staud et al. 2009, Denk, McMahon et al. 2014, Mayer, Knight et al. 2014). Increased pain sensitivity can also be an indication of central nervous system (CNS) hypersensitivity, where there is amplification of nociceptive signals due to increased nociceptive sensitisation, excitation and, or, reduced nociceptive inhibition (Woolf 2011). This can include neuro-immune and neuro-endocrine system interactions contributing to augmented nociceptive processing (Mayer, Knight et al. 2014, Simons, Elman et al. 2014). Such CNS hypersensitivity is discussed as an important mechanism in the generation and maintenance of many persistent clinical pain states (Johnston, Jimmieson et al. 2008, Chien and Sterling 2010, Woolf 2011, Clauw 2014).

Pain sensitivity is emerging as an important factor to help understand the mechanisms contributing to the pain experience and for predicting future pain and disability. Heightened pain sensitivity has utility in assessing for risk for persistence or outcome prediction after musculoskeletal injury (Sterling, Hendrikz et al. 2011, Goldsmith, Wright et al. 2012) or following a range of surgical procedures (Abrishami, Chan et al. 2011, Sangesland, Støren et al. 2017), however this has only been explored for a small range of musculoskeletal conditions and surgeries. While there is also inconsistency between results mainly reflecting the quality of studies, current evidence

shows promise and warrants further high quality studies using pain sensitivity to assist prediction of treatment outcomes (Werner Mads, Jensen Elisabeth et al. 2017). There is also some limited evidence suggesting heightened pain sensitivity may increase the risk for the onset of a new pain disorder (Diatchenko, Slade et al. 2005, Greenspan, Slade et al. 2013). While the knowledge of pain sensitivity is expanding, currently there is a lack of normative data to assist interpretation of pain conditions (Backonja, Attal et al. 2013) and gaps in the understanding of how QST can be utilised in a mechanism-based classification of pain (Cruz-Almeida 2014). Additionally, recent calls highlight a need for pain sensitivity data to be categorised as age-specific (normative and clinical) and here, data is currently lacking in young adults (Skovbjerg, Jørgensen et al. 2017). Current knowledge is also restricted by the number of small studies conducted, introducing a high risk of bias and limiting generalisability to the wider population. Current data can be improved by using larger population-based cohorts to mitigate some of the limitations imposed by smaller studies (Jacobsen, Eggen et al. 2012). The Western Australian Pregnancy Cohort (Raine) Study (http://www.rainestudy.org.au) is a large, rich data set and provides opportunity to explore gaps in current understanding of pain sensitivity, including providing age-specific normative data and the ability to explore correlates of pain sensitivity in young adults while adjusting associations for multiple, potential confounders including sex (Bartley and Fillingim 2013, Tham, Palermo et al. 2016), psychological factors (Klauenberg, Maier et al. 2008, Slater, Paananen et al. 2015), sleep (Sivertsen, Lallukka et al. 2015), physical activity and sedentary behaviour (Naugle, Fillingim et al. 2012), anthropometrics (Neziri, Scaramozzino et al. 2011), ethnicity (Ostrom, Bair et al.) and socioeconomic status (Ostrom, Bair et al.).

Additionally, as Raine Study participants had a variety of multidimensional data collected during gestation and at multiple time points up to young adulthood, an investigation of early life influences of pain sensitivity is possible. This is important as pain sensitivity may be modifiable at a young age by environmental influences such as early life stress, family functioning and socioeconomics (Mustard, Kalcevich et al. 2005, Denk, McMahon et al. 2014, Stickley, Koyanagi et al. 2015, Burke, Finn et al. 2017, Denk and McMahon 2017). An improved knowledge of early life influences of pain sensitivity may help inform more personalised and targeted interventions that potentially lower the future risk for development of persistent musculoskeletal pain. A better understanding of the association between the pain experience and pain sensitivity may potentially be

informative as to some of the underlying mechanisms and factors that drive pain. This may contribute to more targeted, mechanism-based interventions that reflect person-centred, multidimensional and modifiable contributions to musculoskeletal pain (Nielsen, Staud et al. 2009, Arendt-Nielsen and Graven-Nielsen 2011, Backonja, Attal et al. 2013, Denk, McMahon et al. 2014).

Chapter 2   Literature Review

2.1   Measurement of pain sensitivity

QST, the most common way of quantifying pain sensitivity, uses experimental stimuli in a psychophysical test; that is a measurable stimulus with a subjective interpretation and response by the person tested (Backonja and Lauria 2010). QST assesses the responsiveness of the somatosensory system in its entirety, from peripheral receptors that transmit via the peripheral nerves, spinal cord and brainstem to the brain (Backonja, Attal et al. 2013, Cruz-Almeida and Fillingim 2014). If undamaged peripheral tissues are tested, then an increase in pain sensitivity is more likely to be the result of CNS mechanisms, also referred to as augmented central nociceptive processing (Neziri, Scaramozzino et al. 2011). Testing peripheral tissues engages different nerve endings and types of nerve fibres that innervate the skin, muscle and viscera (Cruz-Almeida and Fillingim 2014).

Stimulation modalities used to assess musculoskeletal pain conditions typically include thermal (heat, cold) and mechanical (tactile, pressure, vibration) stimuli (Backonja, Attal et al. 2013, Cruz-Almeida and Fillingim 2014). Thermal stimuli, commonly applied to the skin surface, can test superficial tissue (skin) (Cruz-Almeida and Fillingim 2014). In contrast, mechanical stimuli, commonly applied via pressure, can test both superficial (skin) and deep tissue (muscle and viscera) (Cruz-Almeida and Fillingim 2014).

Pain sensitivity is influenced by many factors (Cruz-Almeida and Fillingim 2014) including sex (Bartley and Fillingim 2013, Tham, Palermo et al. 2016), psychological factors (Klauenberg, Maier et al. 2008, Slater, Paananen et al. 2015), sleep (Sivertsen, Lallukka et al. 2015), physical activity and sedentary behaviour (Naugle, Fillingim et al. 2012), anthropometrics (Neziri, Scaramozzino et al. 2011), ethnicity (Ostrom, Bair et al.) and socioeconomic status (Ostrom, Bair et al.). Females are consistently more pain sensitive than males (Racine, Tousignant-Laflamme et al. 2012, Racine, Tousignant-Laflamme et al. 2012, Bartley and Fillingim 2013, Tham, Palermo et al. 2016). Sensitivity typically alters across the lifespan with normative data showing thermal and pressure sensitivity decreasing with age (Magerl, Krumova et al. 2010, Neziri, Scaramozzino et al. 2011, Skovbjerg, Jørgensen et al. 2017).

There is an absence of a 'gold standard' to test pain sensitivity (Backonja, Attal et al. 2013), with a large variation in QST methods used to quantify pain sensitivity, without evidence that one method is more valid than another. The most contemporary definitive reference standards resulted from a meeting of the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain who formulated recommendations for conducting QST (Backonja, Attal et al. 2013). QST can involve a battery of tests, originally developed to test for somatosensory changes associated with neuropathic pain but which have been applied more widely to various pain disorders including for those of a visceral and musculoskeletal origin (Backonja, Attal et al. 2013).

For musculoskeletal pain conditions, pain sensitivity measurement using QST can be static or dynamic measure either stimuli detection thresholds, pain thresholds or pain tolerance (Backonja, Attal et al. 2013, Cruz-Almeida and Fillingim 2014). More complex dynamic testing can measure nociceptive facilitatory function via temporal summation of pain or nociceptive inhibitory function via conditioned pain modulation (CPM) paradigms (Pud, Granovsky et al. 2009, Backonja, Attal et al. 2013). Temporal summation (TS) testing uses repetitive brief noxious stimuli of the same intensity with a defined inter-stimulus interval. Participants rate the intensity of the pain experienced after each stimulus (Rolke, Mageri et al. 2006) and increased perception of pain to repetitive stimuli indicates increased pain sensitivity due to heightened central nociceptive processing (Latremoliere and Woolf 2009). CPM measures the inhibition of provoked pain in a local area by a second noxious stimulus applied elsewhere in the body (Latremoliere and Woolf 2009). Ineffective or attenuated inhibition indicates attenuated CNS nociceptive modulation (Latremoliere and Woolf 2009, Pud, Granovsky et al. 2009, Backonja, Attal et al. 2013). While dynamic QST can potentially provide additional insight into central nociceptive modulation, the testing process is more complex, requiring higher rater skill, and is more time consuming, making it less practical to use in large population studies.

Pain sensitivity in musculoskeletal conditions can be measured via static QST using mechanical and thermal pain thresholds that are quicker to use, making them more appropriate for cohort studies and requiring less training for raters to become competent compared with dynamic measures (Backonja, Attal et al. 2013). Pain thresholds can be measured applying various methodologies. The most common is the 'method of limits' which is quick and easy to administer (Cruz-Almeida and Fillingim 2014). Pain threshold

testing using the 'method of limits' involves applying a stimulus that gradually increases in intensity, with the test stopped and the intensity recorded when the stimulus first becomes painful or uncomfortable (Rolke, Baron et al. 2006). Another static test is the 'method of levels' where stimulus of set intensity is applied, and the participant reports the pain response (Rolke, Mageri et al. 2006). The test is repeated with progressively increased or decreased intensity to establish the pain threshold, making this method more time-consuming (Cruz-Almeida and Fillingim 2014). There are calls to develop shorter protocols to improve the clinical utility of QST (Cruz-Almeida and Fillingim 2014). Static QST protocols using the 'method of limits', to measure mechanical and thermal pain thresholds have the potential to be applicable in the clinical setting. In pain disorders, pain threshold measurement using pressure or cold is a common, simple, reliable, quick and effective way to quantify pain sensitivity (Walton, MacDermid et al. 2011, Goldsmith, Wright et al. 2012, Cruz-Almeida and Fillingim 2014).

Pressure pain threshold (PPT) measurement has been used extensively to investigate musculoskeletal pain disorders (Slater, Arendt-Nielsen et al. 2005, Zhou, Fillingim et al. 2010, O'Neill, Kjær et al. 2011, Walton, MacDermid et al. 2011, Suokas, Walsh et al. 2012), as has cold pain threshold (CPT) measurement (Chien, Eliav et al. 2009, Borsbo, Liedberg et al. 2012). The psychophysical method of testing results in potential variations in outcome due to variation in procedures, protocols, equipment and the participant's level of attention or concentration (Cruz-Almeida and Fillingim 2014). The application of these tests requires rater training and the use of standardized protocols to minimise variations in outcome (Backonja, Attal et al. 2013).

The assessment of PPT is typically done via a handheld algometer and raters require training to acquire skill that allows reliable measurement of pressure pain thresholds (Walton, MacDermid et al. 2011). While reliability studies for PPT using algometry have been conducted, these have varied with respect to sites assessed, number of raters examined, reliability statistics reported and degree of standardisation of algometry (Tunks, McCain et al. 1995, Nussbaum and Downes 1998, Chesterton, Sim et al. 2007, Walton, MacDermid et al. 2011). The most comprehensive PPT reliability study to date reported excellent interrater reliability (Walton, MacDermid et al. 2011). Reliability studies for PPT are limited due to comparing reliability only between two raters, whereas larger cohort studies typically use multiple raters (Neziri, Scaramozzino et al. 2011). The

measurement of CPT does not involve manual skills and is therefore technically easier to test. Excellent inter-examiner and intra-subject reliability of CPT measurement has been demonstrated with reasonable levels of standard error of measurement (Wasner and Brock 2008, Geber, Klein et al. 2011).

For clarity, a decrease in a PPT measure is used to denote increased pressure pain sensitivity (i.e. perception of pressure as pain at a lower pressure or a reduced threshold) and an increase in a CPT measure is used to denote increased cold pain sensitivity (i.e. perception of cold as pain at a higher temperature or at a reduced threshold).

2.2 Biopsychosocial correlates of pain sensitivity

Pain sensitivity reflects an individual's processing of sensory information at many levels in the nervous system and a difficulty in understanding biopsychosocial correlates of pain sensitivity is that there are many potential influences. Whilst existing studies commonly consider sex and age as potential correlates of pressure and cold pain sensitivity (Jensen, Rasmussen et al. 1992, Torgén and Swerup 2002, Rolke, Baron et al. 2006, Magerl, Krumova et al. 2010), other potential influences on PPT and CPT have rarely been included for statistical analysis (Neziri, Scaramozzino et al. 2011) despite evidence that genetics, body composition, sleep, co-morbid illness, psychosocial status and past pain experiences are known correlates of pain sensitivity.

2.2.1 The association of sex with pain sensitivity

The association of sex with pain sensitivity has been widely examined. A systematic review retrieved 122 articles, published between 1998 and 2008, that examined sex difference in the perception of laboratory induced pain over a broad range of modalities (Racine, Tousignant-Laflamme et al. 2012). Pressure pain using an algometer was examined by 31 studies. Only 5 studies were reported to have sufficient statistical power, with all of them finding females had a lower PPT than males irrespective of body sites tested. Cold pain threshold was measured by 13 studies with only 23% of experiments finding females were more cold pain sensitive than males. The hypothesis of the systematic review was that females would be more cold pain sensitive than males and major reasons discussed for the lack of findings were the insufficient statistical power in the majority of studies and lack of control of potential confounders including age and

pain status. In an earlier meta-analysis of sex differences in experimentally induced pain there was a large to moderate effect size of sex on quantitative measurements of pain; PPT measurement had one of the largest differences in values between sexes, with females having increased pain sensitivity (Riley, Robinson et al. 1998).

In normative data studies that have included pain-free healthy participants or controlled for pain status, females are consistently reported to be more pain sensitive than males (Rolke, Baron et al. 2006, Magerl, Krumova et al. 2010, Neziri, Scaramozzino et al. 2011, Tham, Palermo et al. 2016, Skovbjerg, Jørgensen et al. 2017). Rolke et al (Rolke, Baron et al. 2006) reported higher pain sensitivity in pain-free females (n=110) when compared with pain-free males (n=70), with an effect size of approximately 0.3 for both for PPT and CPT. Magerl et al (Magerl, Krumova et al. 2010) reported significantly higher pressure pain sensitivity in pain-free females in young and middle aged adults but not older adults, however in all age groups females had significantly higher cold pain sensitivity. Neziri et al (Neziri, Scaramozzino et al. 2011) investigated pain-free participants (n=300) reporting that females were significantly more pressure and cold pain sensitive when compared to males. Tham et al (Tham, Palermo et al. 2016) used a population-based study to investigate pain sensitivity in adolescents (age range 15-19 years) with chronic pain (n=197) and without chronic pain (n=744). Pressure pain sensitivity was significantly lower in females than males (p<0.001) and females were more likely to withdraw the hand early on a cold-pressor task (p=0.015). Skovbjerg et al (Skovbjerg, Jørgensen et al. 2017) investigated pressure pain sensitivity in the adult Danish general population (n=2,199, age range 18-70 years, 53% female). In a multiple linear regression analysis, adjusting for age, body mass index (BMI), stress, education level and self-reported pain, females were significantly more pressure pain sensitive than males at both the upper trapezius muscle (p<0.001) and tibialis anterior muscle (p<0.001).

Current knowledge investigating sex differences in pain sensitivity consistently show females are more pain sensitive to pressure and cold pain than males when studies are powered adequately.

2.2.2   The association of age with pain sensitivity

In additions to sex, age is recognised as an important correlate to consider when investigating pain sensitivity, with sensitivity generally decreasing with age. The most

informative data comes from studies using population-based participants. Interpretations of results can be limited by dichotomising or categorising participants into age groups with limited numbers or wide age ranges.

The first population-based studies were done by the German Research Network on Neuropathic Pain to establish age-matched reference values for QST (Rolke, Baron et al. 2006). Rolke et al (Rolke, Baron et al. 2006) found older subjects (≥ 40 years) were significantly less pain sensitive than younger subjects for both PPT and CPT ($p<0.01$). The ability to interpret the results are limited as there was a large age range of the participants (17-75 years, n=180) and the dichotomisation of the age groups resulted in very wide-ranging age groups. Magerl et al (Magerl, Krumova et al. 2010) using the same data as Rolke et al (Rolke, Baron et al. 2006) refining stratification for age and reported less pressure and cold pain sensitivity with increasing age. Using ANOVA, there was a significant sex and age interaction for PPT ($p<0.05$, $F_{4,348}=2.69$) and CPT ($p<0.05$, $F_{4,350}=2.49$). Males were less sensitive to pressure pain than females in young and middle-aged adults (20-50 years of age) but not in the older adults (50-70 ages of age). For females CPT dropped consistently with increasing age, while variation was lesser and less consistent in males. The study used a moving average analysis with an overall number of participants in each sex group of 90 resulting in small numbers in each of the five decadal groups (age range 20-70 years) analysed.

Other population-based studies have sampled a larger number of participants. Neziri et al (Neziri, Scaramozzino et al. 2011) using dichotomized age groups (20-49, n=150 and 50-80 years, n=150) reported a relationship between older age and less cold pain sensitivity ($p<0.001$). For PPT there was a significant interaction with sex and age ($P<0.001$) with women displaying higher pressure pain sensitivity than men in the younger age group with the influence of sex decreasing with increasing age. In an adult Danish population study (n=2,199, age range 18-70 years, 53% female), the effect of age on pressure pain sensitivity was compared across four age groups (18-39, 40-49, 50-59 and 60-70 years) (Skovbjerg, Jørgensen et al. 2017). In the linear regression analysis, the youngest age group (18-39 years) had higher pressure pain sensitivity at the tibialis anterior muscle ($p<0.001$) when compared with the age groups older than 40 years. At the upper trapezius muscle, the two younger age groups (18-39 and 40-49 years) had higher pressure pain sensitivity ($p≤0.02$) when compared with the older age groups (>50

years). Another population study (n=1,000, age 25-64 years) used the mean PPT of 14 cephalic muscle sites (separated into right and left) reporting higher pressure pain sensitivity was associated with younger age in females (ANOVA: right p=0.001, F=5.44; left p=0.008, F=4.02), but not in males (ANOVA: right p=0.129, F=1.89; left p=0.296, F=1.24) (Jensen, Rasmussen et al. 1992).

The association of age with pain sensitivity has also been reported in studies using pain populations or in pain-free populations using low participant numbers. Studies of pain sensitivity in people with Whiplash Associated Disorder (WAD) have found significant associations of decreased pressure and cold pain sensitivity with older age (n=141 and n=76 respectively) (Kasch, Stengaard-Pedersen et al. 2001, Sterling, Jull et al. 2005). However, other studies in both pain-free and pain populations have found no association with age (n=96, n=424 and n=45 respectively) (Sterling, Jull et al. 2003, Chiu, Silman et al. 2005, Walton, MacDermid et al. 2011). The variable findings are probably a reflection of relatively low participant numbers.

Current best practice recommendations are to adjust for age when investigating pain sensitivity (Backonja, Attal et al. 2013) and contemporary higher quality evidence suggests age is an important correlate of pain sensitivity.

2.2.3   The association of adiposity with pain sensitivity

There is some evidence of an association of adiposity with pain sensitivity with BMI being most commonly used to measure and adjust for adiposity in population-based studies (Neziri, Scaramozzino et al. 2011, Tham, Palermo et al. 2016, Skovbjerg, Jørgensen et al. 2017). Using a multivariable regression model, the large normative study of Neziri et al (Neziri, Scaramozzino et al. 2011) reported increased BMI was associated with lower cold pain sensitivity (p=0.010) but not altered pressure pain sensitivity. Tham et al (Tham, Palermo et al. 2016) adjusted for BMI in a multivariable analysis for predictors of PPT in adolescents, there was a significant association with PPT estimated to be higher (3.45kPa) at the shoulder for each increase in BMI of one (p=0.002) but not at the finger (p=0.69). In the adult Danish population study (n=2,199, age range 18-70 years, 53% female), a linear regression model showed no significant association for BMI and PPT at the tibialis anterior muscle (p>0.06) (Skovbjerg, Jørgensen et al. 2017). For PPT at the upper trapezius muscle, participants who were obese (BMI≥30 kg/m^2) and

overweight (BMI≥25 kg/m^2 and <30 kg/m^2) were less pressure pain sensitive than participants of normal weight (BMI<25 kg/m^2) (P<0.001). Other pain threshold normative data has not accounted for the variance in pain sensitivity potentially attributable to adiposity (Rolke, Baron et al. 2006, Magerl, Krumova et al. 2010).

A study in people with WAD also found an association between PPT and BMI, but did not specify the direction of this relationship (Kasch, Stengaard-Pedersen et al. 2001). An investigation of people with sleep disorders reported in a multivariate mixed effects model increased BMI was a significant correlate of PPT at the forearm (p=0.02) but not at a masseter test site (p=0.07) (Smith, Wickwire et al. 2009). Current research on the direction of the relationship between pain sensitivity and adiposity is inconclusive, however the significant associations of adiposity with pain sensitivity suggest adiposity should be considered as a potential correlate of pain sensitivity.

2.2.4   The association of sleep with pain sensitivity

Increased sleep disruption is a common comorbidity for those with chronic pain (Sivertsen, Krokstad et al. 2009) and several studies have investigated the association between pain sensitivity and sleep (Sivertsen, Lallukka et al. 2015, Lautenbacher 2018, Simpson, Scott-Sutherland et al. 2018). The relationship of pain with sleep is considered bidirectional, sleep deprivation can lead to an increase in pain and pain sensitivity, and pain can lead to sleep deprivation (Okifuji and Hare 2011).

While sleep deprivation is known to alter pain modulatory mechanisms (Heffner, France et al. 2011, Karmann, Kundermann et al. 2014), the dosage and timing of sleep interruptions required to affect the pain system is not known (Lautenbacher 2018). Using participants (n=17) in good health, Simpson et al (Simpson, Scott-Sutherland et al. 2018) investigated the effect on pain sensitivity of a restricted sleep model with limited recovery (3 weeks, 5 nights of 4 hours of sleep per night followed by 2 nights of 8 hours of sleep per night) compared to a control protocol (3 weeks, 8 hours of sleep per night). The restricted sleep period was associated with decreased habituation and increased temporal summation to cold pain (p<0.05) and the changes did not completely resolve during recovery sleep (8 hours of sleep per night). Kundermann (Kundermann, Spernal et al. 2004) found increased cold pain sensitivity following sleep deprivation over one

night, but the study was limited by the sample size (n=24) and potentially the short duration of sleep disturbance.

Other investigations have measured sleep disturbance by self-report. The largest investigation (n=10,412, 54% female) used the cross-sectional Tromsø population based study to investigate whether insomnia was associated with pain sensitivity measured using the cold-pressor test (Sivertsen, Lallukka et al. 2015). Participants classified with an insomnia disorder (females=14%, males=6.5%) were more likely to withdraw their hand before the end of the cold-pressor test ($p<0.001$, 42.4% vs 30.9%). Participants reporting an increased frequency of insomnia (>once/week) had a higher hazard ratio (HR) for lower cold-pressor pain tolerance ($p<0.001$, HR=1.52). Another population-based study (n=424) reported increased pressure pain sensitivity (using a mean of 8 test sites, measured bilaterally) was significantly associated with increased sleep disturbance (measured by the sleep problem scale) after adjustment for pain status, age, examiner and sex (Chiu, Silman et al. 2005). High sleep disturbance was associated with increased pressure pain sensitivity (n=173; odds ratio (OR): 1.6, 95% confidence interval (CI): 1.0-2.6).

The association of sleep with pain sensitivity has also been investigated in clinical populations. In female participants with rheumatoid arthritis (n=59), poorer sleep measured across six sleep dimensions including quantity and quality, was significantly associated with increased pressure pain sensitivity at three body sites (thumbnail: $p<0.0005$, wrist: $p<0.0001$, trapezius muscle: $p<0.0008$) (Lee, Chibnik et al. 2009). Sleep insomnia but not sleep apnoea, both categorized by polysomnography and questionnaire (Pittsburgh Sleep Quality Index), was significantly associated with increased pressure pain sensitivity (masseter: $p<0.05$, forearm: $p<0.05$) in participants (n=53) with jaw pain (Smith, Wickwire et al. 2009). Other small studies (n<10) investigating the influence of sleep deprivation on PPT have found no significant affect, however these studies had very low statistical power (Arima, Svensson et al. 2001, Onen, Alloui et al. 2001).

The associations reported above suggest a relationship of increased pressure and cold pain sensitivity with sleep disturbance. However, while the dosage and threshold of sleep disturbance required to induce changes in nociceptive processing is unknown, sleep disturbance should be considered as a potential correlate of pain sensitivity.

2.2.5   The association of psychological factors with pain sensitivity

Psychological factors are known to be predictive of outcome in pain disorders (Jarvik, Hollingworth et al. 2005, Gupta, Silman et al. 2007) and are typically better predictors of future disability than biomedical factors for people with musculoskeletal pain (Campbell and Edwards 2009, Walton, Pretty et al. 2009). However, the relationship between pain sensitivity and psychological aspects, typically fear, anxiety, depression, stress, catastrophizing and post-traumatic stress are variable and sometimes contradictory.

Some population-based studies of pain sensitivity have adjusted for psychological factors with mixed results. Neziri et al (Neziri, Scaramozzino et al. 2011) using normative data (n=300) reported neither PPT or CPT were associated with psychological measures of depression, anxiety and catastrophizing. A multivariable analysis of predictors of pain sensitivity using a population-based study of adolescents (n=941, age range 15-19 years) reported a significant association of higher psychological distress with lower pressure pain threshold at the finger (p=0.008, β(SE)=-34.25(12.86)) and shoulder (p=0.016, β(SE)=-22.60(9.37)) after adjustment for pain status, sex, age and BMI (Tham, Palermo et al. 2016). Another population-based study (n=424) investigated the association of pressure pain sensitivity (using a mean of multiple test sites) with psychological factors of depression and anxiety (measured by the hospital and anxiety depression scales) (Chiu, Silman et al. 2005). A high depression score was associated with increased pressure pain sensitivity (n=162; OR 1.7, 95%CI 1.1-2.6) after adjustment for pain status, age, examiner and sex. A study using people for the adult Danish general population (n=2,199, age range 18-70 years, 53% female) investigated the association of perceived stress (measured by the Perceived Stress Scale which assesses thoughts and feelings during the previous month and the degree to which situations in a person's life are appraised as stressful) with pressure pain sensitivity (Skovbjerg, Jørgensen et al. 2017). There was a significant association between perceived stress and increased pressure pain sensitivity measured at the upper trapezius muscle (p=0.02, β=0.998, 95%CI=0.996-0.999), but not at the tibialis anterior muscle (p=0.72, β=0.999, 95%CI=0.998-1.01) after adjusting for sex, age, self-reported pain and medication use.

A large (n=294) chronic low back pain (LBP) investigation profiled subgroups derived from cluster analysis on a wide range of characteristics including depression, anxiety, stress, fear avoidance and catastrophizing (Rabey, Slater et al. 2015). Multimodal QST

measures were used to explore the existence of subgroups in a cohort without serious spinal pathology, or recent and/or extensive history of spinal surgery. Latent class analysis was used to derive three clusters that were characterised by different sensory characteristics. Cluster 1 (31.9%) was characterised by higher pressure and temperature pain sensitivity, cluster 2 (52.0%) was characterised by higher pressure pain sensitivity and cluster 3 (16.0%) was characterised by lower pressure and temperature pain sensitivity. Depression scores for cluster 1 and 2 were higher than for cluster 3, however the clinical significance of the finding is unclear as average depression scores for all 3 subgroups were within normal range for the population.

When compared to healthy controls, people with major depression have been shown to have increased pressure pain sensitivity (Adler and Gattaz 1993, Lautenbacher, Spernal et al. 1999, Hennings, Schwarz et al. 2012) and increased cold pain sensitivity (Lautenbacher, Spernal et al. 1999, Klauenberg, Maier et al. 2008). However Klauenberg (Klauenberg, Maier et al. 2008) found no difference in PPT between depressed and non-depressed people, potentially a reflection of the low numbers of depressed people (n=25) investigated in the study.

A small study investigated the hypothesis that stress potentially contributes to already heightened nociceptive processing (Cathcart, Petkov et al. 2008). Cephalic and hand PPT and CPT were measured in participants with chronic tension-type headache (n=16) and a healthy control group without history of headache (n=15), before and after completion of a stressful mental task. There were no differences between groups on measures of age, sex, anxiety, depression or stress ratings pre- and post-stress task. Pressure and cold pain sensitivity increased in both groups post-task. A greater reduction in cephalic PPT was reported in the chronic headache group when compared with the control group (F=5.53, d.f.=1-29, p=0.03). While the study was limited by the small sample size, the results indicate stress may have a stronger association with pain sensitivity in those with a pain disorder.

The influence of psychological status on pain sensitivity is being increasingly investigated in WAD with varying results. Altered PPT has been reported to not be associated with depression, anxiety and somatization by some authors (Scott, Jull et al. 2005, Sterling, Hodkinson et al. 2008, Chien and Sterling 2010, Wallin, Liedberg et al. 2011). CPT has been reported to be not associated with anxiety (Scott, Jull et al. 2005) or

depression and somatization (Chien, Eliav et al. 2009, Chien and Sterling 2010). However some authors report increased cold pain sensitivity is associated with catastrophizing (Sterling, Hodkinson et al. 2008, Wallin and Raak 2008, Wallin, Liedberg et al. 2011), anxiety (Wallin, Liedberg et al. 2011) and post-traumatic stress (Sterling, Jull et al. 2006). Borsbo et al (Borsbo, Liedberg et al. 2012) identified a more severe WAD subgroup based on PPT and CPT values, and found significantly higher depression, anxiety, catastrophizing and fear avoidance is this subgroup. In other pain disorders, the influence of psychological variables on pain sensitivity is largely un-investigated. The conflicting results of these studies may reflect small subject numbers, the different types of subjects investigated and a variation in study methods.

The investigations above used a variety of measures to profile psychological factors. The associations reported suggest a relationship of increased pressure and cold pain sensitivity with an increase in psychological distress. However, while the association varies, psychological factors should be considered as a potential correlate of pain sensitivity.

2.2.6   The association of pain coping strategies with pain sensitivity

There are a variety of pain coping strategies reported for people with persistent pain (Keefe, Crisson et al. 1990, Reid, Gilbert et al. 1998) and pain coping strategies may modulate pain sensitivity. One study investigated pain sensitivity using a cold pressor test to assess pain threshold, tolerance and intensity, in adolescents (average age = 19 years, n=412) who were born at a gestational age less than 32 weeks or with a birth weight less than 1,500g (Van Ganzewinkel, Been et al. 2017). The adolescents pain coping strategy was measured at 19 years using the Pain Coping Questionnaire, which is a validated instrument that categorizes 39 coping items across 3 higher order factors (Reid, Gilbert et al. 1998). One higher order factor 'emotion focused avoidance' reflects a maladaptive coping style that comprises externalising and internalising, which represent a tendency to avoid regulating negative feelings while in pain. The two other higher order factors reflect adaptive coping styles. A multivariate Cox analyses (adjusting for sex, birth weight and early life necrotizing enterocolitis) showed 'emotion focused avoidance' was independently associated with higher cold pain sensitivity, reported by an increased risk of a lower pain threshold (hazard ratio (HR) 1.38, 95%CI 1.02-1.87, p=0.04) and lower pain tolerance (HR 1.72, 95%CI 1.21-2.42, p=0.002).

Another study investigated the association of self-efficacy (measured by the Self-efficacy Questionnaire) and pain coping strategies (measured by the Pain Coping Questionnaire) with cold-pressor pain tolerance in children aged between 7 and 14 years (n=53) (Piira, Taplin et al. 2002). There was a significant association between internalising and lower pain tolerance during the cold-pressor test (r_p=0.38, p<0.05). Cognitive distraction was associated with increased pain tolerance to the cold-pressor test. There were no significant associations between problem-focused coping strategies, positive self-statements and externalising with cold-pressor pain tolerance.

Goldberg (Goldberg, Weisenberg et al. 1997) used a cold-pressor task to measure pain tolerance in participants (n=50) before and after cognitive manipulation designed to influence perceived ability to cope with pain. There was increased cold pain tolerance when participants were told they had a better ability to deal with external stress and when participants were informed the results of the cold pressor test depended on you and not on outside factors. The results suggest pain sensitivity is dynamic and can be influenced by cognitive processes.

These studies, while limited in number, suggest the perceived ability to cope with pain can influence pain sensitivity and can be manipulated.

2.2.7 The association between physical activity, sedentary behaviour and pain sensitivity

Core management for persistent musculoskeletal pain disorders increasingly advocates physical activity (PA) (Daenen, Varkey et al. 2015, Sluka, Frey-Law et al. 2018). There is strong epidemiological evidence from large studies supporting independent associations between increasing PA and improved health including decreased cardiovascular mortality, decreased all-cause mortality, reduced cancer incidence, reduced risk of conditions related to psychological wellbeing, and less functional and cognitive decline (Paffenbarger , Hyde et al. 1986, Garber, Blissmer et al. 2011, Kokkinos 2012). In contrast, sedentary behaviour (SB), including time spent being sedentary and how it is accumulated, is associated with poorer health outcomes including all-cause mortality, cardiovascular disease, cancer incidence, psychological wellbeing and type 2 diabetes incidence (Ussher, Owen et al. 2007, Healy, Matthews et al. 2011, Dunstan, Howard et al. 2012, Biswas, Oh et al. 2015). While much is known about the effects of PA and SB on

health and the short-term effect of laboratory-based PA on pain sensitivity, there has been little investigation into the effects of PA and SB on pain sensitivity particularly in large population studies using best practice approaches. This is important because one of the mechanisms proposed for increased PA improving outcomes in musculoskeletal pain disorders, is the association of increased PA and lowered pain sensitivity. Additionally, there are calls to better understand the mechanisms leading to musculoskeletal pain disorders and the association of usual PA and pain sensitivity is important to consider as decreased pain sensitivity in healthy pain-free people might result in less vulnerability to a pain event (Werner, Mjöbo et al. 2010, Van Oosterwijck, Nijs et al. 2013).

2.2.7.1   Physical activity and sedentary behaviour: definition and measurement

To assist interpretation of the review of studies investigating the relationship between PA and pain sensitivity, this section provides an overview of the definitions and measurement of PA and SB. In addition, as there is a paper published for this thesis titled "Associations of physical activity or sedentary behaviour with pain sensitivity in young adults of the Raine Study", this section provides the reader with relevant background with respect to the definitions and measurement on PA and SB.

2.2.7.2   Definition of physical activity and sedentary behaviour

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure above resting levels (Caspersen, Powell et al. 1985, Garber, Blissmer et al. 2011). All people perform physical activity and it includes activities of daily living, work, active transportation and leisure. A metabolic equivalent, or MET, is a unit to describe energy expenditure during physical activity (Ainsworth, Haskell et al. 2000). One MET is the rate of energy expenditure during quiet sitting, light activities are defined as 1.1 to 2.9 METs, moderate intensity activities are defined as 3.0 to 5.9 METs and vigorous activities are defined as 6.0 or more METs (Ainsworth, Haskell et al. 2000). Light activity includes walking at a slow pace on level ground, sitting using the arms for art or craft or doing light household duties (Ainsworth, Haskell et al. 2000). Moderate activity includes moderate paced walking, golf, moderate to vigorous house work, mowing lawns and light jogging (Ainsworth, Haskell et al. 2000). Vigorous activity includes cycling, brisk walking, aerobics and running (Ainsworth, Haskell et al. 2000).

Sedentary behaviour is defined as activity during waking hours that involves little movement or PA with an energy expenditure below 1.5 METs (Garber, Blissmer et al. 2011). Examples are sitting, using a computer, reading, driving and video games. Objectively measured PA reveals a strong inverse relationship between SB and light activity, an increase in sedentary time typically displaces light activity and vice versa (Owen, Sparling et al. 2010, Dunstan, Howard et al. 2012).

2.2.7.2.1 Subjective methods for measuring physical activity and sedentary behaviour

Data collection in population studies often use subjective self-report methods to measure PA and SB over a specific time period and include the use of questionnaires, diaries, logs, surveys and interviews (Dishman, Washburn et al. 2001). The advantage of using subjective methods includes low cost, low participant burden and accessibility (Dishman, Washburn et al. 2001). Self-report questionnaires are widely used worldwide allowing for comparison of data internationally and nationally and are practical for very large population studies (Pedišić and Bauman 2015). The most commonly used subjective method for self-report of PA in pain sensitivity studies is the International Physical Activity Questionnaire (IPAQ) (Craig C. L, Marshall A. L et al. 2003). However, limitations have been recognised using self-report measures of PA and SB, which include recall bias of activity with moderate-vigorous activity typically over-estimated (Armstrong and Welsman 2006, Ottevaere, Huybrechts et al. 2011). In addition, self-report measurement is influenced by personality traits such as social desirability, and perceived cultural norms, that may result in significant over self-estimation of the duration of PA (Adams, Matthews et al. 2005). While people with obesity tend to significantly overestimate their vigorous activity levels (Warner, Wolin et al. 2012), there is some evidence that depression and high pain levels in participants with chronic LBP led to underestimation of their PA via an activity diary compared to their objectively measured activity level (Huijnen, Verbunt et al. 2010). The association between self-reported and objectively measured activity was moderate (β=0.39, P<0.01), and the discrepancy was significantly related to depression (Huijnen, Verbunt et al. 2010). Overall self-report questionnaires show limited reliability and validity when compared with objective methods, particularly for the measurement of light activity levels, the most common form of PA in the general population (Shephard 2003).

2.2.7.2.2 Objective methods for measuring physical activity and sedentary behaviour

As subjective methods have various known limitations, objective methods are being increasingly used to measure PA and SB, particularly as they remove recall and response bias (Prince, Adamo et al. 2008). Objective methods measure PA and potentially SB via quantitative methods using an instrument to detect body movement (e.g. pedometers and accelerometers) and/or physiological sensors to estimate energy expenditure (e.g. metabolic monitors).

Pedometers are most accurate at counting steps taken over a period of time, are readily available and cheap to purchase (Butte, Ekelund et al. 2012). The disadvantage is the inability to measure horizontal or upper body movement during non-ambulatory activity such as swimming, rowing and cycling. (Ainsworth, Cahalin et al. 2015) Also pedometers do not measure the duration and intensity of activity (Armstrong and Welsman 2006). Pedometers lack the ability to measure SB or the pattern of accumulation of PA and SB.

Metabolic monitors are designed to measure energy expenditure via multiple sensors to detect motion, heat flux, skin temperature and galvanic skin response (Hill, Dolmage et al. 2010). They have an advantage over accelerometers in that they can detect changes in energy expenditure associated with a change in load or efficiency imposed with a change in terrain or task demand that doesn't impact on body movement (Hill, Dolmage et al. 2010). The weakness of metabolic monitors is that they are expensive and require sophisticated data processing (Butte, Ekelund et al. 2012, Ainsworth, Cahalin et al. 2015). Despite the potential for better measurement of energy expenditure, previous studies investigating PA, SB and pain sensitivity have not used these monitors.

Accelerometers are sophisticated, portable, lightweight motion sensors that record multidirectional accelerations which are converted to a quantifiable digital signal referred to as 'counts' (Armstrong and Welsman 2006). Modern accelerometers are small, can be worn under clothes and do not interfere with habitual activity. A major advantage of using accelerometry is the detailed and relatively precise ability to measure the intensity, frequency and duration of PA and SB over days or weeks (Trost, McIver et al. 2005, Ainsworth, Cahalin et al. 2015). Activity levels are quantified using counts per minute (CPM). Common thresholds used can class each minute as sedentary (<100

counts per minute, cpm), light intensity (100-1951 cpm), moderate intensity (1952-5724 cpm) or vigorous intensity (>5724 cpm) (Freedson, Melanson et al. 1998, Matthews, Chen et al. 2008). The cut-off values for moderate-vigorous physical activity (MVPA) vary significantly between studies which can limit comparability, while using <100cpm as the cut-off for SB is more consistent (Pedišić and Bauman 2015).

Activity needs to be monitored for sufficient time to establish a person's usual PA level. Using participants (n=92) of average age 45 years, 3-4 days of activity monitoring using accelerometry was required to achieve valid assessment for patterns of time spent in moderate to vigorous activity and at least 7 days for valid assessment for patterns of sedentary time (Matthews, Ainsworth et al. 2002). Between 6% and 32% of participants in large scale population studies did not meet minimum wear criteria (Pedišić and Bauman 2015). Significant differences in a range of sociodemographic, lifestyle and health characteristics have been shown between participants that did, or did not, meet minimum accelerometer wear time restricting the generalisability of findings to a population (Pedišić and Bauman 2015).

There are some limitations to measuring PA and SB using accelerometry. Accelerometers are typically worn on the hip and do not pick up arm movement and are not worn while swimming (Prince, Adamo et al. 2008). Another limitation of accelerometers is they are insensitive to cycling, gradients while walking or running and moderate to vigorous activity that has limited torso activity such as yoga (Armstrong and Welsman 2006, Warner, Wolin et al. 2012). The cost of an accelerometer is relatively high (AUD225 plus accessories) and additional expensive software is required. Significant expertise is required to process and interpret the raw data collected.

2.2.7.2.3   *Correlation between subjective and objective measures of physical activity and sedentary behaviour*

Although correlations between subjective and objective measures of PA and SB are often significant, the strength of the association varies between studies and is generally low to moderate. A systematic review that included 74 studies comparing objective versus self-report measures for assessing PA in adults found the correlations were generally low to moderate but ranged from -0.71 to 0.96 indicating self-report measures can either over or under report PA when compared with objective measurement (Prince, Adamo et al.

2008). In a more recent large multi-site European study using adolescents (n=2018), the correlation between PA measured by the IPAQ and accelerometry was poor to fair, even when stratified by age and sex (r=0.08 to 0.26, p<0.01) (Ottevaere, Huybrechts et al. 2011). Another large study (n=980) reported low to moderate correlations (R = 0.07–0.36) between various PA parameters measured by the IPAQ and accelerometry.

2.2.7.2.4 *Summary of the measurement of physical activity and sedentary behaviour*

Although accelerometry has limitations including insensitivity to specific activities and lack of validity with insufficient wear time, for measuring PA and SB it remains the best compromise between affordability, validity and ease of use. In addition, accelerometry is the most widely used objective method for measuring PA and/or SB. Accelerometry has been the standard for pain sensitivity studies and large epidemiological studies due to the ability to accurately measure PA intensity and SB, including how it is accumulated (Trost, McIver et al. 2005, Ainsworth, Cahalin et al. 2015).

2.2.7.3 Investigation of the association between physical activity and pain sensitivity using laboratory intervention studies

There are many studies investigating the association of laboratory-based PA and short-term changes in pain sensitivity. The association has been investigated using 3 types of exercise: isometric, aerobic and dynamic. Aerobic exercise typically involves stationary cycling, treadmill running or step exercise. Isometric exercise uses static muscle contractions without joint movement, and dynamic exercise uses joint movement varying in intensity, duration and body location. Pain sensitivity is measured pre and post-exercise by various experimental methods including pain threshold and pain tolerance. Laboratory based studies have used healthy pain-free participants and/or participants with pain.

2.2.7.3.1 *Investigation of the association between physical activity and pain sensitivity using laboratory intervention studies and participants without pain*

In healthy pain-free participants, most laboratory-based PA has been reported to reduce pain sensitivity, however the effect is transient (Naugle, Fillingim et al. 2012).

When PA results in decreased pain sensitivity, it is commonly referred to as exercise induced hypoalgesia (EIH) (Koltyn 2000). The results of a meta-analytic review of 20 studies, showed all 3 types of laboratory based PA reduced experimental pain sensitivity in healthy pain-free participants, with the effect size varying from small to large depending on how pain sensitivity was measured and the type of exercise protocol used (Naugle, Fillingim et al. 2012). While the mix of males and females in the included studies was reported, the potential effect of sex on the results was not reported. Aerobic exercise varying from 50% to 85 % VO_{2max} and 10 to 30 minutes duration, reduced pain sensitivity across all methods of measurement with the largest effect size for pressure stimuli and the smallest for cold and heat stimuli (Naugle, Fillingim et al. 2012). The effects of laboratory based exercise studies on pain sensitivity typically lasted 15 minutes following the cessation of exercise and were trivial at 30 minutes (Naugle, Fillingim et al. 2012). However, the time period post-exercise pain sensitivity was measured is often not reported (Naugle, Fillingim et al. 2012) or only tested immediately post-exercise (Kodesh and Weissman-Fogel 2014). Based on the meta-analytic review, healthy participants undergoing a variety of laboratory-based exercise protocols demonstrate EIH, however the resulting decrease in pain sensitivity appears to be transient.

The duration or type of exercise that can influence EIH has been investigated. Some studies have demonstrated that as the intensity of continuous aerobic exercise increases, there is a greater effect in reducing pain sensitivity (Koltyn 2000, Koltyn 2002, Hoffman, Shepanski et al. 2004). Interval training is also effective at reducing pain sensitivity. High intensity interval training at 85% heart rate reserve (HRR) was compared with continuous aerobic exercise (70% HRR) and both demonstrated significant and similar reduction in pain sensitivity (Kodesh and Weissman-Fogel 2014). Isometric exercise reduced pain sensitivity in 11 studies across protocols varying in intensity, exercise location and duration, with moderate intensity contractions resulting in the largest reductions (Naugle, Fillingim et al. 2012). There are limited studies using dynamic exercise, however the pooled results of a meta-analysis suggest a moderate effect size measured for a limited period post-exercise (Naugle, Fillingim et al. 2012).

The short-term effect (i.e. more than transient) of laboratory-based exercise on EIH in pain-free participants has had limited investigation. In a lateral epicondylalgia study, healthy controls (n=20, female=10) underwent an eccentric exercise protocol to induce

delayed onset of muscle soreness in the wrist extensors (Slater, Arendt-Nielsen et al. 2005). Pressure pain sensitivity was assessed bilaterally at 3 lateral elbow sites (common extensor origin (CEO) at the lateral epicondyle, musculo-tendinous junction of extensor carpi radialis brevis ECRB) and the radial head (RH)) pre-exercise and post-exercise, and at 1-day and 7-days post-exercise. When compared pre-exercise and post-exercise, pressure pain sensitivity increased bilaterally at the CEO at 1 day ($F_{2,38}=6.6$, $p<0.003$) but there was no significant change at the ECRB muscle or RH test sites. When compared to 1-day post-exercise, there were no significant differences in PPT at 7-days post-exercise in either arm or test site. Another study investigated PPT response using healthy subjects (n=13, female=7), measured at 3 lateral elbow sites (as above), to 4 weekly bouts of low load exercise (repeated eccentric or concentric-eccentric wrist extension at 30% maximal wrist extension force) (Slater, Thériault et al. 2010). Both exercise protocols resulted in a significant decrease in pressure pain sensitivity at all test sites over the four-week exercise period (CEO: $F_{(5, 60)}=7.30$, $p<0.001$; ECRB: $F_{(5, 60)}=8.75$, $p<0.001$; CEO: $F_{(5, 60)}=3.61$, $p<0.001$). For both protocols, in comparison to pre-exercise testing at week 1, pressure pain sensitivity at week 5 was significantly decreased ($p<0.001$). The study is unique in investigating the effect of repeated laboratory sessions on pain sensitivity over time and demonstrates repeated low load exercise can induce changes in nociceptive processing over time. Interpretation of the study is limited by the small sample size.

2.2.7.3.2 Investigation of the association between physical activity and pain sensitivity using laboratory intervention studies and participants with pain

Findings on the association of laboratory-based PA and pain sensitivity in populations with pain are variable. In the following studies pain sensitivity testing was done pre and immediately, but no greater than 20 minutes, post exercise. Due to the common finding of augmented central nociceptive processing in people with Fibromyalgia Syndrome (FMS) (Clauw 2014), it is the most common pain disorder investigated in laboratory intervention studies. Older FMS criteria result in almost all patients being female and using the updated diagnostic criteria there is a female:male ratio of 2:1 (Clauw 2014). Consequently, most investigations have only used female participants. The pathogenesis of FMS, characterised by widespread pain and generalised tenderness, and chronic fatigue syndrome in which the majority of people experience

widespread musculoskeletal pain, is widely researched and discussed, with most discussion considering them a syndrome involving augmented central nociceptive processing (Gracely, Petzke et al. 2002, Meeus, Nijs et al. 2007, Staud 2009, Blumenstiel, Gerhardt et al. 2011, Clauw 2014).

Participants with FMS or chronic fatigue syndrome can exhibit increased pain sensitivity (measured by PPT and thermal pain ratings) during or directly after aerobic or isometric exercise (Whiteside, Hansen et al. 2004, Staud, Robinson et al. 2005, Lannersten and Kosek 2010, Meeus, Roussel et al. 2010). Meeus (Meeus, Roussel et al. 2010) investigated three groups of people with chronic fatigue syndrome suffering persistent pain (n=26), people with chronic low back pain who were sedentary (defined as having a sedentary job and performing <3 hours of moderate PA/week (n=21)) and sedentary healthy pain-free participants (n=31). Change in PPT, adjusted for age and sex, was examined in response to an incremental sub-maximal exercise bike protocol that ceased when the participant was fatigued or could no longer maintain a set pedalling frequency. People with chronic fatigue syndrome displayed increased pain sensitivity following exercise, whereas both the low back pain and pain-free groups displayed EIH following exercise (p<0.01). A small study of people (n=5) with chronic fatigue syndrome reported significantly increased pressure pain sensitivity following three, five-minute periods of high intensity treadmill exercise (where the incline started at 5° increased to 10° then 15° at each stage of the test), while the pressure pain sensitivity of a sedentary control group (n=5) was unaltered (Whiteside, Hansen et al. 2004). Staud et al (Staud, Robinson et al. 2005) reported sustained isometric exercise at 30% of maximum voluntary contraction (MVC) increased pain sensitivity (using PPT and thermal pain ratings) in females with FMS (n=12), with opposite effects of lowered thermal pain ratings and decreased pressure pain sensitivity in a female pain-free control group (n=11). Lannersten et al (Lannersten and Kosek 2010) investigated females with FMS (n=20), females with shoulder pain (n=20; pain intensity >30mm on a 100mm visual analogue scale and pain duration>6 months) and female pain-free controls (n=20), and examined change in PPT (bilateral infraspinatus muscle and mid-quadriceps muscle) during and 10 minutes after a sustained isometric contraction (shoulder external rotation and knee extension) at 20-25% of MVC. The females with FMS exhibited no change in pressure pain sensitivity at any test site with sustained isometric contraction. The females with shoulder pain exhibited no change in pressure pain sensitivity with the

shoulder contraction but decreased pressure pain sensitivity with the knee extension. The pain-free group exhibited decreased pressure pain sensitivity with sustained isometric contraction at both test sites. In summary, those with shoulder pain failed to demonstrate EIH at the shoulder indicating an inability to activate local nociceptive inhibition mechanisms, whereas the people with FMS failed to demonstrate EIH with either shoulder or knee muscle contraction, indicating a generalised inability to activate nociceptive inhibitory mechanisms.

The above findings of an association of increased pressure pain sensitivity or no EIH with PA in participants with FMS, are in contrast to three studies demonstrating an opposite effect of decreased pain sensitivity with PA. Newcomb et al (Newcomb, Koltyn et al. 2011) randomly assigned 21 females with FMS to a 20 minute aerobic cycle ergometry exercise session at an average intensity of either 45% or 62% age-adjusted heart-rate maximum, finding pressure pain tolerance measured at the right forefinger was improved at 15 minutes post-exercise. Kadetoff et al (Kadetoff and Kosek 2007) reported decreased pressure pain sensitivity ($p<0.001$), measured at the mid-thigh and lateral shoulder, in females with FMS (n=17) during and 15 minutes after low intensity isometric exercise sustained to exhaustion at an intensity of 10% MVC. Staud et al (Staud, Robinson et al. 2010) measured pressure pain sensitivity (upper trapezius, tibialis anterior and hand) in females with FMS (n=34) and a pain-free control group (n=36) before and after two brief (5 minute) periods of strenuous cycle ergometer exercise. Results were only reported for the upper trapezius test site, a simple contrast showed less pressure pain sensitivity for both groups from prior to the first exercise period to following the second exercise period ($F_{(1,69)}=7.2$, $p=0.009$).

People with FMS and chronic fatigue syndrome demonstrate a variable effect of laboratory-based PA on pain sensitivity, with most increasing pain sensitivity in the short term, but under certain conditions there is a short-term decrease in pain sensitivity. The studies predominantly used female subjects, limiting interpretation to males with FMS. The mixed results potentially reflect relatively small participant numbers and variable protocols.

There are limited laboratory-based studies that did not include participants with either FMS or chronic fatigue syndrome. Cook et al (Cook, Stegner et al. 2010) investigated the effect of 30 minutes of cycle ergometry at 70% of maximal oxygen

uptake on pain sensitivity in male gulf war veterans classified either with widespread chronic musculoskeletal pain (n=11) or as healthy pain-free controls (n=16). Following exercise, the participants with pain rated heat-pain stimuli as more intense than the control group ($F_{6, 20}$=5.90, p<0.01), but there was no change in heat pain threshold or PPT (p>0.05). Van Oosterwijck et al (Van Oosterwijck, Nijs et al. 2012) investigated change in PPT (measured at the hand, upper calf muscle and lumbar spine) following a 15 minute submaximal cycle ergometer stress test with an increasing workload until a maximum heart rate of 80% of the age-predicted maximum heart rate, in female participants with chronic WAD (n=22) and sedentary healthy pain-free controls (n=22). The change in PPT from pre-exercise to immediately post-exercise was significantly different between the WAD and control group (hand p=0.044, back p=0.021, calf p=0.029). Following the exercise test, at all test sites, pressure pain sensitivity increased in the participants with chronic WAD compared with a decrease in pressure pain sensitivity in the healthy controls. The experiment was repeated using a self-paced and physiologically limited exercise test (heart rate not exceeding 80% of maximum). There were no significant differences between groups found for heart rate, workload, lactate levels or time cycled (p>0.05). In the control group, pressure pain sensitivity (all sites) decreased post-exercise and in the WAD group pressure pain sensitivity increased at the hand and lumbar spine. There were significant group differences in PPT at the hand (p=0.028) and back (p=0.004). Interestingly, daily activity level, measured via accelerometry during a baseline period prior to the exercise test, was not significantly different between the two groups. The difference in results in the two studies potentially reflect the different conditions studied, the use of sex-specific samples and the small size and thus low power of the studies.

The short-term effect (i.e. more than transient) of laboratory-based exercise on EIH in patients with persistent lateral epicondylalgia (>3 months duration and only unilateral symptoms, n=20, female=10) and pain-free controls (n=20, female=10) was investigated (Slater, Arendt-Nielsen et al. 2005). Participants underwent an eccentric exercise protocol to induce delayed onset of muscle soreness in the wrist extensors. Pressure pain sensitivity was assessed bilaterally at 3 lateral elbow sites (CEO, ECRB, RH) pre-exercise and post-exercise, and at 1-day and 7-days post-exercise. The patient group demonstrated significantly increased pressure pain sensitivity bilaterally at the CEO when compared to the pain-free control group ($F_{1, 38}$=4.7, P<0.04). When compared with pre-exercise and post-exercise test points, there was no significant change in PPT in the

patient group at any test site (healthy control findings are reported in the previous section). The findings suggest altered central nociceptive processing in the patient group, specifically ineffective EIH. More sufficiently powered studies are required that test the temporal association of pain sensitivity and exercise, particularly protocols incorporating more than one exercise session that aim at normalising pain sensitivity in patient populations.

2.2.7.4 Investigation of the association between physical activity and pain sensitivity using field intervention studies

While laboratory exercise studies have measured transient changes (< 1 week) in pain sensitivity in response to predominantly single exercise sessions, evaluation of the effect of short to medium term PA interventions on pain sensitivity allows an examination of how pain sensitivity might change over a longer period in response to repeated exercise. Field intervention studies have evaluated how short to medium term changes in PA alter pain sensitivity over the time frame of the intervention. However, there are few studies that have investigated changes in the pain sensitivity after an exercise intervention.

Hennings et al (Hennings, Schwarz et al. 2012) investigated the change in PPT (4 bilateral sites: middle deltoid, thumbnail, fibula, upper trapezius) in response to a week of at least 30 minutes of moderate PA per day and also a week of reduced PA, in participants with either major depression (n=38, female=22), persistent and medically unexplained bodily symptoms (n=26, female=20) and in healthy participants (n=47, female=31). Accelerometry was used to confirm there were appropriate PA levels for the active and passive week. There was decreased pressure pain sensitivity following the active week compared with baseline values (mean difference=0.19, p<0.05). There were no differential effects of activity variation between group and time ($F_{4,88}$=0.18, p>0.10).

Nielsen et al (Nielsen, Andersen et al. 2010) investigated the effect of physical training on PPT (upper trapezius muscle, middle of the tibialis anterior muscle) in actively employed female office workers (n=42) who had chronic (pain >30days in the past year) and frequent (>once/week) pain in the area of the trapezius muscle. There was a pain-free control group (n=20). Participants with pain were randomly divided into 3 groups doing either specific shoulder-neck strength training (n=18), aerobic fitness training via a

cycle ergometer (n=16) or no physical training but receiving general health advice (n=9). After 10 weeks, the pressure pain sensitivity decreased at the tibialis anterior in both the strength training (275kPa to 392kPa, $p<0.001$) and aerobic training group (311kPa to 386kPa, $p<0.01$), but not in the no physical training group. Pressure pain sensitivity was decreased at the trapezius muscle in the strength training group only (267kPa to 343kPa, $p<0.05$), suggesting a localised PNS and CNS effect of the strength training on pain sensitivity. The decreased pressure pain sensitivity of the aerobic training group at only one test site suggests an intervention may need to specifically target the painful body site when there is a localised musculoskeletal pain disorder present.

Waling et al (Waling, Sundelin et al. 2000) also studied female office workers with pain in the area of the trapezius muscle (n=126). Participants were randomly divided into 4 equally sized groups receiving either neck and shoulder strength training, neck and shoulder endurance training, coordination training through body awareness (based on Tai Chi) or no training. Exercise interventions were performed three times per week for 10 weeks. Pressure pain threshold was measured bilaterally over six trigger points in the trapezius muscle. On average, pressure pain sensitivity improvement at individual test sites in the strength and endurance group ranged between 3 and 75kPa. The co-ordination group demonstrated improved pressure pain sensitivity at 5 sites with values ranging between 16 and 47KPa, one site worsened by -9kPa. The control group had a range of pressure pain sensitivity changes ranging between -18 to 20kPa. While there was a trend of decreased pressure pain sensitivity in the intervention groups, only three out of 18 measures (6 measures per intervention group) demonstrated significant change when compared with the control group. There were no significant differences between the intervention groups indicating that training can reduce local pressure pain sensitivity and the type of training may not be important, or the interventions were not specific enough and more individually, targeted functional exercise considering cognitive function should be considered (Vibe Fersum, O'Sullivan et al. 2013, O'Sullivan, Dankaerts et al. 2015).

While some of the results demonstrating a sustained improvement in pain sensitivity from a short to medium term increase in PA show promise, compared to the immediate and brief changes observed in laboratory exercise studies, there is a need for more research in this area. Current studies are limited by low power and varying PPT protocols.

2.2.7.5 Investigation of the association between physical activity and pain sensitivity using observational studies

While laboratory and field intervention studies are important in demonstrating PA can affect pain sensitivity in the immediate and short to medium term respectively, the association between regular or usual PA in community settings with pain sensitivity is also important. This is because monitoring PA over time reflects habitual activity behaviour and can provide better insight into the longer-term associations between habitual PA and pain sensitivity. Non-interventional population cohort studies are appropriate for evaluation of these associations, particularly when adjusting for potential confounders of pain sensitivity (Gierthmuhlen, Enax-Krumova et al. 2015).

The association of PA and pain sensitivity in healthy pain-free people in observational studies has been largely assessed using subjective methods to measure PA. A systematic review and meta-analysis using 15 studies (Tesarz, Schuster et al. 2012) compared pain sensitivity in athletes (studies were included when people were participating in competitions or training ≥ 3 hours per week) and healthy controls (defined as PA < 3 hour per week with no active participations in organised sport). Twelve included studies assessed pain tolerance and 9 studies assessed pain threshold. All the pain tolerance studies demonstrated athletes possessed higher pain tolerance compared with normally active controls (pooled data effect size calculated as Hedges' g=0.87, 95%CI 0.53 to 1.21; p<0.001). Five studies showed athletes had significantly higher pain thresholds (method of measurements not reported) and 4 studies showed no significant difference, however the pooled data showed athletes had significantly higher pain thresholds than controls (Hedges' g=0.69, 95%CI 0.16 to 1.21; p=0.01). The results were strongly influenced by sex, with female athletes having significantly higher pain thresholds compared to normally active female controls, whereas there were no significant differences for males. A limitation of the meta-analysis is the high heterogeneity of pain tolerance and threshold measurement methods, different subgroups of athletes included, issues of quality of the studies included and lack of consideration in the meta-analysis of correlates such as psychological factors.

Naugle et al (Naugle and Riley 2014) using healthy participants (n=48) investigated the association of PA, measured via the IPAQ, and pain sensitivity while controlling for age, sex and psychological variables. There was no association found between PA levels

and noxious heat or cold stimuli. However, a greater level of total and vigorous PA predicted reduced pain facilitatory function (measured by temporal summation) and enhanced pain inhibitory function (measured by conditioned pain modulation) ($p<0.05$).

Another study (Andrzejewski, Kassolik et al. 2010) used a brief non-validated self-report questionnaire with people who were physically active, to allocate students (n=38, mean age=22years) and older participants aged 50-75 years (n=38, mean age=65years), into moderate or vigorous activity level groups. Students in the vigorous activity group demonstrated significantly less pressure pain sensitivity than students in the moderate activity group ($p<0.05$), whereas there was no significant association between activity level and pain sensitivity in the older participants. There was no control for confounding variables such as sex. In the older group, not controlling for pain experience may have influenced results.

In conclusion, observational studies in pain-free participants measuring PA via self-report questionnaires, suggest an association with increased vigorous activity and lower pain sensitivity. However, all studies have used relatively small participant numbers (n<72).

One small study used accelerometry (using a minimum wear-time of 3 days, 10 hours per day) to measure physical activity using a 7-day protocol in healthy females (n=21) dividing them into a group who met recommended activity levels (n=12, average 118mins/day moderate activity plus 16mins/day vigorous activity) and a group not meeting recommended activity levels (n=9, average 87mins/day moderate activity and 4mins/day vigorous activity) (Ellingson, Colbert et al. 2012). Heat stimuli consisting of seven temperatures ranging from 43°C to 49°C in 1°C increments were applied at the base of the right thumb and participants rated the pain intensity and pain unpleasantness (how bothersome the stimulus was) at each temperature. The results demonstrated the active group had significantly lower pain unpleasantness ratings to heat stimuli compared with the inactive group ($F_{1, 19} = 7.30$, $p=0.01$), but no significant difference for average pain intensity ($F_{1, 19} = 3.14$, $p=0.09$). However, the study did not adjust for potential confounders of this group difference, used a limited number of participants and only included females.

Only one study has examined the association between PA assessed using subjective methods and pain sensitivity in a pain population. A large low back pain study (n=294) assessed PA using the IPAQ and categorised participants according to whether they were above or below 300 minutes per week of moderate PA (Rabey, Slater et al. 2015). A cluster analysis placed participants in one of 3 categories based on pain sensitivity. Participants in a cluster demonstrating average to high pressure pain sensitivity and thermal pain sensitivity had a significantly higher proportion of participants achieving less than 300 minutes per week of moderate PA (16.3%) than those in clusters characterised by average to high pressure pain sensitivity (31.3%), or low temperature and pressure pain sensitivity (32.6%).

Only one study has examined the association between PA assessed using objective methods and pain sensitivity in a pain population. McLoughlin (McLoughlin, Stegner et al. 2011) used accelerometry in addition to the IPAQ to monitor physical activity over 7-days in female (n=16) participants with FMS and in healthy pain-free females (n=18). Within the FMS group, both higher self-reported PA and greater time in MVPA, as measured by accelerometry, were significantly associated with lower pain ratings to heat stimuli, whereas the healthy controls demonstrated no significant relationships between activity levels and pain ratings. The study was limited to female participants, had a small number of participants and did not control for potential confounders.

2.2.7.6 Summary of the association between physical activity and pain sensitivity

The association between PA and pain sensitivity has been largely investigated in laboratory settings over very short-term periods. A variety of laboratory-based exercise protocols using healthy pain-free participants are consistently associated with a transient decrease in pain sensitivity. The effect of laboratory-based PA on pain sensitivity in participants with pain is often conflicting and reflects the heterogeneity of participants, the use of single-sex samples or inadequate consideration of sex as a confounder, variation in methodology and low powered studies. In participants with FMS, lower intensity (Kadetoff and Kosek 2007, Newcomb, Koltyn et al. 2011) or less duration (Staud, Robinson et al. 2010) of laboratory-based exercise was associated with decreased pain sensitivity. This may be an important consideration for exercise prescription, as participants with FMS typically had an association of increased pain sensitivity with PA.

The effects of laboratory-based exercise on pain sensitivity have only been measured immediately post-exercise and appear to be transient because when pain sensitivity is tested 30 minutes post-exercise, EIH is minimal. Additionally, investigation is largely based around a single exercise session limiting the generalizability of the findings to clinical populations.

The effect of exercise interventions and habitual PA on pain sensitivity is of interest. The effect of exercise interventions on pain sensitivity represent short to medium term changes in pain sensitivity, while monitoring habitual activity over time provides insight into how PA might influence pain sensitivity over the long term. The results from the limited number of field intervention studies highlight the potential for PA to reduce pain sensitivity in a musculoskeletal pain population. While PA assessed via self-report questionnaire suggests an association between increased vigorous PA in healthy people and decreased pain sensitivity, subjective measurement to assess PA is limited by the poor correlation with objective measurement of PA. Observational studies using objective measurement to investigate the association of PA and pain sensitivity are very limited in number, use small participant numbers and are inconclusive. They are less controlled than interventional studies that allow standardised protocols, where pain sensitivity is tested pre and post intervention, and as a result there is a need to consider confounders. However, observational studies using objective measurement of PA, probably represent the best insight into the long-term association between habitual PA and pain sensitivity.

2.2.7.7   The association between sedentary behaviour and pain sensitivity

In contrast to the body of research evaluating the association between PA and pain sensitivity, the analysis of the association between SB and pain sensitivity has remained mostly unconsidered. Laboratory intervention studies do not have the ability to investigate the effect between SB and pain sensitivity. A limitation of the field studies is that there is no analysis or interventions evaluating the effect of decreasing sedentary behaviour on pain sensitivity. There have been no observational studies using objective measurement of SB. Objective measurement of SB offers the opportunity to measure the amount of time spent sedentary plus more importantly how sedentary time is accumulated. The association between SB and pain sensitivity is of interest, and the potential mechanisms and importance are highlighted below.

2.3   Normative data for pressure and cold pain thresholds

Despite the growing research to suggest the role that pain sensitivity has in pain disorders, surprisingly there is a lack of large population studies that have investigated 'normal' pain sensitivity distributions. Lack of robust normative data complicates interpretation of clinical studies as pain thresholds need to be compared and related to reference values using the same test sites and protocols (Sterling 2011, Rabey, Slater et al. 2015).

To date, there are only 6 studies using PPT and/or CPT reported that have collected pain sensitivity data on more than 100 people (Jensen, Rasmussen et al. 1992, Lee, Lee et al. 1994, Torgén and Swerup 2002, Chesterton, Barlas et al. 2003, Rolke, Baron et al. 2006, Magerl, Krumova et al. 2010, Neziri, Scaramozzino et al. 2011). Jensen (Jensen, Rasmussen et al. 1992) provided PPT values for multiple neck and head sites, with normative values presented for adults (n=178) in the 25-34 age group. Torgen (Torgén and Swerup 2002) investigated CPT (hand and foot) and PPT (hand) values for adults (n=484) aged between 41 and 58 years. However, both these studies used adults from the general population which included people with pain disorders and therefore, these data are not representative of pain sensitivity in a healthy control population.

The other four data sets only included pain-free participants. Chesterton (Chesterton, Barlas et al. 2003) for example provided sex specific PPT (hand test site) values for 19 to 57 year old adults (n=240, mean age 25 years). Interpretation of the values reported is limited as the data reported were not age specific. Whilst Neziri (Neziri, Scaramozzino et al. 2011) reported CPT and PPT values for 300 participants, the numbers within each sex and age range were quite small, for example 75 males and females were in the 20-34 age range. Lee (Lee, Lee et al. 1994) reported PPT values for multiple head and neck sites in 104 males and 103 females in the 10-59 age range. Sex and age specific data were reported for each decade, but there were only small numbers in each sex-age group. Rolke (Rolke, Baron et al. 2006) and Magerl (Magerl, Krumova et al. 2010) obtained PPT and CPT from six body regions from 180 pain-free adults aged 17 to 75 years. Rolke (Rolke, Baron et al. 2006) only reported pain sensitivity by two age groups (above and below 40 years), whilst Magerl (Magerl, Krumova et al. 2010) reported normative data for 5 decade specific age groups from 20 to 70 years of age, using a moving average analysis. Whilst their data was sex specific, again there were only small

numbers in each sex – age group. Therefore, the current samples are too small to provide precise estimates, highlighting a gap in knowledge of what normal pain sensitivity distributions are in young pain-free adults.

2.4   Why large prospective cohorts are important

Prospective cohort studies by their design are observational and unlike clinical trials there are typically no interventions or exposure assigned to specific participants. There are strengths and weaknesses of cohort study designs.

Due to the observational nature of cohort studies, they can be cheaper than clinical trials (Morrow 2010). Cohort studies are an important first step in prognostic research by exploring the natural course of a condition informing the plausibility of future clinical trials (Morrow 2010). Recall bias is minimised in cohort studies as data is collected at regular study follow-ups, unlike retrospective designs, such as case-control studies (Setia 2016). Information may still contain recall bias however it will be over a shorter timeframe (Setia 2016). Importantly, the information will be collected before participants are diagnosed with a condition or disease, limiting preconceptions about the association between the condition or disease and risk factor (Sedgwick 2013, Setia 2016).

The Raine Study is an excellent example of a large prospective cohort, being established in 1989-1991 with the purpose of developing a large cohort of Western Australian children to allow studies from gestation to "ascertain the relative contributions of familial risk factors, fetal growth, placental development and environmental insults to outcome in infancy and to the precursors of adult morbidity" (Straker, Mountain et al. 2017). Initially there was combined funding for a randomised controlled trial to investigate the influence of fetal ultrasounds on birth outcomes and funding to investigate "the origins of disease in the fetus, the child and the young adult" (Straker, Mountain et al. 2017). The study has since evolved into a life-course framework capturing multiple domains including genetics, phenotype, behaviour, environment and developmental outcomes (Straker, Mountain et al. 2017). One of the main strengths of cohort study design is the data is longitudinal, such as in the Raine Study, capturing the temporality between exposure and outcome (Setia 2016). A strength of the Raine Study has been the regular follow-up of participants (1, 2, 3, 5, 8, 10, 14, 17, 20 and 22-years of age) allowing comprehensive, longitudinal data to be collected, however there is a risk

of survivor bias due to loss of contact at follow-up (Sedgwick 2013). There were 2,868 live births in the Raine Study, at the Gen2-22 year follow-up there were 2,262 eligible participants contacted and 1,234 (43% of original Gen2 participants) participated in data collection (Straker, Mountain et al. 2017).

Cohort studies include a broad range of participants and may offer better external validity (generalizability of findings to the population) than a randomised controlled trial (Thadhani and Tonelli 2006). Consequently, the representativeness of the sample compared with the general population should be checked (Sedgwick 2013). In the Raine Study, the characteristics of the participants were compared with census data collected in 2011 on all similarly aged young adults in Western Australia and showed that the sample remains widely representative on a range of variables including education level, employment status, income, marital status, number of offspring, hours worked, and occupation (Straker, Mountain et al. 2017).

The representativeness and size of the Raine Study provides opportunities to investigate normative data, such as required for pain sensitivity. The capture of multiple domains across many time points is important as this allows comprehensive investigation of independent correlates of pain sensitivity that can also be considered as potential confounders in multivariable models.

A disadvantage of cohort studies is caution is required assigning causality to the association between exposure and outcome (Morrow 2010). However well designed cohort studies can provide results similar to randomized controlled trials and in particular bypass the limitations of interpreting data from small clinical cohorts (Song and Chung 2010). Cohort studies can be expensive to run due to the large number of subjects required. Other issues are confounders and exposures may change over time (Morrow 2010).

2.5   Pain sensitivity in musculoskeletal pain disorders

Pain sensitivity measurement has been increasingly used to help identify nociceptive processes and somatosensory profiles that characterize musculoskeletal pain disorders (Backonja, Attal et al. 2013). Specifically, and most commonly, PPT and CPT have been used as measures to assist the identification of altered nociceptive processes in various

localised and widespread musculoskeletal pain disorders. Increased pain sensitivity discrete from or remote from pain sites, suggesting augmented central nociceptive processing, has been reported in localised pain disorders such as knee OA (Suokas, Walsh et al. 2012), low back pain (O'Neill, Kjær et al. 2011), neck pain (Scott, Jull et al. 2005, Javanshir, Ortega-Santiago et al. 2010, Van Oosterwijck, Nijs et al. 2012) and elbow pain (Slater, Arendt-Nielsen et al. 2005). Additionally, conditions with widespread pain and unknown pathogenesis such as FMS and chronic fatigue syndrome have demonstrated increased pain sensitivity compared with localised pain disorders (Hurtig, Raak et al. 2001, Desmeules, Cedraschi et al. 2003, Neville, Clauw et al. 2018, O'Brien, Deitos et al. 2018).

2.5.1 Pain sensitivity in localised musculoskeletal pain disorders

Musculoskeletal pain can be localised in one body area or can be multisite pain. Examples include musculoskeletal disorders with pain localised to the neck, lower back, upper back, arm or leg. Multisite musculoskeletal pain would include presentations with pain in more than one localised body area. Examples include someone with neck and knee pain or widespread pain conditions such as FMS. Typically pain sensitivity in those with localised musculoskeletal pain is compared to a healthy control group. It would also be important to understand how pain sensitivity differs within specific localised musculoskeletal pain disorders, and also between different localised musculoskeletal pain disorders.

2.5.1.1 Pain sensitivity in spinal pain disorders

Pain sensitivity in localised musculoskeletal pain disorders has been most widely investigated in neck pain. A precise patho-anatomical diagnosis in WAD is usually not possible, significant soft tissue trauma is typically not identifiable using available imaging modalities and changes seen on imaging do not predict outcome at 12 months (Kongsted, Sorensen et al. 2008). Consequently, to assist the characterisation of neck pain disorders, pain sensitivity has been investigated for those with WAD and idiopathic neck pain.

2.5.1.1.1 *Pain sensitivity in neck pain disorders*

There is consistent evidence demonstrating somatosensory disturbances in patients with WAD who do not have a specific patho-anatomical diagnosis pathology or

neurological signs. One example investigated participants with chronic WAD (n=115) and healthy pain-free participants (n=95), with PPT measured locally at the cervical spine and remotely in the lower limb (Sterling, Treleaven et al. 2002). Participants with WAD had significantly higher pressure pain sensitivity (p<0.001) compared with controls, both local to and remote from the neck pain. Higher sensitivity at the remote site suggested augmentation of central nociceptive pathways was contributing to the pain experience of WAD participants (Sterling, Treleaven et al. 2002). Interpretation of the findings is limited by the statistical analysis only adjusting for age and sex. Another study using local and remote (leg) PPT test sites compared chronic WAD (n=50), chronic idiopathic neck pain (n=28) and healthy controls (n=31) (Chien and Sterling 2010). The WAD group had higher local and remote pressure pain sensitivity (p<0.01) compared to healthy controls, and only higher remote pressure pain sensitivity (p=0.02) when compared to the idiopathic neck pain group (Chien and Sterling 2010). The WAD group also demonstrated higher cold pain sensitivity, measured at the neck and hand, compared to the idiopathic and healthy control groups (p<0.03), but there was no difference between the idiopathic and healthy control groups (Chien and Sterling 2010). The statistical analysis adjusted for age, sex and psychological distress using the global severity index (Rhudy and Meagher 2000). These findings suggest alterations in nociceptive processing may contribute to neck pain disorders and the nature of this may vary according to the type of disorder. The findings from these investigations showing regional variation and condition-specific differences in sensitivity are consistent with findings of other studies using PPT (Kasch, Stengaard-Pedersen et al. 2001, Scott, Jull et al. 2005, Rebbeck, Moloney et al. 2015) and CPT (Rebbeck, Moloney et al. 2015).

2.5.1.1.2 *Pain sensitivity in low back pain disorders*

Despite being the number one cause of years lived with disability worldwide (James, Abate et al. 2018), the mechanisms associated with LBP, have received less investigation than neck pain. Current evidence suggests that changes in nociceptive processing are heterogenous in people with LBP and these changes are different when compared to those with multisite pain.

The largest investigation used multimodal QST to explore the existence of subgroups in a cohort (n=294) with chronic LBP without serious spinal pathology, or recent and/or

extensive history of spinal surgery (Rabey, Slater et al. 2015). Using latent class analysis, three clusters were derived that were characterised by different sensory characteristics. Cluster 1 (31.9%) was characterised by higher pressure and temperature pain sensitivity, cluster 2 (52.0%) was characterised by higher pressure pain sensitivity and cluster 3 (16.0%) was characterised by lower pressure and temperature pain sensitivity. The clusters suggest each subgroup may have different underlying nociceptive mechanisms contributing to the sensitivity profiles, reflecting the heterogeneous nature of chronic LBP. A strength of the study by Rabey et al (2015) was the relatively large clinical sample size allowing for appropriately powered statistical analysis, multimodal sensory testing and consideration of psychological, lifestyle and general health factors in the cluster analysis.

Another study investigated pain mechanisms using clinical features to classify a chronic LBP group as either having a 'mechanical pain profile' (proportionate pain response to physical examination, specific activities, movements and postures) or 'non-mechanical pain profile' (pain more spontaneous and constant, with a disproportionate response to mechanical factors like movement and posture) (O'Sullivan, Waller et al. 2014). The 'non-mechanical profile' group (n=19) was characterised by higher pain levels, more pain areas and greater disability. Estimates demonstrated that participants in the 'non-mechanical pain' profile group had 18.4 times (95%CI: 2.5-133.1, p=0.004) the odds of having elevated cold pain sensitivity at the wrist compared to participants in the 'mechanical pain' profile group (n=17), after adjusting for confounding factors of sex, depression, anxiety, stress and sleep. There was no evidence of group differences in CPT at the lumbar spine and leg, or PPT between groups at any of the three anatomical test sites (wrist, tibialis anterior and lumbar spine). The increased cold pain sensitivity in the 'non-mechanical pain' profile group was suggestive of augmented central nociceptive processing when compared to those with a 'mechanical' pain profile. The study controlled for a range of potential confounders but was limited by the small sample size and thus only powered to detect large group differences, with wide confidence intervals.

Another small study compared pain thresholds at the back and wrist in patients with chronic LBP (n=23), FMS (n=21) and healthy controls (n=20) (Blumenstiel, Gerhardt et al. 2011). When tested at the back, the FMS patients showed significantly increased pressure and cold pain sensitivity compared with the healthy controls (p<0.001 and p<0.01 respectively), and significantly increased cold pain sensitivity when compared

with the chronic LBP group (p<0.01). When tested at the wrist, the FMS patients had higher pressure (p<0.05) and cold pain sensitivity (p<0.01) compared with the healthy controls. The chronic LBP group demonstrated increased pressure pain sensitivity (p<0.01) at the back compared with healthy controls. The study suggests different nociceptive processing associated with FMS, a widespread pain disorder, compared with chronic LBP. The study is limited by the small number of participants and limited control for confounding, while only age was used as a covariate in the statistical analysis. Investigating non-chronic LBP, a study of the difference in PPT measured locally at the low back in sub-acute (1 to 3 months) LBP (n=87) and healthy controls (n=64) found significantly heightened pressure pain sensitivity (p<0.001) in the sub-acute LBP group (Farasyn and Meeusen 2005). Sub-grouping those with sub-acute LBP into high and low disability using an Oswestry Disability Index (ODI) cut-off of 40, revealed no between group differences. The study was limited by only testing pain sensitivity locally at low back.

2.5.1.1.3   *Pain sensitivity in acute and subacute spinal pain disorders*

While somatosensory changes reflective of augmented central nociceptive processing have been consistently demonstrated in chronic neck and back pain, it is difficult to know for each individual whether the changes occur after the onset of a pain episode or whether augmented nociceptive processing is present prior to an episode of pain, potentially increasing risk for the transition from acute to chronic pain. A recent systematic review and meta-analysis investigated early changes in somatosensory function in spinal pain disorders (Marcuzzi, Dean et al. 2015). Fifteen studies were included and grouped according to WAD, idiopathic neck pain and nonspecific LBP. The review found consistent evidence for increased pressure and cold pain sensitivity, reflecting augmented central nociceptive processing in the acute stage following a whiplash injury, however no evidence for similar changes in the acute and subacute stage of idiopathic neck pain. In the early stages of nonspecific LBP, there was heightened pressure pain sensitivity local to the lumbar spine, but conflicting evidence for widespread changes in pressure pain sensitivity at more remote test sites. Limitations of current studies were stated as lack of control for potential confounders, risk of bias in studies due to lack of assessor blinding, sample size, low disability levels of the samples and unclear sampling methods.

2.5.1.2   Pain sensitivity in peripheral musculoskeletal pain disorders

Pain sensitivity has been investigated in peripheral musculoskeletal pain disorders including OA. A systematic review and meta-analysis reviewed the use of QST to evaluate nociceptive processing in those with OA (Suokas, Walsh et al. 2012), and included 41 studies that used a variety of mechanical, electrical and thermal pain sensitivity measures, with seven studies providing adequate data for meta-analysis. The seven studies included for meta-analysis allowed comparison of local and remote PPT measures to the affected joint that was either the knee, hip or hand. People with OA demonstrated heightened pressure pain sensitivity when compared with healthy controls at both the affected joint (standardized mean difference (SMD)=-1.24, 95%CI -1.54, -0.93) and at remote sites (SMD=-0.88, 95%CI -1.11, -0.65). The meta-analysis strongly supports current evidence of augmented widespread pain sensitivity in OA, likely reflecting involvement of altered central nociceptive processing. The review authors concluded that more work is required to identify subgroups using pain phenotypes to help understand nociceptive processing in OA and to guide future research using treatments that target subgroups.

Whether there is a relationship between the severity of knee OA pain or pathology and pain sensitivity has also been investigated (Finan, Buenaver et al. 2013). Knee OA participants (n=113) were sub-grouped according to a dichotomized knee pain score (median split) and knee OA grade scores based on radiology (grades 1-2 versus 3-4). Four sub-groups resulted: low pain/low knee OA grade (n=24), high pain/high knee OA grade (n=32), low pain/high knee OA grade (n=27) and high pain/low knee OA grade (n=30). A multivariate analysis adjusting for age, sex, race and psychosocial measures revealed significantly heightened pain sensitivity in the high pain/low knee OA grade group and significantly lower pain sensitivity in the low pain/high knee OA grade group. Specifically, the high pain/low knee OA grade group had significantly higher pressure pain sensitivity remotely at the trapezius muscle (p<0.05) and a significantly higher pain rating to a sustained immersion of the hand in 4°C water (P<0.05) than the low pain/high knee OA grade group. Patients with the highest reports of clinical pain, with only mild knee joint pathological changes on radiography were the most pain sensitive group, suggesting a contribution of augmented central nociceptive processes may be implicated in the pain experience of this group. This study's outcomes provide support for the existence of

different pain phenotypes within the same condition (OA) that are discordant from pain severity and pathology.

Lateral elbow epicondylalgia, consistent with pain at the CEO at the lateral elbow, typically has pathology including degenerative changes of the tendon and intrinsic muscle pathology (Coombes, Bisset et al. 2009). However, the tissue-based pathology does not adequately explain the chronic nature of lateral epicondylalgia, leading to studies using QST to characterise somatosensory function and implicate pain mechanisms underlying the disorder. Three small studies used PPT to investigate pain mechanisms in patients with lateral epicondylalgia (Slater, Arendt-Nielsen et al. 2005, Fernandez-Carnero, Fernandez-de-las-Penas et al. 2009, Fernández-Carnero, Fernández-de-las-Peñas et al. 2009). There were consistent results in all three studies showing significant increases in pressure pain sensitivity at test sites remote and local to the elbow, suggesting augmented central nociceptive processing is a feature of lateral elbow epicondylalgia.

2.5.2   Pain sensitivity in widespread musculoskeletal pain disorders

There has been investigation comparing differences in pain sensitivity between chronic localized pain disorders and chronic widespread pain disorders. The most common widespread pain disorder is FMS affecting from 2% to 8% of the population, with patients tending to have lifelong histories of persistent pain (Clauw 2014). The original diagnostic criteria for FMS were first published in 1990 and were based on a chronic widespread pain presentation with a specified number of tender points (Wolfe, Smythe et al. 1990). Using the original criteria relied on a skilled physical examination and resulted in a high percentage of patients with FMS being women because they have more tender points than men (Clauw 2014). In 2010 the diagnostic criteria were updated to be entirely symptom based and no longer require counts of tender points (Wolfe, Clauw et al. 2011). FMS is considered to be a "centralized pain state" with 'centralized' referring to the CNS origin of pain (Clauw 2014). Typically there are poor outcomes of most therapeutic interventions (Arnold, Choy et al. 2016).

QST has been used to investigate nociceptive processing in widespread pain disorders, including FMS. As discussed above, the pain sensitivity of FMS patients has been compared to patients with chronic LBP and healthy controls (Blumenstiel, Gerhardt et al. 2011). To recap, compared with the healthy controls and chronic LBP group, FMS

patients showed significant increases in pressure and cold pain sensitivity at local back and remote test sites suggestive of augmented central nociceptive processing. Another study sub-grouped female FMS patients (n=29) following QST testing into a low thermal pain sensitivity group (heat pain threshold: mean=44.1°C, CPT mean=13.6°C) and high thermal pain sensitivity group (heat pain threshold mean=39.2°C, CPT: mean=23.5°C) (Hurtig, Raak et al. 2001). A multivariate regression analysis revealed significant sub-group differences with higher local pain intensities, increased number of tender points and poorer sleep in the high thermal pain sensitivity group. This suggests that differences in sub-groups could be accounted for by severity of condition, however measuring the severity of FMS is complex with causality unclear. It is unknown whether the severity of FMS is reflected in augmented central nociceptive processing or whether augmented central nociceptive processing increases the severity of FMS. One study investigated whether FMS represents the end of a continuum of augmented nociceptive processing in patients with chronic, diffuse musculoskeletal pain (Carli, Suman et al. 2002). The study investigated people with diffuse musculoskeletal pain (n=145) of more than three months' duration, with the participants divided into five subgroups of increasing severity according to the American College of Rheumatology criteria for widespread pain and tender point counts, with FMS used to describe the subgroup with highest severity. However, it is important to note that using number of tender points to classify widespread pain has now been dropped from the American College of Rheumatology criterion (Wolfe, Clauw et al. 2011). Healthy pain-free participants (n=22) were used as a control group. Six quantitative sensory tests using heat, cold and pressure were used to measure pain thresholds and tolerance. The results indicate heightened sensitivity reflecting augmented nociceptive processing in participants sub-grouped with the least severe classification of "multiregional pain" when compared to healthy controls. As the number of areas of pain and number of tender points increased, the number of quantitative sensory tests with values more sensitive than healthy pain-free controls increased ($p<0.001$), suggesting widespread pain is a continuum of increasing central nociceptive dysfunction with FMS at the upper extremity.

Further, although LBP may be considered a localised musculoskeletal pain condition, a recent study demonstrated that a greater number of body pain areas was associated with higher cold pain sensitivity measured remotely to the back in people with LBP (O'Sullivan, Waller et al. 2014). This study investigated pain sensitivity (PPT and CPT at

the dorsal wrist, lumbar spine and leg) in patients with 'mechanical' chronic LBP (n=17), patients with 'non-mechanical' chronic LBP (n=19) and healthy pain-free controls (n=19). The 'non-mechanical' pain profile group was characterised by heightened cold pain sensitivity at the wrist, higher pain intensity levels, a higher number of body pain areas and greater disability.

The studies above consistently demonstrate heightened sensitivity as a reflection of augmented central nociceptive processing when there is an increase in pain area, or 'non-mechanical' pain behaviour.

2.5.3   The association of pain sensitivity with disability in musculoskeletal pain disorders

The association between disability and pain sensitivity has also been investigated with the hypothesis that heightened pain sensitivity is associated with increased disability. The largest study is a systematic review and meta-analysis that investigated the relationship between pain threshold and disability in people with spinal pain using pooled data from 23 studies (Hübscher, Moloney et al. 2013). The pooled estimate for the correlation between pain threshold (mechanical and thermal) and disability was -0.16 (95%CI: -0.22 to -0.10) (Hübscher, Moloney et al. 2013). While the correlation indicates that increased pain sensitivity was correlated with increased disability, a subgroup analyses and meta-regression found the association was not moderated by test site (local versus remote), pain condition (back or neck pain), pain duration (<12 weeks or ≥3 months) or type of stimulus (mechanical versus thermal). The association was small, potentially reflecting that many participants may not have had significantly heightened pain sensitivity as measured by the QST measures. The authors of this review proposed that better subgrouping of participants based on valid clinical assessment and a broader capture of the pain experience would be of future research interest.

The findings above are consistent with those of others who have demonstrated that persistent musculoskeletal pain is not always associated with heightened pain sensitivity. A large investigation previously discussed used multimodal QST to explore the existence of subgroups in a cohort (n=294) with chronic LBP without serious spinal pathology or recent and/or extensive history of spinal surgery (Rabey, Slater et al. 2015). Three clusters derived were characterised by different sensory characteristics. Cluster 1 (31.9%)

was characterised by higher pressure and temperature pain sensitivity, cluster 2 (52.0%) by higher pressure pain sensitivity and cluster 3 (16.0%) by lower pressure and temperature pain sensitivity. There was no significant difference in disability across these subgroups, measured using the Roland Morris Disability Questionnaire, although the clusters did differ in relation to psychological symptoms, sleep disturbance and activity levels, with cluster 1 having the highest levels of psychological symptoms, sleep disturbance and physical inactivity. The subgroups highlight the heterogeneity of chronic LBP with differences reported in pain mechanisms, psychological symptoms, sleep quality and activity levels in those with a common chronic condition, however this did not result in a difference in disability between subgroups.

Although the Hübscher (Hübscher, Moloney et al. 2013) review and Rabey (Rabey, Slater et al. 2015) investigation showed small and no correlation between pain threshold and disability respectively, other studies have shown larger correlations. Female participants (n=62) with persistent knee pain scheduled for total knee replacement demonstrated a univariable association of increased difficulty with physical activities (measured using the physical activities subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)) and increased pressure pain sensitivity at a number of local (8 knee) and remote (9 back and pelvis) test sites (P<0.05) (Imamura, Imamura et al. 2008). Further analysis used step-wise multiple linear regression models to determine the relationship between PPT measures, pain intensity, and WOMAC and Short Form-36 subscales. Higher pressure pain sensitivity was correlated with greater pain intensity, increased difficulty with physical activity and poor quality of life (p<0.01). The significant results reported by this study, but not others, potentially reflect the higher disability of a cohort scheduled for knee replacement surgery. The sample size of the study was relatively small, with further studies necessary to support these findings.

The relationship between pain sensitivity and disability has been explored more widely in people with neck pain. Higher disability in people with neck pain has been associated with higher pressure and cold pain sensitivity. One longitudinal study investigated the association of early changes in pain sensitivity to either recovery, mild pain and disability, or moderate/severe pain and disability at 6 months post-injury (Sterling, Jull et al. 2003). Pain sensitivity (pressure and cold) was measured at 1, 2, 3 and 6 months post-injury in participants with WAD (n=76) and outcome was classified at 6

months post-injury using the Neck Disability Index (NDI) and pain score. Compared to a control group (n=20), all participants demonstrated significantly increased pressure pain sensitivity in the neck at 1 month post-injury ($p<0.01$). However, the recovered and mild pain groups at 2 months post-injury were no longer demonstrating increased pressure pain sensitivity when compared to the control group. The pressure pain sensitivity of the moderate/severe group at 6 months was higher compared with the other two whiplash groups and controls ($p<0.01$) and did not change over 6 months. The group with persistent moderate/severe pain and disability at 6 months, demonstrated significantly higher mean CPT (increased cold pain sensitivity, 19.2°C) than the recovered WAD group (11.6°C), the mild WAD symptom group (11.4°C) and the control group (9.7°C). The time point of this difference was not reported. For the CPT measurement, there was no interaction effect between group and time post-injury when CPT was measured ($p<0.09$). The study is limited by only adjusting for age and sex. A similar study of participants with WAD (n=62), measuring PPT and CPT at <3 weeks, 3 and 6 months post-injury, demonstrated pressure and cold hypersensitivity at each test point only in participants with persistent moderate/severe pain and disability (Sterling 2010). Another study compared two groups, one of participants with chronic WAD and higher disability (n=50, mean NDI score 47.4) and a chronic idiopathic neck pain group (n=28, mean NDI score 27.3) (Chien and Sterling 2010). The chronic WAD group had significantly higher pressure pain sensitivity compared to the chronic idiopathic neck pain group at the tibialis anterior ($p=0.02$), but not at the neck or median nerve. The chronic WAD group also had significantly greater cold pain sensitivity at the neck ($p=0.03$) and hand ($p=0.02$) compared to the chronic idiopathic neck pain group. These findings suggest that the association of higher disability with increased distal or remote pressure and cold pain sensitivity in the chronic WAD group compared with the chronic idiopathic neck pain group, may indicate different degrees of altered central nociceptive processing underlying the two pain conditions and their related disability. Females with chronic WAD have also been sub-grouped by cluster analysis based on pain thresholds for pressure, cold and heat measured at the neck and tibialis anterior (Borsbo, Liedberg et al. 2012). Two subgroups were identified, one sensitive (n=21) and one less sensitive subgroup (n=6). While there was a tendency of higher pain and disability in the sensitive subgroup, there were no significant differences between the groups. The study was limited by the small sample size.

Current studies reveal a variable association of pain sensitivity with disability across different musculoskeletal conditions. The current literature is limited by the heterogenous nature of musculoskeletal pain disorders resulting in variable case-mixes, different methodologies to measure pain sensitivity, small samples sizes and limited adjustment for potential confounders.

2.5.4   The association of pain sensitivity with pain experience in musculoskeletal pain disorders

The link between the experience of pain and pain sensitivity is important to explore as there is an association between pain sensitivity and musculoskeletal pain. This makes sense as pain is a subjective sensation that is challenging to measure objectively (Denk and McMahon 2017) with variations explained in part by wide ranging environmental, biological and genetic influences (Denk, McMahon et al. 2014). Using a unidimensional pain intensity scale to try and capture the complexity of the pain experience has limited validity (Hübscher, Moloney et al. 2013, Morse 2015). A systematic review and meta-analysis investigated the relationship between pain threshold and pain intensity in people with spinal pain, pooling data from 34 studies (Hübscher, Moloney et al. 2013). The pooled estimate for the correlation between pain threshold and pain intensity was -0.15 (95% CI: -0.18 to -0.11) indicating that lower pain thresholds (i.e. increased pain sensitivity) were correlated with higher pain intensity, however the association was weak. Consideration of only a single aspect of pain such as intensity will not capture a broader pain experience and hence this limitation makes sense of the lack of stronger associations with pain sensitivity data. While this previous study adjusted for chronicity (<3 months versus ≥3 months), other parameters such as higher levels of pain frequency and number of pain locations and are important considerations as there is an association with higher disability (Hoftun, Romundstad et al. 2011).Measuring multiple aspects of the pain experience may be a better method of measuring pain status and can potentially improve clinical phenotyping.

Recent large population-based studies have used different pain parameters and varying methods to help characterize pain status and analyse the relationship between pain experience and pain sensitivity. A population-based study of adolescents in the Tromsø region in Northern Norway measured pressure pain threshold and tolerance at the

trapezius and finger (n=941) (Tham, Palermo et al. 2016). Pressure pain sensitivity in adolescents with chronic pain (defined as having pain >3 months and at least once per week, n=197) was compared to those without chronic pain (n=744). Those reporting pain for more than 3 months but reporting pain less than once per week were excluded (n=37). Compared to adolescents without chronic pain, those with chronic pain had significantly lower pressure pain tolerance (572 vs 634 kPa, p=0.014) and threshold (264 vs 292 kPa, p=0.027) at the trapezius. There was no significant difference between groups for pressure pain sensitivity at the finger, heat pain sensitivity at the forearm or for a cold-pressor tolerance test using the hand submerged in 3°C water. Only analysing the adolescents with chronic pain (n=197), linear regressions adjusting for sex and age examined associations between QST responses and clinical pain characteristics. A higher number of pain locations was significantly associated with decreased pressure pain tolerance at the finger (p≤0.001) and trapezius (p<0.001), and with pressure pain threshold at the finger (p=0.008). Longer pain duration was significantly associated with pressure pain tolerance at the finger (β=24.99, p<0.05) and trapezius (β=40.33, p<0.01). Findings were limited by the chronic pain group inclusion criteria that considered only two pain characteristics (duration and frequency of pain) leaving the intensity of pain and number of pain areas unconsidered. The chronic pain group inclusion criteria was based on consensus opinion and may have been better determined by using a statistical procedure such as cluster analysis to better phenotype participants.

Another population study (n=2,199) used the number of sites and pain severity in a summary score as a covariate in an investigation of the association of pain sensitivity with age and sex but did not specifically examine the association between pain experience and pain sensitivity. The study used an ordinal scale ranging from 0 (no pain) to 28 (Skovbjerg, Jørgensen et al. 2017), which included the number of body sites with pain in the last 12 months and a 5-point Likert scale to rate the degree of pain (with 1= "not at all" and 5= "very much"). There was no detail provided on how the scores were summarised or the results of the questionnaire.

There is a lack of large population-based studies using QST to assist our understanding of pain mechanisms, particularly in young adults. Stronger QST associations may be identified if multiple aspects of the pain experience were considered simultaneously, including number of pain sites, pain frequency, pain intensity and pain duration.

2.5.5 Predictive utility of pain sensitivity measures in musculoskeletal pain disorders

Pain sensitivity may be important in the development of musculoskeletal pain (Nielsen, Staud et al. 2009). Specifically, pain sensitivity measures have been used to try and predict the onset of a new musculoskeletal pain disorder and to predict the outcome of an existing musculoskeletal pain disorder. However, in this context, there is a limited body of work investigating the utility of pain sensitivity in predicting the risk of future onset of musculoskeletal pain and findings have been mixed. The use of QST to predict the outcome of an existing musculoskeletal pain disorder has been more widely investigated and current literature suggests higher pain sensitivity partially predicts poorer outcomes of pain and disability (Georgopoulos, Akin-Akinyosoye et al. 2019).

2.5.5.1 Predictive utility of pain sensitivity measures for the onset of a musculoskeletal pain disorder

Understanding whether pain sensitivity predicts the onset of a pain disorder is important, but conclusions are difficult due to the very limited investigation. The largest study on pain sensitivity and risk of onset of musculoskeletal pain recruited a cohort of people (n=2,737) without initial temporomandibular disorder and this cohort was followed up to 5.2 years (Greenspan, Slade et al. 2013). During the follow-up time, 260 (9.5%) people developed first-onset temporomandibular pain. Pressure pain threshold, measured at 3 cranial sites showed hazard ratios ranging from 1.15 (95% CI=1.00-1.30) to 1.20 (95% CI=1.05-1.37), indicating a decrease in one standard deviation of PPT (greater pressure sensitivity) resulted in a 15-20% increase in risk of developing temporomandibular disorder.

Another smaller, 3-year prospective study of female participants also investigated the risk of developing temporomandibular pain (n=202), (Diatchenko, Slade et al. 2005). A pain sensitivity score was developed at baseline by combining 16 pain measures of thermal pain thresholds, temporal summation, ischemic pain and pressure pain thresholds. The pain sensitivity score was associated (p=0.0004) with 3 genetic variants (haplotypes) of the gene encoding catecholamine-O-methyltransferase (COMT) that were designated as either low pain sensitivity, average pain sensitivity and high pain sensitivity haplotypes. The number of participants who developed temporomandibular

pain was 15 (7.4%). The haplotype linked with low pain sensitivity diminished the risk of developing temporomandibular pain by as much as 2.3 times.

Using neck or shoulder discomfort as an outcome measure, a small group (n=12) of newly employed female filleting workers without neck or shoulder discomfort were tested within 1 month of employment and after 6 months of employment (Madeleine, Lundager et al. 2003). Pain sensitivity was measured using PPT applied at the cervical spine, shoulder and knee, with the mean PPT used for analysis. Six employees (50%) developed neck or shoulder discomfort over 6 months. Those who developed pain had lower initial PPT values (high pressure pain sensitivity, 240.8 vs 337.7 kPa) when compared to participants who did not develop pain ($p<0.05$). However, this sample size was insufficient to allow the results to be interpreted with confidence.

In contrast, O'Neill (O'Neill, Kjær et al. 2011) examined 40 year old people without LBP (n=170). In this group, high baseline pressure pain sensitivity (defined by baseline PPT in the lower 10% of the PPT distribution) did not constitute a significant risk factor for incident LBP in the 1-year period preceding a 4- and 8-year follow up. The study is limited by the low sample numbers with high pain sensitivity, meaning that the high pain sensitivity group consisted of only 17 subjects.

Similarly, a Danish population-based study (n=1,000) investigated primary headache disorders and pain sensitivity, reporting that higher pressure pain sensitivity at baseline did not predict the onset of chronic tension type headache over a 12-year period (Buchgreitz, Lyngberg et al. 2008). For those who developed chronic tension type headache, pressure pain sensitivity when compared from baseline was increased at the 12-year follow-up ($p=0.025$), but not in those who developed frequent episodic tension type headache. The study concluded that increased pressure pain sensitivity was a consequence of developing chronic tension type headache rather than being a risk factor.

Collectively taken, the mixed findings in these aforementioned studies potentially reflects variable study designs and methodologies. Additionally, there have only been a limited number of musculoskeletal pain disorders investigated, namely temporomandibular pain, neck pain, LBP and headache. Interpretation of results is limited by most studies having limited sample sizes. This highlights the need for future prospective studies to use large cohorts and investigate musculoskeletal

pain disorders more widely, as the heterogeneous nature of each musculoskeletal disorder requires consideration. Additionally, there are many potential confounders of pain sensitivity and properly powered studies are required to ensure robust statistical analysis by adjusting for potential confounders in the statistical analysis.

2.5.5.2 Predictive utility of pain sensitivity measures for the prognosis of an existing musculoskeletal pain disorder

Pain sensitivity has also been used to predict future disability in people who already have a musculoskeletal pain disorder. Common musculoskeletal disorders such as LBP, neck pain and OA frequently become persistent pain disorders (James, Abate et al. 2018). While the onset of a musculoskeletal pain disorder may result from tissue injury, persistent pain is commonly associated with augmented nociceptive processing (O'Neill, Kjær et al. 2011, Suokas, Walsh et al. 2012, Van Oosterwijck, Nijs et al. 2013).

A recent systematic review and meta-analysis investigated the ability of QST to predict musculoskeletal pain disorder outcomes (Georgopoulos, Akin-Akinyosoye et al. 2019). There were 37 studies (n=3860 participants) identified, with pain used as an outcome in 30 studies and disability used as an outcome in 11 studies. Unadjusted data from 18 studies examined the ability of baseline QST to predict follow-up pain with a correlation of 0.31 (95%CI: 0.23 to 0.38). The adjusted data (adjusting for a range of correlates and confounders), also from 18 studies, showed a correlation of 0.18 (95%CI: 0.11 to 0.25) and studies that also adjusted for baseline pain (13/18) showed a correlation of 0.13 (95%CI: 0.06 to 0.20). Unadjusted data from 11 studies examined the ability of baseline QST to predict disability outcome with a correlation of 0.30 (95%CI: 0.19 to 0.40). The adjusted data from 11 studies showed a correlation of 0.35 (95%CI: 0.21 to 0.49). The studies analysed included multiple musculoskeletal disorders (OA, LBP, WAD, post-operative pain) that affected multiple pain sites (knee, hip, low back, neck and shoulder). Pain sensitivity was measured using different modalities, including pressure and cold, and demonstrate a relationship between increased baseline pain sensitivity and poorer prognosis.

The largest body of work for a specific disorder has examined cohorts with WAD, with multiple studies investigating pain sensitivity as a predictor of future disability following a whiplash injury. Systematic reviews indicate recovery from idiopathic neck

pain (Hush, Lin et al. 2011) and WAD (Kamper, Rebbeck et al. 2008) is poor for many people, reporting at least 50% of people have persistent pain and disability. There is a poor response to conservative treatment approaches for WAD, even when using individualized management (Jull, Kenardy et al. 2013). However a recent randomised controlled study of participants (n=108) with acute WAD (<4 weeks) at risk of poor recovery (NDI≥32% and ≥3 in the hyperarousal scale of the Posttraumatic Stress Diagnostic Scale) investigated the effect of Physiotherapist delivered stress inoculation training combined with guideline-based exercise intervention versus guideline-based physiotherapy exercise alone as the intervention (Sterling, Smeets et al. 2019). The stress inoculation training combined with guideline-based exercise resulted in greater, clinically significant improvements in pain related disability when compared with guideline-based exercise alone, with the benefit maintained at 12-month follow-up. The results highlight the potential for psychological treatment combined with exercise to modulate pain related disability, how this is mediated is speculative and is potentially via reduction in stress and pain sensitivity.

A systematic meta-review of prognostic factors following whiplash injury included 12 systematic reviews of at least moderate quality (Sarrami, Armstrong et al. 2017). Prognostic factors were divided into categories: 'associated', 'non-associated', 'controversial' or 'lack of evidence'. Heightened cold pain sensitivity was found to be 'associated' with poorer outcome in 7 systematic reviews. Other factors 'associated' with poorer outcome were high post-injury pain and disability, post-injury anxiety, catastrophizing, and compensation and legal factors. Pressure pain sensitivity was not analysed in the systematic meta-review thereby precluding consideration of this measure as a potential predictor of outcome.

Specific examples of cold pain sensitivity predicting outcome include a study of participants with acute WAD (n=76) that investigated the predictive capacity of early (<1 month) post-injury measures of physical impairment, pain sensitivity (pressure and cold pain thresholds) and psychological impact on disability (measured using the NDI) six months post-injury (Sterling, Jull et al. 2005). A multivariable model reported moderate to severe disability at 6 months was significantly predicted by increased cold pain sensitivity at the neck (OR=1.29, 95% CI = 1.05-1.58), independent of high initial disability (OR=1.06, 95% CI = 1.007-1.12), older age (OR=1.13, 95% CI = 1.03-1.23), and higher post-traumatic

stress (OR=1.11, 95% CI = 1.03-1.20)). A similar study of participants with WAD (n=155) assessed disability (measured using the NDI) at <1 month, 3, 6 and 12 months post injury (Sterling, Hendrikz et al. 2011), and found that baseline measurements of cold pain sensitivity at the neck (CPT≥13°C, OR = 26.32, 95% CI = 4.98–139.09), pain level (OR = 4.3, 95% CI = 4.98–139.1) and age (OR = 1.109, 95% CI = 1.04–1.18) predicted a chronic/severe disability trajectory, after adjusting for pain level and age.

Due to PPT being more easily accessible and practical as a clinical tool, one study investigated whether pressure pain sensitivity was predictive of short-term disability in people with acute WAD (Walton, MacDermid et al. 2011). Participants (n=45) underwent PPT testing at an initial assessment less than 30 days post-injury and subsequently completed an NDI questionnaire between 1 and 3 months following the initial assessment. At follow-up, a significant association was found between higher disability and increased baseline pressure pain sensitivity at the tibialis anterior (standardised beta coefficient = -0.30, 95% CI -0.60 to -0.06), after adjusting for sex and baseline pain intensity. The prognostic value of increased pressure pain sensitivity at the tibialis anterior test site (i.e. an area remote from the neck), possibly suggests augmented central nociceptive processing contributes to disability at short-term follow-up. However, while the study controlled for sex and age, the small sample size prohibited the ability to control for other potential confounders such as psychosocial factors.

A recent systematic review summarized evidence for the prognostic value of QST measures in people with LBP (Marcuzzi, Dean et al. 2016). Three prospective longitudinal studies were identified that assessed at least one QST measure in people with LBP and reported the association of pain sensitivity with LBP status at follow-up. All studies measured pain sensitivity at the lower back and remotely to the lower back using pressure stimuli, with two studies using cold stimuli. LBP status included measures of pain intensity, disability, work status, global perceived recovery and health-related quality of life. None of the three included studies reported a significant association, after adjusting for age and sex, between baseline QST responses and LBP status at follow-up between 4 months and 2 years. There were methodological limitations noted for studies included in this review. Two of the included studies had a mean pain duration of over 6 years at baseline raising concerns of how representative the samples were of a broader LBP population. Prognostic studies are more relevant when using inception cohorts (Beattie and Nelson 2007).

Another study used 108 candidate variables, including a battery of nociceptive QST, to examine predictors of LBP pain and disability at 1-year (Rabey, Smith et al. 2017). There was no prognostic influence of pain sensitivity, again may be reflective of the duration of pain reported for the cohort (medium = 120 months). This contrasts to the WAD studies that assembled inception cohorts and pain sensitivity measures were of useful prognostic value. The third study had 65% of participants with pain less than 30 days, however failed to report the pain duration of the other 35% of participants. There were also methodological concerns expressed that related to the poor clarity provided on the QST protocols including order of tests, blinding of assessors and assessor training.

Lateral epicondylalgia is a common musculoskeletal condition with many experiencing persistent symptoms for years and symptoms are commonly recurrent (Hudak, Cole et al. 1996, Coombes, Bisset et al. 2013). The consistent finding of augmented central nociceptive processing in people with lateral epicondylalgia may partially explain the persistent symptoms (Fernández-Carnero, Fernández-de-las-Peñas et al. 2009, Coombes, Bisset et al. 2012). One prospective study was identified that investigated the use of QST measures to help predict outcome in lateral epicondylalgia (Coombes, Bisset et al. 2015). This study examined patients (n=41) with unilateral lateral epicondylalgia assigned to placebo in a prospective randomized controlled trial. The study revealed cold pain sensitivity can help to predict poorer outcomes in people with lateral epicondylalgia. At baseline, PPT, CPT, pain-free grip and psychological factors were measured. The outcome measures used were pain and disability as measured by the Patient-rated Tennis Elbow Evaluation (PRTEE) scale, with PPT at the affected elbow taken at 2 and 12 months after baseline. A higher PRTEE score (higher scores equal more pain and disability) at 2 months was predicted by greater baseline cold pain sensitivity (β=0.77; 95% CI, 0.21-1.33; p=0.008), adjusting for baseline pain and disability. PRTEE at 12 months was predicted by greater baseline cold pain sensitivity (β=0.61; 95% CI, 0.05-1.17; p=0.034). Although the study is limited by the small number of participants, these results suggest heightened pain sensitivity may contribute to persistent pain and disability in those with lateral epicondylalgia.

2.5.6   Summary: pain sensitivity in musculoskeletal pain disorders

There is good evidence to support the use of PPT and CPT to assist with the identification and characterisation of somatosensory phenotypes in various localised and

widespread musculoskeletal pain disorders. These phenotypes may reflect altered nociceptive processing including peripheral and central nociceptive augmentation. People with musculoskeletal pain disorders consistently demonstrate augmented nociceptive processes when compared with healthy controls, however changes in nociceptive processing vary within individuals including over time, within specific conditions and between conditions (Backonja, Attal et al. 2013, Cruz-Almeida and Fillingim 2014, Marcuzzi, Dean et al. 2015). However, it should be noted that heightened sensitivity is not always associated with musculoskeletal pain disorders, nor is it a pre-requisite for persistent pain. This highlights the mandate for broader consideration of the multiple dimensions interacting over time in people with musculoskeletal pain disorders.

The understanding of the relationship of pain sensitivity to the pain experience and disability associated with musculoskeletal pain disorders is complicated by inconsistent results. Here, it is important to remember that any pain experience is complex, subjective, and highly personal. Only considering pain intensity or disability limits the potential for understanding pain sensitivity in the context of the multiple contributing and interacting dimensions and constructs of the pain experience. Other contributions to these variable study findings include; systematic reviews and meta-analyses using the available small samples with varying case mixes and conditions; application of varying QST methodologies that do not always adhere to best practice recommendations; most studies being cross-sectional with limited data from longitudinal studies; assessors not being blinded; and a lack of control for confounding by factors that may potentially influence pain sensitivity.

Measuring baseline QST can help predict prognosis of musculoskeletal pain disorders and has potential to guide stratification of care to improve pain and disability (Georgopoulos, Akin-Akinyosoye et al. 2019). However, understanding pain sensitivity in people with musculoskeletal pain is often limited as studies use a variable battery of QST measures, taken at single time points, and measured at single sites (locally) without the addition of a remote test site away from the main pain site. Collectively, this limits the ability to differentiate the relative contributions of peripheral and central nociceptive mechanisms to the pain disorder.

Further longitudinal studies are required if we are to better understand the contribution of pain sensitivity to musculoskeletal pain, including how pain sensitivity

contributes to the onset of a disorder and how early changes in pain sensitivity following the onset of a pain disorder are mechanistically related to the development and maintenance of persistent pain. Changes in pain sensitivity may also be relative to the individual and to time, with some individuals starting with relatively higher pain sensitivity and recovering (normal pain sensitivity), while others start with high pain sensitivity and do not recover or start with low sensitivity with increasing sensitivity evident over time.

2.6   Putative mechanisms underpinning the variation in human pain sensitivity

Genetic, biological, physical, lifestyle and psychosocial factors all have the potential to influence pain sensitivity (Denk, McMahon et al. 2014, Denk and McMahon 2017). While there are known associations between pain sensitivity, and age and sex, it is important to note that these should be seen to "…reflect proxies for mechanisms influencing pain rather than mechanisms themselves" (Fillingim 2017). Here, the sex of a person reflects differing sex-related biological and psychological processes, rather than necessarily being a direct mechanism influencing pain sensitivity (Fillingim 2017). Factors can be defined as intrinsic to the individual, including sex, age and genetics (Denk, McMahon et al. 2014). Biological markers associated with pain reflect differences within individuals and are potentially direct mechanisms influencing pain (Fillingim 2017). Extrinsic factors include psychological considerations and the social context or environment (Denk, McMahon et al. 2014).

2.6.1   Potential mechanisms underlying sex differences in pain sensitivity

Females have consistently been reported to show greater pain sensitivity than men over a wide range of standardised measures of experimental pain sensitivity measures (Mogil 2012, Fillingim 2017). Females are also significantly more likely than males to present with a chronic musculoskeletal pain condition (Fillingim, King et al. 2009, Mogil 2012). There are multiple mechanisms proposed to explain sex differences in pain sensitivity (Mogil 2012, Fillingim 2017). Ultimately, sex differences in pain sensitivity are hypothesized to exist due to the evolution of different nociceptive modulatory systems influenced by the exposure of males to traumatic pain and females to visceral pain (Mogil

2012). Another influence of sex maybe due to the accepted social mores and expectations about the behavioural expression and reporting of pain, with males socially discouraged from exhibiting pain behaviours and females expected and accepted to behaviourally express pain (Robinson, Riley et al. 2001). Sociocultural reasons may also include different gender roles and societal expectations of genders (Sanford, Kersh et al. 2002, Wise, Price et al. 2002).

Current evidence for mechanisms for sex differences in pain sensitivity is limited, however there are multiple mechanisms proposed (Mogil 2012, Fillingim 2017). The heightened pain sensitivity in females maybe influenced by differences in ascending and descending pain modulation pathways (Popescu, LeResche et al. 2010). Pain modulation may vary due to sex chromosome effects that can influence nociception (Gioiosa, Chen et al. 2008). Endogenous steroids may play a key role in the modulation of pain with evidence for sex steroid-based influences on neurotransmitters that control pain mechanisms (Mensah-Nyagan, Meyer et al. 2009). Evidence for the effects of sex hormones on pain is mixed with animal studies showing conflicting results (Mogil 2012). A meta-analysis that reviewed human studies, investigated the effect of different phases of the menstrual cycle concluding there is a mild to moderate increase in pain sensitivity peri-menstrually and mid-cycle (Martin 2009). However knowledge of the mechanisms of how ovarian hormones influence pain sensitivity is limited (Martin 2009). Oestrogen may be important as receptors are widely distributed with complex interactions in biological processes, including those associated with nociceptive processing (Craft 2007, Ma, Yu et al. 2011).

Sex differences in pain sensitivity may be influenced by the psychological state (such as stress or anxiety) or pain coping strategies by their effect on modulating the nociceptive system (Jackson, Iezzi et al. 2002, Wise, Price et al. 2002, Jones, Zachariae et al. 2003, Edwards, Haythornthwaite et al. 2004, Bartley and Fillingim 2013). For example, catastrophizing is associated with greater report of pain and delayed recovery in pain disorders (Linton, Nicholas et al. 2011, Wertli, Eugster et al. 2014). In a study of college students (n=150), females reported higher pain catastrophizing scores than males (p=0.03) and catastrophizing partially mediated sex differences in cold pain tolerance (p=0.01) (Forsythe, Thorn et al. 2011). Pain coping strategies differ with males tending to use behavioural distraction to manage pain which potentially is reflected by lower pain

sensitivity and females tending to use a range of strategies which potentially drive higher pain sensitivity including social support and techniques that focus on emotion, cognition and attentional focus (Fillingim, King et al. 2009, Racine, Tousignant-Laflamme et al. 2012). While there are sex differences in catastrophizing and coping mechanisms, the biological mechanisms underpinning their influence on pain are speculative (Fillingim 2017). Currently, the putative mechanisms for sex differences in pain sensitivity are complex and current evidence is limited.

2.6.2   Genetic influences on pain sensitivity

There is wide variation of pain sensitivity reported in people without pain (Rolke, Baron et al. 2006, Neziri, Scaramozzino et al. 2011) and a proportion of individual variation in pain sensitivity is related to hereditary factors (Nielsen, Stubhaug et al. 2008, Denk, McMahon et al. 2014). Initial investigation into heritability of pain sensitivity was investigated in animals with several studies using varying pain modalities estimating between 28% to 76% of the variance in pain sensitivity was attributable to genetic differences (Nielsen, Stubhaug et al. 2008). The relevance of animal studies for humans is however unknown. Twin studies have tried to quantify the size of risk for chronic pain accounted for by genetics. There are only a few studies investigating the heritability of pain sensitivity. An adult twin study compared PPT in 269 pairs of monozygotic and 340 pairs of dizygotic twins, finding a statistically non-significant heritability for PPT of only 10% (MacGregor, Griffiths et al. 1997). Another smaller study examined hereditability of cold-pressor pain and contact heat pain in 53 monozygotic and 39 dizygotic twin pairs (Nielsen, Stubhaug et al. 2008). The genetically mediated variance in cold-pressor pain was estimated at 60% and heat pain variance was estimated at 26% (Nielsen, Stubhaug et al. 2008). The differences in hereditability may be partially explained by the different peripheral nervous system mechanisms that are stimulated by the different test modalities. Heat pain stimulates mechano-heat nociceptors (Raja, Meyer et al. 1988). Cold pain stimulates venous nociceptors and the TRP family of peripheral nociceptors (Klement and Arndt 1992, Vriens, Nilius et al. 2014) inducing a significant rise in blood pressure (al'Absi and Petersen 2003), implying sympathetic nervous system involvement in cold nociceptive processing. The cold-pressor pain test involved holding the hand in cold water (0-2.5°C) for a maximum of 60 seconds (Nielsen, Stubhaug et al. 2008). CPT heritability and nociceptive response may vary from cold-pressor pain heritability due to

the exposure to cold at a higher temperature, over a smaller area and for a briefer duration. PPT heritability may be low due to the brief exposure to pain and a relatively small stimulus area compared with the cold-pressor test (Nielsen, Stubhaug et al. 2008).

Nociceptive processing in humans is known to be influenced by several genes (Mogil 2012, Crow, Denk et al. 2013) with emerging data suggesting some specific genetic associations with pain sensitivity. Diatchenko et al (Diatchenko, Slade et al. 2005) identified three variants of the gene encoding COMT that were designated as either low pain sensitivity, average pain sensitivity and high pain sensitivity haplotypes. The presence of the variant of COMT linked with low pain sensitivity decreased the risk of developing jaw pain up to 2.3 times (Diatchenko, Slade et al. 2005). Kim et al (Kim, Mittal et al. 2006) found an association between genetic variations of COMT, receptor A subtype 1, fatty acid amide hydrolyase and cold pain sensitivity. COMT is known to be involved in the regulation of metabolism of key neurotransmitters involved in pain perception including dopamine, epinephrine and norepinephrine (Young, Lariviere et al. 2012). The μ-opioid receptor gene (OPRM1) alters pain sensitivity via influencing opioid receptor function (Young, Lariviere et al. 2012). A study of healthy participants without 'clinical' pain (n=167) investigated the association of polymorphisms of OPRM1 and pain response to experimental pressure pain (Fillingim, Kaplan et al. 2005). A rare allele of OPRM1 that occurred in 24 females and 12 males was significantly associated with higher pressure pain thresholds at the trapezius (p=0.002), masseter (p=0.023) and ulna (p=0.49) compared to those with the common allele. There were no significant associations with heat or ischemic pain stimuli. Using healthy, pain-free subjects (n=390), Tegeder et al (Tegeder, Costigan et al. 2006) investigated the association between heat, ischemic and pressure pain sensitivity and variations of the human gene encoding GTP cyclohydrolase (GCH1). GCH1 influences the rate of biosynthesis of serotonin, dopamine, norepinephrine, epinephrine, and nitric oxide, which all play a role in nociceptive processing (Young, Lariviere et al. 2012). A protective nociceptive haplotype was significantly associated (p=0.006) with less pressure pain sensitivity but not with heat (p=0.25) and ischemic pain (p=058). Two birth cohorts showed a genetic variant in the beta-2 adrenergic receptor (ADRB2) but not COMT, displaying an association with chronic disabling widespread pain (Hocking, Smith et al. 2010, Skouen, Smith et al. 2012). However, these two studies did not investigate the association with pain sensitivity. In a systematic review, Limer et al (Limer, Nicholl et al. 2008) found nine genes showing an

association with pain sensitivity without definite results and these authors concluded that more investigation was warranted, particularly with better information on pain status and potential psychological and environment confounders.

2.6.3 Mechanisms for variation of pain sensitivity in people with non-neuropathic musculoskeletal pain

2.6.3.1 Different nervous system mechanisms modulating pressure versus cold stimuli

The putative mechanisms discussed here that underpin pain sensitivity will focus on non-neuropathic musculoskeletal pain. Mechanisms that modulate pain sensitivity can occur at any stage of nociceptive processing, from peripheral nociceptors through to the nociceptive regulating mechanisms (facilitatory and inhibitory) in the spinal cord and higher centres in the brain. In the periphery, noxious pressure and cold stimuli of adequate intensity stimulate both medium diameter myelinated Aδ and small diameter unmyelinated C peripheral nociceptive fibres. Once a stimulus reaches the noxious range, affected nociceptive fibres stimulate their corresponding CNS neurons in the dorsal horn of the spinal cord (or cervico-trigeminal nucleus in the case of head and face pain), brain stem and widespread cortical areas in the brain (Beissner, Brandau et al. 2010). Modulation of nociception within the CNS occurs once nervous system activity reaches the dorsal horn and this is a very important mechanism modulating nociceptive input to higher centres potentially influencing an emergent pain experience (Woolf 2011, Cohen and Mao 2014).

Mechanical stimuli create a sensation of local pressure, that if sufficient, excites nociceptors in deep somatic tissues such as muscles, fascia and aponeuroses, plus superficial cutaneous nociceptors (Graven-Nielsen 2006). Studies in humans suggest blunt pressure applied via an algometer, stimulates Aδ fibres and C nerve fibres from deep tissue (Graven-Nielsen 2006, Beissner, Brandau et al. 2010).

In contrast, non-noxious cold stimuli stimulate superficial Aδ nerve fibres and noxious cold stimulate superficial C nerve fibres (Chong and Cros 2004, Chien, Eliav et al. 2009). The nociceptive apparatus includes receptors that are individually tuned sensory cells coded to specific stimuli (Vriens, Nilius et al. 2014). There are different cutaneous thermosensitive neurons that respond specifically to heat or cold, with a skin

temperature of approximately 33°C considered to be thermoneutral (Vriens, Nilius et al. 2014). Various types of ion channels have been identified as sensitive to cold, including transient receptor potential (TRP) channels (Vriens, Nilius et al. 2014). Using TRP antagonists to block receptors alters the ability to perceive cold and can influence pain sensitivity (Vriens, Nilius et al. 2014). There is evidence cold pain in humans is mediated via nociceptors of cutaneous veins (Klement and Arndt 1992) with cold stimuli affecting the sympathetic nervous system inducing increases in blood pressure and eliciting a cortisol response (al'Absi and Petersen 2003). The sympathetic nervous system is involved in central nociceptive processing and can be sensitized by the stress regulation system, particularly by the hypothalamic-pituitary-adrenal (HPA) axis and subsequent alteration of circulating cortisol levels (McEwen 1997, Nees, Löffler et al. 2019).

There is some evidence suggesting the involvement of the sympathetic nervous system in heightened cold pain sensitivity. Increased cold pain sensitivity has been associated with sympathetic nervous system impairment in people with WAD, providing evidence for sympathetic nervous system disruption in the presence of cold hyperalgesia (Sterling, Jull et al. 2003). In young female adults of the Raine Study (22-year follow-up, n=432) 'severe' menstrual pain severity (visual analogue scale pain rating, 8-10) or 'mixed' menstrual pain severity (visual analogue scale pain rating, 8-10) was associated with increased cold pain sensitivity (measured at the wrist, i.e., remote from the pelvis) after adjusting for potential confounding variables including musculoskeletal pain (Slater, Paananen et al. 2015). The changes in cold pain sensitivity reported were suggested to reflect altered central nociceptive processing due to disruption of thermosensation and thermoregulation which are modulated by central systems regulating homeostasis (Vriens, Nilius et al. 2014, Slater, Paananen et al. 2015).

2.6.3.2 Peripheral nervous system mechanisms modulating pain sensitivity

Sufficient injury, infection, trauma or inflammation typically results in the activation and sensitization of peripheral nociceptors. Nociceptors possess biophysical and molecular properties that enable them to respond differentially to noxious stimuli (Basbaum, Bautista et al. 2009) resulting in the release of various chemical mediators including kinins, amines, prostanoids, cytokines, growth factors and chemokines that unite tissue responses (Woolf and Ma 2007). Specific chemical mediators decrease the

nociceptor threshold and increase the responsiveness of the nociceptor terminal resulting in hyperactivity of the nervous system to promote guarding and promote healing of the injured, infected or inflamed area (Woolf and Ma 2007, Basbaum, Bautista et al. 2009). In addition, the cell bodies of the nociceptive neurons in the dorsal root ganglion respond to the peripheral noxious events, with a graded response that may involve the transcription of neuropeptides, brain-derived neurotrophic factor and sodium channels augmenting central transmission of nociceptive signals and underlying the phenomenon of peripheral sensitization (Mannion, Costigan et al. 1999). Activation of the immune system can also be triggered in this process, with specific chemicals binding to immune-competent cells including macrophages, T-cells and mast cells (Sandkühler 2017). For example, in the case of inflammation, mast cells respond by releasing pro-inflammatory cells including cytokines, serotonin and histamine (Sandkühler 2017). In addition to noxious stimuli creating action potentials in C-fibres that conduct orthodromically towards the CNS, antidromic axon reflexes are generated inducing the release of molecular mediators that have inflammatory actions (Chiu, von Hehn et al. 2012). When there is sufficient duration and magnitude of nociceptive input that will typically activate NMDA receptors (Latremoliere and Woolf 2009), these pro-inflammatory cells can further sensitize peripheral nociceptive C-fibres resulting in the amplification of nociceptor signals (Basbaum, Bautista et al. 2009). In addition these receptor pathways that involve inflammatory cells, also trigger innate immune cells resulting in the PNS directly communicating with the immune system and coordinating the non-neuronal components of the inflammatory response to underpin sensitisation (Chiu, von Hehn et al. 2012). The coordinated response of the neuronal and non-neuronal cells is considered to be triggered by neuronal activity and is called 'neurogenic inflammation' (Chiu, von Hehn et al. 2012).

2.6.3.3 Central nervous system mechanisms modulating pain sensitivity at spinal levels

In parallel, increased neuronal activity from primary afferents results in similar inflammatory reactions in the CNS, including at the dorsal horn, to those exhibited in the periphery regarding 'neurogenic inflammation'. These central events are described as 'neuroinflammation' and involve the recruitment of immune cells, such as microglia and astrocytes, that are not present in peripheral tissue, as well as vascular responses to

inflammation (Sandkühler 2017). Activity dependent changes to synaptic plasticity in the dorsal horn correspond to enhanced membrane excitability, increased facilitation or reduced inhibition of synapses in nociceptive pathways (Latremoliere and Woolf 2009). Nociceptive C-fibres are dominated by input from monosynaptic and polysynaptic synaptic potentials from nociceptors in their receptive field, however they typically have additional input from low-threshold afferents (e.g. light touch Aß fibres) and from nociceptive C-fibres that come from outside their normal receptive fields (Latremoliere and Woolf 2009).

Neuroinflammation and subsequent changes in the dorsal horn, convert nociceptive-specific neurons to wide-dynamic neurons allowing access of low-threshold afferents to CNS nociceptive specific neurons (Latremoliere and Woolf 2009). This underlies allodynia where innocuous stimuli such as light touch or cold, normally perceived as not painful can be perceived as painful (Latremoliere and Woolf 2009). Additionally, wide dynamic neurons respond to an area beyond the normal receptive field of that neuron (secondary hyperalgesia) and stimuli that are normally painful can elicit pain of greater intensity (hyperalgesia) (Latremoliere and Woolf 2009). These synaptic changes are also referred to as heterosynaptic potentiation, noxious input from a set of synapses augments subsequent activity in other, non-activated groups of synapses (Latremoliere and Woolf 2009). Neuroinflammation results in longer lasting changes in the CNS, pain can be triggered by less intense inputs and CNS changes can be maintained by a lower level or different type of input (Latremoliere and Woolf 2009). Homosynaptic potentiation on the other hand is facilitation of a synapse that is evoked by activation of that same synapse and this type of facilitation contributes to primary hyperalgesia (pain sensitivity occurring directly in the damaged tissues) (Latremoliere and Woolf 2009).

Prolonged stimulus of Aδ and C nociceptors has been show to result in lower mechanical and temperature thresholds (Basbaum, Bautista et al. 2009), reflecting the plasticity of the neuronal tissues to activity-dependent somatosensory inputs. The normal healing response results in the resolution of the peripheral inflammation and gradual return of the nociceptive apparatus and nociceptor thresholds to pre-injury levels.

2.6.3.4 Central nervous system mechanisms modulating pain sensitivity at supraspinal levels

Excitation of peripheral nociceptive fibres leads to activation of synapses in the dorsal horn of the spinal cord, and transmission of nociceptive information via second order neurones to the brain stem and cortex with potentially concurrent recruitment of descending inhibitory controls. This means that nociceptors are constantly under real-time regulation (facilitation and inhibition) from higher centres with the potential to alter nociceptor sensitivity. Ultimately, these complex neuronal filtering and modulation processes may result in the experience of pain, as one possible outcome (Woolf 2011) if the brain evaluates this input as dangerous (Moseley and Butler 2015). When the brain perceives input as dangerous or threatening, descending facilitation can increase sensitivity of spinal nociceptors and if the brain perceives input as not dangerous, then descending inhibition decreases sensitivity of spinal nociceptors (Moseley and Butler 2015). Consequently, current models of pain consider a widely-distributed brain network model with the brain acting as a start point with ascending input being modulated and influencing further input (Moseley and Butler 2015). Put simply, if the brain perceives the body is in danger and requires protecting, it will increase the likelihood and intensity of pain and if the brain perceives the body is safe it will decrease the likelihood and intensity of pain (Moseley and Butler 2015).

The processing of nociception in higher centres is complex, highly individual and includes a widely distributed and interconnected neural network that is tightly regulated. Key areas include: the anterior cingulate cortex which is involved in attention to pain, anticipation of pain and motor responses; the insular cortex plays a role in the affective aspects of pain contributing to emotional responses and pain behaviours; the prefrontal cortex which helps sensory integration via decision making, retrieving memories and processing attentional aspects of pain and; the limbic system including the amygdala and hippocampus is involved in the storage of emotional memories affecting attention to pain and fear that accompanies pain (Bornhovd, Quante et al. 2002, Jaggi and Singh 2011).

2.6.3.5 Central nervous system mechanisms for ascending and descending modulation of pain sensitivity

The widely-distributed brain network model and subsequent modulation of nociception can help to make sense of how the brain modulates pain sensitivity. The

ascending somatosensory system is modulated in the spinal cord by endogenous descending, inhibitory modulation mechanisms (Melzack and Wall 1965). Descending modulation refers to pathways that descend from the brain to the dorsal horn in the spinal cord modifying the processing of somatosensory information such that reactions to somatosensory stimuli are altered, resulting in either increased or decreased nociceptor sensitivity (Cohen and Mao 2014). Conditioned pain modulation (CPM) testing represents is a proxy measure of descending pain modulation pathways. CPM is measured via instructing participants to report the intensity of a primary noxious stimulus in the presence and absence of a secondary noxious stimulus (Yarnitsky, Granot et al. 2014). A reduced response to the CPM test is thought to possibly represent impaired function of endogenous pain-inhibitory systems that act via serotonergic and noradrenergic systems (Nir, Granovsky et al. 2011, Vaegter, Handberg et al. 2016). An impaired CPM response has been demonstrated in pain conditions including FMS (Kosek and Hansson 1997, Lautenbacher and Rollman 1997), chronic WAD (Daenen, Nijs et al. 2013), OA (Arendt-Nielsen, Andresen et al. 2012) and LBP (Correa, Costa et al. 2015). Alternatively, repeated or sustained nociceptive stimulus can amplify pain and can be measured by temporal summation (TS) (Cohen and Mao 2014). A meta-analysis examining TS and CPM in participants with FMS examined twenty-three studies (625 females/23 males with FMS and 591 females/81 males as healthy controls) reporting a TS relative difference of 68% between participants with FMS and healthy controls (effect size 0.53, $p<0.001$, 95% CI 0.23-0.83) and a 65% relative difference for CPM (effect size 0.53, $p<0.001$, 95% CI 0.23-0.83) (O'Brien, Deitos et al. 2018). The meta-analysis highlights FMS has both increased facilitation and impaired descending inhibition of nociceptive input. However, modulation of nociceptive input varies between conditions.

2.6.4 Mechanisms for modulation of pain sensitivity by stress

Another mechanism underlying variation in pain sensitivity involves the homeostatic regulation of stress (Nees, Löffler et al. 2019). The activity and responsiveness of the HPA axis can mediate the relationship between pain sensitivity and stress (McEwen and Kalia 2010). Adaption to stressors occurs by tight coordination and regulation of the autonomic, neuroendocrine and immune biologic systems (McEwen and Kalia 2010). Hormones of the HPA axis are involved, being activated in response to either physical or emotional stress, and ultimately stress may result in the release of cortisol from the adrenal cortex (McEwen and Kalia 2010). A majority of studies support the HPA axis

acting as a self-regulating negative feedback system with the expression of cortisol due to stress a significant marker of HPA axis and stress regulation function (Nees, Löffler et al. 2019). Cortisol levels also respond to emotional stress and associations between elevated psychological stress levels and several chronic pain syndromes have been reported (Vachon-Presseau 2018). Chronic stress can result in increased pain sensitivity and lower cortisol response to stress via dysfunctional activity and responsivity of the HPA axis may be an important mediator.

A study using Raine Study participants (n=805) investigated the association of cortisol response to stress, musculoskeletal pain and pain sensitivity (Paananen, O'Sullivan et al. 2015). At 18-years of age, HPA axis function was evaluated using the Trier Social Stress Test and cortisol data were analysed using a group-based trajectory modelling approach. A three-group model was the best fit for the data with the cortisol response of the participants classified as hypoactive, normal or hyperactive. Pain sensitivity was measured at 22-years of age with PPT and CPT measures using methodologies analogous to those used in the studies for this thesis. Females with cold pain sensitivity above the median (median CPT =15°C) demonstrated an association of a hypoactive cortisol response to the Trier Social Stress Test at 18-years with increased severity of pain problems at 22-years (OR 2.3, 95% CI 1.0-5.0) and any musculoskeletal pain (OR 2.8, 95% CI 1.1-6.8). Females with the hypoactive cortisol response also demonstrated higher likelihood of increased severity of pain problems if PPT was below the median (median PPT=318kPa; OR 3.5, 95% CI 1.3-9.7). Lower cortisol levels are observed more often in females than males, possibly providing some explanation of the higher prevalence of pain disorders in females (Kudielka and Kirschbaum 2005) and the lack of significant results for males in the above study (Paananen, O'Sullivan et al. 2015).

Three other studies have demonstrated similar findings, reporting an association of a hypoactive cortisol response with the report of musculoskeletal pain and increased pain sensitivity (Kuehl, Michaux et al. 2010, Godfrey, Strachan et al. 2014, Nees, Löffler et al. 2019). The hypoactive cortisol responses, representing lower cortisol levels, potentially effects pain sensitivity by reduced repression of pro-inflammatory genes thereby increasing sensitization within the peripheral and central nervous system (Cruz-Topete and Cidlowski 2015). Other studies have shown conditions such as FMS and CFS are associated with lower cortisol levels and higher levels of pro-inflammatory cytokines partially explaining the hyperalgesia associated with these conditions (McEwen 2010).

The HPA axis is an important mediator of the relationship between stress and pain sensitivity (McEwen and Kalia 2010). In acute situations it facilitates tissue healing responses and stimulates a rapid response to threat in conjunction with neuronal and immune systems (Vachon-Presseau 2018) including lowering pain sensitivity enabling escape from danger (Nees, Löffler et al. 2019). Prolonged stress can result in HPA axis dysfunction chronically lowering cortisol levels and responses (McEwen 2008), along with heightening pain sensitivity (Paananen, O'Sullivan et al. 2015, Nees, Löffler et al. 2019).

2.6.4.1 Mechanisms for future pain sensitivity being modulated by early life stress

Early life, antenatally and in the first 3 years postnatally, is a critical developmental period when biological systems undergo maturation and associated changes can become enduring (Maniam, Antoniadis et al. 2014, Agorastos, Pervanidou et al. 2019). Early life stress (ELS) represents any threat to an organism's homeostasis, in early life, which induces a physiological response in biological systems (Maniam, Antoniadis et al. 2014). Prolonged or repetitive activation of stress response systems, particularly during the critical early life period, can alter developmental trajectories and induce changes in stress reactivity in adulthood (Musazzi and Marrocco 2016). Emerging data suggest that ELS can potentially increase future pain sensitivity through biological, psychological and social pathways (Cole 2013, Nelson, Cunningham et al. 2017). ELS can increase vulnerability to future pain sensitivity and pain events, and potentially increasing the risk of poorer health outcomes (Denk, McMahon et al. 2014, Denk and McMahon 2017, Nelson, Cunningham et al. 2017, Agorastos, Pervanidou et al. 2019).

Multiple factors could manifest as ELS directly (for example significant life stress events), are proxies for ELS (for example income) or are consequences of ELS (for example child behaviour). Socioenvironmental conditions during early life can be considered as ELS, such as exposure to smoking, multiple stressful events, financial stress, poor family functioning and less breastfeeding, and these are all associated with poorer health outcomes into adolescence and adulthood (Gupta, Silman et al. 2007, O'Sullivan, Straker et al. 2008, Robinson, Oddy et al. 2008, Robinson, Mattes et al. 2011). ELS may also manifest as problematic behaviours (Robinson, Oddy et al. 2008, Robinson, Mattes et al. 2011).

Findings from both basic animal studies, human experimental pain studies and clinical studies provide some insights into the role of ELS on pain sensitivity. Data from animal studies on the effect of early life social stressors, reveal alterations in adult biological processes mediated via complex interactions between epigenetic, endocrine and immune systems (Zhang, Labonté et al. 2013). One example is better quality of parental care by rat mothers improving stress responses in adult rats (Zhang, Labonté et al. 2013). Socioenvironmental conditions perceived as threatening, stressful, socially isolated or uncertain create a transcriptional response inducing up-regulation of pro-inflammatory genes and down-regulation of antibody and antiviral related genes (Irwin and Cole 2011). These changes in immune-cell gene response provide an understanding of why social adversity could be associated with inflammatory related common diseases such as neoplastic, cardiovascular, metabolic and musculoskeletal (Irwin and Cole 2011, Cole 2013). A pro-inflammatory state can prime the nervous system ultimately increasing the risk for persistent pain (Denk and McMahon 2017, Karshikoff, Tadros et al. 2019).

In humans, current evidence suggests ELS alters corticosteroid regulation of stress via changes to the HPA axis that are partially mediated by epigenetic mechanisms (Zhang, Labonté et al. 2013). A meta-analysis assessed the effect of early life adversity on cortisol response to social stress in individuals (n=4292) of varying ages (Bunea, Szentagotai-Tatar et al. 2017). The results support an association (moderate effect size: g=-0.39) between early life adversity and a hypo-responsive cortisol response to social stress. This is important in the context of emerging evidence that a hypo-responsive HPA-axis is associated with higher pain sensitivity (Kuehl, Michaux et al. 2010, Paananen, O'Sullivan et al. 2015, Nees, Löffler et al. 2019).

Psychological and physical stressors can affect the gut microbiome and there is strong speculation changes to the gut microbiome, including via ELS, increases future vulnerability to anxiety, depression and chronic pain (Mayer, Knight et al. 2014). Additionally, the gut microbiome and brain interactions are a mechanism that can potentially influence pain sensitivity by effecting the regulation of nociception (Cryan and Dinan 2012, Mayer, Knight et al. 2014).

Childhood maybe a key window for identifying predictors of future pain and targets for intervention (Incledon, O'Connor et al. 2016). Current emerging evidence, along with plausible mechanisms suggest early pain experience or early life adversity can change adult

nociceptive processing and molecular processes potentially increasing a person's risk of developing future persistent pain (Denk, McMahon et al. 2014, Denk and McMahon 2017).

2.6.4.2 Evidence for future pain sensitivity being modulated by early life experience

Current evidence suggests early life is a critical stage of development that can significantly influence future pain sensitivity and subsequent pain experience (Denk, McMahon et al. 2014). Animal studies reveal alteration in adult pain sensitivity from early life environmental adversity. For example ELS induced via unpredictable maternal separation induced visceral hypersensitivity in adult mice (Moloney, O'Leary et al. 2012). Rats who experienced a hind-paw incision injury at 3 days of age, exhibited hyperalgesia following incision in adulthood compared to rats without exposure to an early life pain experience (Beggs, Currie et al. 2012). The prior injury also resulted in an enhanced neuroimmune response following incision in adulthood measured by increased intensity, spatial distribution and duration of the dorsal horn microglial response.

Human studies report long-term changes in pain sensitivity following exposure to neonatal pain. One study investigated pain sensitivity (hyperalgesia was defined by the need for more intraoperative fentanyl, higher postoperative COMFORT 'behaviour' scale and VAS scores, greater epinephrine plasma concentrations and more postoperative morphine compared with infants with no prior surgery) in infants (n=164) undergoing major abdominal or cardiac surgery (Peters, Schouw et al. 2005). Infants were allocated to one of three groups based on undergoing surgery for the: first time (control groups, n=129); second time but not in the same dermatome as their first operation (n=13) or; second time in the same dermatome as their first operation (n=22). Post-surgery, infants who were operated on in the same dermatome had significantly higher COMFORT and VAS scores than the other two groups. They had greater epinephrine plasma concentrations and required more morphine than the control group. Infants who had surgery in another dermatome had significantly greater analgesic requirements and epinephrine plasma concentrations when compared with the control group. The results suggest that the higher pain sensitivity in those who had the second operation in the same dermatome was modulated by the combination of spinal and supraspinal mechanisms, compared to the group who had the second operation not in the same dermatome where the pain sensitivity was modulated by only supraspinal mechanisms.

Another study investigated pain sensitivity using a cold pressor test to assess pain threshold, tolerance and intensity, in adolescents (average age = 19 years, n=412) who were born at a gestational age less than 32 weeks or with a birth weight less than 1,500g (Van Ganzewinkel, Been et al. 2017). Participants who had experienced a painful condition as an infant (necrotizing enterocolitis, n=30) had significantly higher CPT (hazard ratio 1.47; 95%CI 1.01-2.14) and cold pain tolerance (hazard ratio 1.63; 95%CI 1.09-2.41). These two studies suggest long-term changes in nociceptive processing at spinal and supraspinal levels following a significant pain experience.

Other studies have shown contradictory results. A cohort study performed QST at 11 years on participants born extremely pre-term (<26weeks, n=43) and in controls (term-born, age and sex matched, n=44) (Walker, Franck et al. 2009). Cool, cold, warm and hot sensation detection was tested on the thenar eminence of the non-dominant hand. Thermal perception was less sensitive for cold (cold detected at a lower temperature) and hot (hot detected at a higher temperature) for pre-term children when compared with controls (p<0.01). The result did not test pain sensitivity due to the age of participants and this may account for the contradictory result compared with the previous studies. The same cohort were re-examined aged 18-20 years with QST (including PPT and CPT) at the thenar eminence and chest wall (Walker, Melbourne et al. 2018). There was less pain threshold sensitivity to pressure and cold in pre-term males who had neonatal surgery (P<0.01) but increased sensitivity to prolonged noxious cold in pre-term females who had neonatal surgery (P<0.01). The results suggest sex-dependent patterns of alterations in pain sensitivity persisted into early adulthood.

In conclusion, current literature suggests ELS can alter biological systems into adulthood. ELS can have an effect on pain sensitivity into adulthood, suggesting early life experience should be considered when evaluating pain sensitivity, pain experience and risk for persistent pain.

2.6.5 Potential mechanisms for the association between physical activity and pain sensitivity

There are several mechanisms hypothesized to be responsible for changes in pain sensitivity via exercise (Koltyn, Brellenthin et al. 2014, Sluka, Frey-Law et al. 2018). Potential direct mechanisms involve recruitment of endogenous pain inhibition;

including opioid (beta-endorphin) and non-opioid (e.g. serotonin, norepinephrine, endocannabinoid) systems (Millan 2002, Fuentes C, Armijo-Olivo et al. 2011). The endogenous pain system is the body's innate pain relieving system, with opioids and non-opioids produced via the nervous system to act as neurotransmitters and neuromodulators to induce analgesia (Holden, Jeong et al. 2005). Endogenous pain inhibition with PA or EIH can be demonstrated by an increase in PA being associated with a decrease in pain sensitivity.

Higher intensity or vigorous PA is known to increase circulating beta-endorphins in the blood (Angelopoulos 2001). Beta-endorphin levels in the blood demonstrate significant increases after exercise in endurance trained runners after a 110km race (Fournier, Stalder et al. 1997), in twins following thirty minutes of anaerobic treadmill exercise (Di Luigi, Guidetti et al. 2003) and in endurance athletes following thirty minutes of sub-maximal treadmill exercise (Farrell, Gates et al. 1982). Some studies found no increase of plasma endorphin levels with PA and these findings were probably related to the moderate intensity of exercise used (Elias, Iyer et al. 1986, Langenfeld, Hart et al. 1987). The increase in concentration of opioids during exercise shows high inter-individual variation, while resting levels fail to demonstrate any difference between trained and untrained individuals (Bender, Nagy et al. 2007).

Koltyn (Koltyn, Brellenthin et al. 2014) using short duration low intensity (25% MVC) isometric exercise in healthy pain free people (n=58, 50% male, mean age = 21) investigated opioid and endocannabinoid mechanisms of EIH. Pressure and thermal pain sensitivity decreased following exercise with males and females having an equivalent response. A double-blind administration of either an opioid antagonist or placebo post-exercise did not result in significant differences in pain sensitivity, potentially indicating a non-opioid mechanism in EIH. However, blood opioid concentration was not measured, and it cannot be certain whether the short protocol low intensity isometric exercise was enough to activate an opioid response. Circulating endocannabinoid concentration significantly increased following exercise suggesting potential of a non-opioid mechanism in EIH. Another study using healthy participants (n=100 demonstrated significantly decreased pain sensitivity to electrical stimulation and elevation of plasma endorphins (opioids) and non-opioids with exercise (Droste, Greenlee et al. 1991). However,

administration of an opioid antagonist failed to alter pain thresholds suggesting altered pain thresholds with PA are not directly related to plasma endorphin levels.

A systematic review on the physiological effects of exercise therapy on the endogenous pain system in people with musculoskeletal pain only found 1 relevant study of low methodological quality (Fuentes C, Armijo-Olivo et al. 2011). The study reported an increase in serotonin levels following low intensity spinal stabilisation exercises in participants with chronic low back pain (Sokunbi, Watt et al. 2007). The review concluded there is very limited evidence to show effects of exercise on levels of circulating pain relieving peptides (opioids and non-opioids) in patients with musculoskeletal pain (Fuentes C, Armijo-Olivo et al. 2011). Further study is required to investigate the effects of varying intensities of exercise on the release of pain-relieving peptides in pain populations.

Although the studies above suggest potential short-term mechanisms for EIH, long-term changes in pain sensitivity in response to exercise, including the dose and type of exercise to achieve optimal changes in pain sensitivity, are of interest for pain management. The brain has areas linked with nociceptive processing and systemic pain modulation (Woolf 2011). When compared with pain free participants, patients with persistent pain show changes in similar areas of the brain related to upregulation of pain and downregulation of endogenous pain inhibition (May 2008, Moseley 2008, Wand, Parkitny et al. 2011). For example, FMS patients demonstrate significant less grey matter volume in pain related areas of the brain without global grey matter atrophy (Robinson, Craggs et al. 2011).

Using magnetic resonance spectroscopy to detect alterations in biochemistry in the anterior cingulate cortex, prefrontal cortex and thalamus, which are nociceptive processing regions of the brain, patients with LBP (n=32) were compared to healthy participants (n=33) (Siddall, Stanwell et al. 2006). The comparison was able to discriminate between subjects with LBP and healthy controls with accuracies of 100%, 99% and 97% using spectra from the anterior cingulate cortex, thalamus and pre-frontal cortex respectively.

FMS patients, where CNS processing of nociceptive input is said to be altered, have been investigated to see if there is a relationship between PA and brain responses to painful stimuli (McLoughlin, Stegner et al. 2011). Thirty-four female participants (n=16 FMS, n=18 controls) had their activity assessed via self-report and accelerometer measures, and

underwent functional magnetic resonance imaging (fMRI) during the application of a painful heat stimulus. The FMS patients were split into a high and low activity group via a median split based on self-report of activity. Brain responses, measured via fMRI, were significantly different in between FMS patients categorized as low active (n=8, 28 minutes moderate activity/day self-reported) and high active (n=8, 115 minutes moderate activity/day). The high active group had significantly lower pain ratings to heat stimuli. Greater PA was related to more efficient brain responses in pain regulatory regions, suggesting a greater capacity to engage endogenous pain modulatory networks. Less PA was related to increased brain responses in sensory/discriminative regions of the brain, suggesting an association of giving more attention to nociceptive input with increased PS. A similar study (Ellingson, Shields et al. 2012) used female participants (n=11) with FMS who completed accelerometer measures of PA and underwent fMRI during the application of a painful heat stimulus. The results suggested greater PA was significantly (P<0.005) related to improved CNS regulation of nociception in the dorsolateral prefrontal cortex, the dorsal posterior cingulate and the periaqueductal grey. Improving function in areas of the brain related to better pain modulation is potentially a mechanism that partially explains a relationship between PA and sustained changes in pain sensitivity. However, the current studies have limited numbers, largely test females and have tested relatively sedentary individuals with limited consideration of the potential influence of sedentary behaviour.

The variable association of PA with pain sensitivity in participants with pain is thought to be due to the altered functioning of the endogenous pain system during an increase in physical activity. The short-term response of pain sensitivity to PA is variable. Participants with chronic fatigue syndrome or FMS can exhibit an increase in pain sensitivity during or directly after aerobic or isometric exercise suggesting dysfunctional pain inhibitory mechanisms resulting in hyperalgesia following exercise as opposed to EIH (Whiteside, Hansen et al. 2004, Staud, Robinson et al. 2005, Lannersten and Kosek 2010, Meeus, Roussel et al. 2010). Absence of EIH has also been demonstrated in people with chronic pain (Cook, Stegner et al. 2010, Lannersten and Kosek 2010, Van Oosterwijck, Nijs et al. 2012). The above findings are in contrast to PA being associated with decreased pain sensitivity and effective EIH in participants with FMS when the exercise was of a lower intensity (Kadetoff and Kosek 2007, Newcomb, Koltyn et al. 2011) or less duration (Staud, Robinson et al. 2010). Chronic low back pain patients also demonstrated decreased pain sensitivity with PA (Meeus, Roussel et al. 2010).

As well as physiological changes as a direct result of PA influencing pain sensitivity, there are other factors that may be influenced by PA and these factors may consequently indirectly influence pain sensitivity. Sleep maybe one of these factors. In adults (n=3,081) whose PA was assessed by accelerometry, those who did not meet PA guidelines compared with those meeting PA guidelines, after controlling for age, BMI, health status, smoking status and depression, the relative risk of feeling overly sleepy during the day compared to never feeling sleepy during the day increased by a factor of 0.65 (95% CI: 0.44-0.97) (Loprinzi and Cardinal 2011). Adolescents (n=14,782), when subjectively measured PA met weekly guidelines for MVPA (physically active for ≥60 minutes, 7 days per week), had higher odds (1.67, 95%CI 1.46, 1.91) of sufficient sleep (≥ 8 hours of sleep) than those who were not physically active for ≥60 minutes on any day (Foti, Eaton et al. 2011). Those who were physically active for ≥ 60 minutes on 4 days per week still had significantly higher odds (1.31, 95%CI 1.09-1.58) of sufficient sleep than those who were not physical active for ≥60 minutes on any day. There are a number of studies demonstrating a significant association of poorer quality sleep with increased pain sensitivity (Hurtig, Raak et al. 2001, Chiu, Silman et al. 2005, Lee, Chibnik et al. 2009, Smith, Wickwire et al. 2009). Disturbed sleep is considered to alter nociceptive processing (Kundermann, Spernal et al. 2004) and it has been suggested that altered neuro-immunologic pathways are involved (Heffner, France et al. 2011). The links with sleep to PA, pain, health and pain sensitivity are potential indirect mechanisms influencing the association of PA and pain sensitivity.

PA may also indirectly influence pain sensitivity through an association with psychological symptoms or disorders. A literature review reported a positive association with higher PA and lower prevalence and incidence of depression and anxiety disorders (Ströhle 2009). Psychological factors are known to be predictive of pain disorders (Jarvik, Hollingworth et al. 2005, Gupta, Silman et al. 2007) and are better predictors of future disability than biomedical factors in chronic pain (Campbell and Edwards 2009, Walton, Pretty et al. 2009). Increased pressure pain sensitivity has been associated with major depression (Adler and Gattaz 1993, Lautenbacher, Spernal et al. 1999, Hennings, Schwarz et al. 2012). Increased cold pain sensitivity has been associated with major depression (Lautenbacher, Spernal et al. 1999, Klauenberg, Maier et al. 2008). The influence of psychological status on pain sensitivity is being increasingly investigated in people with WAD with some results showing an increase in psychological symptoms being associated

with an increase in pain sensitivity (Sterling, Hodkinson et al. 2008, Wallin, Liedberg et al. 2011) and other results showing no association of psychological status with PS (Scott, Jull et al. 2005, Chien, Eliav et al. 2009, Chien and Sterling 2010, Borsbo, Liedberg et al. 2012). The conflicting results reflect small subject numbers, the different types of subjects investigated and variation in methods. In other pain disorders, the influence of psychological variables on pain sensitivity is largely un-investigated. The link between psychological status and PA, pain and pain sensitivity suggest an indirect mechanism whereby PA could potentially influence pain sensitivity via a psychological effect.

2.6.6 Proposed mechanisms for the relationship between sedentary behaviour and pain sensitivity

Sedentary behaviour has been linked to an increased risk of musculoskeletal pain (Ijmker, Huysmans et al. 2007, Wærsted, Hanvold et al. 2010, Costigan, Barnett et al. 2013) and this may in part be a result of SB leading to increased pain sensitivity. While there has been little investigation into the association of SB on pain sensitivity, there has been some investigation into the effects of SB on metabolic health. During SB the skeletal muscles become inactive and as a result unique cellular responses are initiated that are different from those initiated via PA (Hamilton, Hamilton et al. 2007). The effects of SB on metabolic health appear to be partially mediated by changes in lipoprotein lipase (LPL) activity independent of MVPA levels (Hamilton, Hamilton et al. 2007, Tremblay, Colley et al. 2010). LPL is an enzyme that helps the uptake of triglycerides and glucose into skeletal muscle and adipose tissue (Hamilton, Hamilton et al. 2007). The loss of muscle contraction with SB reduces LPL activity, reducing the capacity of skeletal muscle to use triglycerides and glucose (Bey and Hamilton 2003). LPL activity decreases due to both acute and chronic SB, and results in an increase of circulating triglycerides, decreased high-density lipoprotein cholesterol and increased risk of cardiovascular disease (Hamilton, Hamilton et al. 2007, Tremblay, Colley et al. 2010). The change in LPL levels due to increased SB reveal how SB independent of PA can affect health and it is plausible to expect physiological effects of SB on the nervous system and pain sensitivity.

Sedentary behaviour may influence pain sensitivity indirectly through central obesity. There is a strong positive association between SB and both BMI and waist circumference (Cameron, Welbron et al. 2003). After adjusting for confounders, a positive association

between an increasing waist-hip ratio (WHR) and higher pressure pain sensitivity has been reported in young adults without current pain (Waller 2016). An increase in WHR, which reflects central obesity, is strongly associated with metabolic risk, (Welbron, Dhaliwal et al. 2003, Kuk, Katzmarzyk et al. 2006). Current evidence suggests central obesity increases levels of circulating pro-inflammatory cells and this finding suggests shared underlying mechanisms proposing a role of SB in modulating both pain sensitivity and metabolic health via central obesity (McVinnie 2013, Price, Asenjo et al. 2013).

In addition to the total time spent in SB, the way sedentary time is accumulated could be important for health outcomes. A large (n=4757 adults), multi-ethnic, population-based study used accelerometry to examine the associations of total sedentary time and breaks in sedentary time with cardio-metabolic and inflammatory risk biomarkers (Healy, Matthews et al. 2011). More breaks in sedentary time, independent of total sedentary time and potential confounders, were associated (p<0.05) with lower waist circumference, lower inflammatory marker concentration (C-reactive protein) and improved plasma glucose levels. A smaller (n=168) study using accelerometry had similar findings showing more breaks in sedentary time, independent of total sedentary time and moderate to vigorous PA, is beneficially associated (p<0.5) with a lower waist circumference and improved plasma glucose levels (Healy, Dunstan et al. 2008). The physiological effects of uninterrupted SB indicate mechanisms whereby less unbroken SB could be independently associated with increased PS due to improved central adiposity and lower circulating inflammatory markers.

2.6.7   Summary: putative mechanisms underpinning the variation in human pain sensitivity

There are a wide range of complex mechanisms that account for variation in pain sensitivity to noxious stimuli in people without pain and people with pain. Most studies have used PPT and CPT to explore and show differences between people with and without specific musculoskeletal pain disorders. While the knowledge of mechanisms that account for the variation in pain sensitivity is nascent, current knowledge covers genetic, environmental, biological and psychological mechanisms that can influence pain sensitivity in the individual. Pain sensitivity can change in response to disruption to the homeostasis of the nervous system which is modulated by complex and dynamic

interactions across multiple systems including the peripheral and central nervous systems, neuroimmune and neuroendocrine system and autonomic nervous system.

2.7   Summary and aims

The Western Australian Pregnancy Cohort (Raine) Study[1] is a large, rich data set and provides opportunity to explore gaps in current understanding of pain sensitivity, including providing age-specific normative data and the ability to explore correlates of pain sensitivity in young adults cross sectionally and longitudinally while adjusting associations for multiple, potential confounders including sex (Bartley and Fillingim 2013, Tham, Palermo et al. 2016), psychological factors (Klauenberg, Maier et al. 2008, Slater, Paananen et al. 2015), sleep (Sivertsen, Lallukka et al. 2015), PA and sedentary behaviour (Naugle, Fillingim et al. 2012), anthropometrics (Neziri, Scaramozzino et al. 2011), ethnicity (Ostrom, Bair et al.) and socioeconomic status (Ostrom, Bair et al.). Importantly PA and sedentary behaviour has been measured using accelerometry rather than self-report, which is unusual for a large, longitudinal cohort study.

Additionally, Raine Study participants had data collected during gestation and at multiple time points up to young adulthood allowing investigation of early life influences of pain sensitivity, with the understanding that pain sensitivity may be modifiable at a young age by environmental influences such as ELS, family functioning and socioeconomics (Mustard, Kalcevich et al. 2005, Denk, McMahon et al. 2014, Stickley, Koyanagi et al. 2015, Burke, Finn et al. 2017, Denk and McMahon 2017). An improved knowledge of early life influences of pain sensitivity may help inform more personalised and targeted interventions that potentially lower the future risk for development of persistent musculoskeletal pain. A better understanding of the association between the pain experience and pain sensitivity can also help to characterize the underlying mechanisms and factors that drive persistent musculoskeletal pain disorders. This may contribute to more targeted, mechanism-based interventions that reflect person-centred, multidimensional and modifiable contributions to persistent musculoskeletal pain (Nielsen, Staud et al. 2009, Arendt-Nielsen and Graven-Nielsen 2011, Backonja, Attal et al. 2013, Denk, McMahon et al. 2014).

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[1] http://www.rainestudy.org.au

This doctoral thesis consists of five published studies presented in chapters 3 to 7. The aims of this doctoral thesis are:

1. Study 1 (Chapter 3): assess the intrarater and interrater reliability, including systematic bias, of pressure pain threshold testing by the same method (handheld algometer) and at the same body sites (lumbar spine, tibialis anterior, neck and dorsal wrist) as in the used for the Gen2-22 year follow-up of the Raine Study;

2. Study 2 (Chapter 4): (i) provide sex-specific reference values of pressure and cold pain thresholds in young pain-free adults; (ii) examine the association of potential correlates of pain sensitivity with pain threshold values;

3. Study 3 (Chapter 5): investigate the cross-sectional associations between musculoskeletal pain experience and measures of pressure and cold pain sensitivity;

4. Study 4 (Chapter 6): explore the relationships of physical activity (PA) and sedentary behaviour (SB) with pain sensitivity measured by pressure pain thresholds and cold pain thresholds, considering the presence of single-site and multisite pain and controlling for potential confounders;

5. Study 5 (Chapter 7): evaluate a range of early life stressors (prenatal and first three years) for association with pressure and cold pain sensitivity in Raine participants at age 22, and to investigate if pain experience at age 22 moderated any associations.

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Chapter 3   Reliability of Pressure Pain Threshold Testing in Healthy Pain Free Young Adults

Observational study

Reliability of pressure pain threshold testing in healthy pain free young adults

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HIGHLIGHTS

- Pressure pain threshold measurement is reliable using multiple research assistants.
- This study supports the use multiple research assistants in large cohort studies.
- It is recommended that raters are checked for systematic bias.
- Sample size calculations are provided for evaluating effects of interventions.

ARTICLE INFO

ABSTRACT

Background and aims: Investigation of the multidimensional correlates of pressure pain threshold (PPT) requires the study of large cohorts, and thus the use of multiple raters, for sufficient statistical power. Although PPT testing has previously been shown to be reliable, the reliability of multiple raters and investigation for systematic bias between raters has not been reported.

The aim of this study was to evaluate the intrarater and interrater reliability of PPT measurement by handheld algometer at the wrist, leg, cervical spine and lumbar spine. Additionally the study aimed to calculate sample sizes required for parallel and cross-over studies for various effect sizes accounting for measurement error.

Methods: Five research assistants (RAs) each tested 20 pain free subjects at the wrist, leg, cervical and lumbar spine. Intraclass correlation coefficient (ICC), standard error of measurement (SEM) and systematic bias were calculated.

Results: Both intrarater reliability (ICC = 0.81–0.99) and interrater reliability (ICC = 0.92–0.95) were excellent and intrarater SEM ranged from 79 to 100 kPa. There was systematic bias detected at three sites with no single rater tending to consistently rate higher or lower than others across all sites.

Conclusion: The excellent ICCs observed in this study support the utility of using multiple RAs in large cohort studies using standardised protocols, with the caveat that an absence of any confounding of study estimates by rater is checked, due to systematic rater bias identified in this study.

Implications: Thorough training of raters using PPT results in excellent interrater reliability. Clinical trials using PPT as an outcome measure should utilise a priori sample size calculations.

1. Introduction

Pressure pain threshold (PPT) measurement has been used extensively to investigate pain sensitivity (PS) in pain disorders [1–5]. Additionally, it is increasingly used as an outcome measure for evaluating interventions in musculoskeletal pain [6–11]. There are many potential biopsychosocial influences on PS that have not been comprehensively investigated to date and there is a lack of studies controlling for the multiple factors that potentially influence pain sensitivity. Large epidemiological cohorts provide an ideal opportunity to investigate PS where potential factors

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Keywords: PPT (Pressure pain threshold) Reliability, Multiple raters, Standard error of measurement

3.1 Introduction

Pressure pain threshold (PPT) measurement has been used extensively to investigate pain sensitivity (PS) in pain disorders (1-5). Additionally, it is increasingly used as an outcome measure for evaluating interventions in musculoskeletal pain (6-11). There are many potential biopsychosocial influences on PS that have not been comprehensively investigated to date and there is a lack of studies controlling for the multiple factors that potentially influence pain sensitivity. Large epidemiological cohorts provide an ideal opportunity to investigate PS where potential factors contributing to PS can be examined concurrently. However the logistics of data collection in large cohort studies or randomised controlled trials often require multiple raters (12) raising the potential concern of interrater reliability.

Although previous interrater reliability studies for PPT using algometry have been conducted, these have varied with respect to sites assessed, number of raters examined, reliability statistics reported and degree of standardisation of algometry (1, 13-15). The most comphrehensive PPT reliability study to date reported excellent interrater reliability (1). However, stated limitations of the study were the unknown applicability of the reliability estimates to raters with less training than the participating physiotherapists, and the inability to investigate potential systematic biases by rater.

The purpose of the current study was to assess the reliability of PPT measurement by research assistants (RAs), who were employed to take a range of measures including PPT in a large cohort study of healthy young adults. The study aimed to assess the intrarater and interrater reliability, including systematic bias, of PPT testing by the same method (handheld algometer) and at the same body sites (wrist, leg, cervical and lumbar spine) as in the larger cohort study. Additionally the study aimed to calculate sample sizes required for parallel and cross-over studies for various effect sizes accounting for measurement error.

3.2   Methods

3.2.1   Subjects

The raters were five female RAs collecting data for the Western Australian Pregnancy Cohort (Raine) study. The mean (SD) age, weight and height respectively were 37 (10) years, 64.4 (5.7) kgs and 167 (9) cms. Four raters had obtained a Bachelor of Science degree and one a Bachelor of Arts degree. The RAs had on average 5.4 years' experience of data collection, performing a wide range of physical measures and tests.

A convenience sample of twenty pain-free young adults were recruited from students of the Faculty of Health, Curtin University as test subjects. Subjects were included on the basis that they had not reported wrist, lower leg, neck or low back pain in the previous 3 months. Subjects were excluded if they did not perceive pressure below 1000 kPa during PPT testing. All participants signed an informed consent form prior to testing and basic demographic data consisting of age, weight, sex and height was obtained. All aspects of the study were approved by Curtin University Human Research Ethics Committee.

3.2.2   Study Protocols

Phase 1: Rater training

The raters were formally trained in subject instruction and pressure algometer application for a total of 3 hours over 3 occasions. The algometer (Somedic AB, Sweden) used had a circular contact area of $1cm^2$. Raters were trained in standardizing their rate of pressure application, accurate land marking of test sites, applying pressure perpendicular to the skin and correct handling of the algometer to achieve effectiveness of pressure application, particularly for when a subject had a PPT near the 1,000kPa cut off. Raters were tested in their consistency of pressure application and over five consecutive applications were required to achieve, a rate of 50 kPa/s over a ten second period. The rate of pressure application was considered acceptable if force was applied at a rate of 50 kPa/s +/-10 kPa/s, resulting in a pressure reading of 500kPa +/- 100kPa after 10 seconds. This threshold of variation in the rate of pressure application has been used in previous reliability studies (1, 13).

Phase 2: Reliability testing

Four sites were tested in the following sequence; the dorsal wrist, upper leg, cervical spine and lumbar spine. The wrist was tested at the middle of the dorsal aspect of the wrist joint line. The leg was tested on the muscle belly of tibialis anterior, approximately 2.5 cm lateral and 5cm distal to the tibial tubercle. The neck was tested on the trapezius muscle, at the mid-point between the C7 spinous process and the lateral acromion. The lumbar spine was tested at the erector spinae, 2cm lateral to the L4/L5 interspinous space. The right side was used for all subjects. The test sites were identified by each rater prior to testing and participants were positioned in a standardised manner. The algometer was applied perpendicularly to the skin at each of the four sites tested.

PPT was defined as the moment pressure increased to a point where it first felt uncomfortable or painful. Prior to testing standardised instructions read to participants included, "Pressure will be applied at a gradual rate. Allow the pressure to increase until it reaches a point where it first feels uncomfortable or painful and then press the button. This means the very first onset of discomfort or pain and not the most pressure that you can bear." The pressure started at 0 kPa and increased at a constant rate of 50 kPa/s until pain threshold was reached and the participant terminated the test by pressing a hand held switch. A maximum of 1000 kPa was set for safety purposes.

Testing was performed on one day in a large, temperature-controlled room, with five raters positioned at stations separated by curtains. Subjects rotated between the five raters according to a pre-specified randomised order, with a ten minute rest between stations. Subjects were blinded to their PPT test values, and raters were blinded to other raters test values. The rater who tested a subject first performed three tests at each site (the first allowed familiarization with the testing procedure and was not used for analysis) and two tests on subsequent subjects. A ten second rest was given between tests at the same site.

3.2.3   Statistical Analysis

A-priori power calculation indicated a sample size of 20 participants and 2 tests per tester would provide over 90% power to detect a standard error of measurement exceeding an acceptable limit of 100kPa (16). Data was analysed using IBM SPSS Statistics 21.0 (Chicago, USA). Relative estimates of interrater and intrarater reliability (ICCs) were

calculated using an ICC for absolute agreement estimated under a two-way random effects model, using both measures taken by each rater for intrarater ICCs and the average of the two measures taken by each rater for interrater ICCs. Intrarater ICCs were calculated for each rater. Standard error of measurement (SEM) was used as an absolute estimate of interrater reliability and was calculated for each site as the square root of the mean square error term of the repeated measures analysis of variance test (17), which also assessed systematic differences between raters. Lastly, sample sizes required for parallel and cross-over studies to detect changes or differences from baseline for each testing site adjusted for measurement error were calculated. A range of change or difference from 10 to 30% using the mean of the sample as baseline was adjusted for measurement error using Guyatt's responsiveness index (18) (change divided by the square root of two times the mean squared error term from the repeated measures analysis of variance test). G*Power 3.1 (19) was used for sample size calculations.

3.3   Results

3.3.1   Subjects

20 pain free subjects (50% female) between the ages of 20 to 33 years old were tested. The mean (SD) age, weight and height respectively were 23.3 (3.8) years, 73 (13.3) kgs and 175 (11) cms. The mean (SD) values for PPT at the wrist, leg, neck and back were respectively 472 kPa (146), 501 kPa (183), 413 kPa (133) and 606 kPa (224).

3.3.2   Intrarater reliability

Excellent values for intrarater reliability were obtained at all sites. ICC (absolute) values for the 5 raters ranged from 0.81-0.97 at the wrist, 0.96-0.98 at the leg, 0.92-0.98 at the neck and 0.94-0.99 at the back.

3.3.3   Interrater reliability

Excellent ICC and SEM values for interrater reliability were also obtained at all sites (Table 3.1). Systematic differences were detected between raters at the back (p=.003), neck (p=.013) and leg (p<.001) testing sites but not at the wrist (p=.252). The maximum interrater difference observed was 190 kPa at the leg, 79 kPa at the neck and 129 kPa at the back, with no single rater tending to consistently rate higher or lower than others across all sites.

Table 3.1   Interrater reliability

Site	ICC absolute (95% CI)	SEM (kPa)
Wrist	0.93 (0.87 – 0.97)	84
Leg	0.92 (0.84 – 0.97)	93
Neck	0.92 (0.85 – 0.97)	79
Back	0.95 (0.90 – 0.98)	100

Abbreviations: ICC, intraclass correlation coefficient; CI, confidence interval; SEM, standard error of measurement.

3.3.4   Sample Size Calculation

Table 3.2 presents sample size requirements for a 10 to 30% change in PPT at each test site accounting for measurement error using means of the sample as initial mean values for percentage change calculations.

Table 3.2   Sample size calculations

Site (initial mean value)	% Change	SEM (KPa)	ES	Sample size required for crossover design		Sample size required for parallel design	
				80% power	90% power	80% power	90% power
Wrist (472KPa)	30%	84	1.19	8	10	26	32
	25%	84	0.99	11	13	36	46
	20%	84	0.79	15	19	54	70
	15%	84	0.60	24	32	90	120
	10%	84	0.40	52	68	200	266
Leg (501KPa)	30%	93	1.14	9	11	28	36
	25%	93	0.95	11	14	38	50
	20%	93	0.76	16	21	58	76
	15%	93	0.57	27	35	100	132
	10%	93	0.38	57	75	220	294
Neck (413KPa)	30%	79	1.11	9	11	28	38
	25%	79	0.92	12	15	40	52
	20%	79	0.74	17	22	60	80
	15%	79	0.55	28	37	106	142
	10%	79	0.37	60	79	232	310
Back (606KPa)	30%	100	1.29	7	9	22	28
	25%	100	1.07	9	12	30	40
	20%	100	0.86	13	17	46	60
	15%	100	0.64	22	28	80	106
	10%	100	0.43	45	59	172	230

Abbreviations: SEM, standard error of measurement; ES, effect size (Gyatt's responsiveness index = percentage change divided by the square root of two times the mean square error term from the repeated measures analysis of variance test)

3.4   Discussion

The results of this study demonstrate high intrarater reliability of RAs when measuring PPTs over the four sites. This study adds to existing data and the results compare favourably to previous investigations in pain free subjects. Walton et al (1) and Persson et al (20) found intrarater ICCs of 0.97 and 0.70-0.90 respectively for PPT measurement at the upper trapezius, comparable to the range of ICCs for the 5 raters of 0.92-0.98 in the current study. Walton et al (1) also tested PPT reliability at the tibialis anterior and found an intrarater ICC of 0.94, again comparable to the result of 0.96-0.98 for the raters in this study.

The results of this study also demonstrate high interrater reliability as measured by relative measures (ICCs). The interrater ICCs of 0.95 (95%CI: 0.90-0.98) at the leg and 0.92 (95%CI: 0.85-0.97) at the neck compare favourably to previous reports of Walton et al (1) at these sites for pain free individuals of 0.84 (95%CI: 0.75-0.90) at the leg and 0.79 (95%CI: 0.66-0.87) at the neck. Reliability of PPT measurement at the lumbar spine and dorsal wrist have not been reported previously, and this study confirms high interrater reliability can be achieved at these sites. Other previous reliability studies for PPT have shown high levels of interrater reliability using only 2 raters (1, 14, 21-23) at sites in the upper quarter in pain-free individuals. The current study evaluated raters who were RAs rather than physiotherapists used by Walton et al (1)and Nussbaum et al (14), and provides evidence that with systematic training excellent measures of relative reliability can be achieved by raters of differing backgrounds.

Although interrater ICCs, which are based on rankings, were excellent, these do not highlight the magnitude of between rater variation in measures or any systematic bias. Inter-rater SEM results of 79kPa at the neck and 93kPa at the leg were somewhat higher than Walton et al (1) who reported 53kPa and 59kPa at the neck and leg respectively. We also detected systematic bias, and this might be partly the reason for the higher SEMs in this study. This finding is important with regard to studies seeking to evaluate associations between PPT and other factors, or differences in PPT between pain/disorder groups, using more than one rater. Systematic bias of raters, means that there is the potential that measures of association or difference will be confounded by rater. Therefore, for studies of associations or differences between PPT and other factors using multiple raters, it is

recommended that a sensitivity analysis be performed by adjusting estimates for rater, to avoid confounding of group differences or associations by rater bias.

PPT is increasingly being used as an outcome measure in clinical trials for musculoskeleta pain (6-9). However, only a few studies report a priori sample size calculation (6, 10, 11) (Venancio 2013, Fuentes 2011, Kardouni 2015). For sample size calculations it is advantageous to account for spurious change (i.e. measurement error) to achive sufficient power to detect minimal clinically important changes or differences that exceeds measurement error. Table 3.2 presents a guide for sample size calculations according to percentage change, accounting for measurement error.

3.5 Conclusion

In conclusion, this study established the reliability of PPT measurement using handheld algometry by multiple RAs at multiple body sites. Large studies with sufficient power to identify the many likely multivariable correlates of pain sensitivity are needed, and this often necessitates the use of multiple raters. The sample size calculations presented will assist researchers to determine sample sizes which account for measurement error for interventions using PPT as an outcome measure. The results of this study support the utility of using multiple RAs in large cohort studies using standardised protocols, with the caveat that an absence of any confounding of study estimates due to potential systematic rater bias be checked.

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Chapter 4   Pressure and Cold Pain Threshold References Values in a Large, Young Adult, Pain-Free Population

Clinical pain research

Pressure and cold pain threshold reference values in a large, young adult, pain-free population

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HIGHLIGHTS

- Provides reference pressure and cold pain threshold data for a 'healthy' young adult population.
- The data represent the most comprehensive and robust data available for young adults aged 21–24.
- Statistically significant, independent correlates of pain sensitivity measures are provided.
- The data enable more accurate interpretation of pain sensitivity in clinical pain disorders.
- Provides insight into the complex associations of pain sensitivity for use in future research.

ARTICLE INFO

ABSTRACT

Background and aims: Currently there is a lack of large population studies that have investigated pain sensitivity distributions in healthy pain free people. The aims of this study were: (1) to provide sex-specific reference values of pressure and cold pain thresholds in young pain-free adults; (2) to examine the association of potential correlates of pain sensitivity with pain threshold values.
Methods: This study investigated sex specific pressure and cold pain threshold estimates for young pain free adults aged 21–24 years. A cross-sectional design was utilised using participants ($n = 617$) from the Western Australian Pregnancy Cohort (Raine) Study at the 22-year follow-up. The association of site, sex, height, weight, smoking, health related quality of life, psychological measures and activity with pain threshold values was examined. Pressure pain threshold (lumbar spine, tibialis anterior, neck and dorsal wrist) and cold pain threshold (dorsal wrist) were assessed using standardised quantitative sensory testing protocols.
Results: Reference values for pressure pain threshold (four body sites) stratified by sex and site, and cold pain threshold (dorsal wrist) stratified by sex are provided. Statistically significant, independent correlates of increased pressure pain sensitivity measures were site (neck, dorsal wrist), sex (female), higher waist-hip ratio and poorer mental health. Statistically significant, independent correlates of increased cold pain sensitivity measures were, sex (female), poorer mental health and smoking.
Conclusions: These data provide the most comprehensive and robust sex specific reference values for pressure pain threshold specific to four body sites and cold pain threshold at the dorsal wrist for young adults aged 21–24 years. Establishing normative values in this young age group is important given that the transition from adolescence to adulthood is a critical temporal period during which trajectories for persistent pain can be established.
Implications: These data will provide an important research resource to enable more accurate profiling and interpretation of pain sensitivity in clinical pain disorders in young adults. The robust and comprehensive data can assist interpretation of future clinical pain studies and provide further insight into the complex associations of pain sensitivity that can be used in future research.

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Abstract

Background and aims: Currently there is a lack of large population studies that have investigated pain sensitivity distributions in healthy pain free people. The aims of this study were: (1) to provide sex-specific reference values of pressure and cold pain thresholds in young pain-free adults; (2) to examine the association of potential correlates of pain sensitivity with pain threshold values.

Methods: This study investigated sex specific pressure and cold pain threshold estimates for young pain free adults aged 21 to 24 years. A cross-sectional design was utilised using participants (n=617) from the Western Australian Pregnancy Cohort (Raine) Study at the 22-year follow-up. The association of site, sex, height, weight, smoking, health related quality of life, psychological measures and activity with pain threshold values was examined. Pressure pain threshold (lumbar spine, tibialis anterior, neck and dorsal wrist) and cold pain threshold (dorsal wrist) were assessed using standardised quantitative sensory testing protocols.

Results: References values for pressure pain threshold (four body sites) stratified by sex and site, and cold pain threshold (dorsal wrist) stratified by sex are provided. Statistically significant, independent correlates of increased pressure pain sensitivity measures were site (neck, dorsal wrist), sex (female), higher waist-hip ratio and poorer mental health. Statistically significant, independent correlates of increased cold pain sensitivity measures were, sex (female), poorer mental health and smoking.

Conclusions: These data provide the most comprehensive and robust sex specific reference values data for pressure pain threshold specific to four body sites and cold pain threshold at the dorsal wrist for young adults aged 21-24 years. Establishing normative values in this young age group is important given that the transition from adolescence to adulthood is a critical temporal period during which trajectories for persistent pain can be established.

Implications: These data will provide an important research resource to enable more accurate profiling and interpretation of pain sensitivity in clinical pain disorders in young adults. The robust and comprehensive data can assist interpretation of future clinical pain studies and provide further insight into the complex associations of pain sensitivity that can be used in future research.

Keywords: reference values; pain thresholds; pain sensitivity; quantitative sensory testing; Raine Study

4.1   Introduction

Quantitative sensory testing (QST) as a measure of pain sensitivity, is being increasingly used to generate somatosensory profiles of patients in clinical pain studies (1, 2) and to measure outcomes in randomised controlled trials (3, 4). However meaningful interpretation of data from these studies requires appropriate reference values for what is 'normal'. This ideally should be drawn from large population-based samples of 'healthy pain-free participants', adjusted for age, sex, and other potential confounders (5), thereby allowing for generalisability. Currently there is a lack of large population studies that have investigated pain sensitivity distributions in healthy people.

While there are some 'normative' datasets against which to reference clinical QST data (6-12), currently there is no comprehensive reference QST data specific to young adults. As the transition from adolescence to adulthood is a critical time during which trajectories for persistent pain can become established (13-16) there is value in establishing normative data for this young age group. Issues with the utility of current normative datasets for QST include a lack of adherence to recent calls for standardised definitions, and best practice recommendations to adjust for potential confounding variables such as age and sex (17); datasets that include participants with pain (7, 8); having relatively small numbers in each age and sex range (9-11); or wide ranging age groups (12). There is thus a gap in knowledge of normal age-sex specific pain sensitivity distributions.

Further, without large cohort reference values to define 'normal' and an understanding of potential correlates, the interpretation of QST measures in pain studies is severely limited, as is their utility in management of people with pain (5, 18). Potential independent correlates associated with increased pain sensitivity to pressure and cold stimuli include younger age (6), female sex (19), increasing Body Mass Index (6, 20), higher psychological symptoms of depression, anxiety, stress and catastrophizing, (2, 6, 21-23), decreased health related quality of life (6), lower physical activity and increased sedentary behaviour, (21, 24, 25), and smoking (8, 26). Only one normative study of pain sensitivity has investigated a broad range of potential correlates (demographic, psychological and health-related factors), but this study was limited by a relatively wide age range with small age-specific participant numbers (6).

Clinically, the assessment of an individual's pain sensitivity can inform treatment options (27). In this context, exploring normative ranges for deep tissue pain sensitivity

(pressure pain threshold: PPT) is particularly important given deep tissues are implicated in musculoskeletal conditions (28-32). With the availability of affordable algometers, there is increasing use of PPT testing in clinical settings to assess and monitor tissue sensitivity levels Cold hypersensitivity (cold pain threshold: CPT) has also demonstrated clinical utility for predicting poor prognosis in whiplash associated disorders (33) and differentiating pain mechanisms in musculoskeletal pain conditions (18, 23, 34, 35). These two clinically relevant nociceptive stimuli can form part of a shorter QST protocol by limiting participant burden and improving time efficiency (36).

The large birth cohort investigated here provided an opportunity to capture more precise sex specific pressure and cold pain threshold estimates for young, pain-free adults. The aims of this study were: (1) to provide sex-specific reference values of pressure and cold pain thresholds in young pain-free adults; (2) to examine the association of site, sex, ethnicity, height, weight, smoking, health related quality of life, psychological factors and physical activity levels with pain threshold values.

4.2   Methods

4.2.1   Study Population

Cross-sectional data for this study was obtained from the Western Australian Pregnancy Cohort (Raine) Study (http://www.rainestudy.org.au). This is an ongoing birth cohort study that commenced with 2900 women who enrolled in the study before the 18th gestation week and 2,868 children born, entered the initial birth cohort. Data has been collected at 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22 years. The characteristics of the active participants were compared with census data collected in 2011 on all similarly aged young adults in Western Australia. The comparison showed that the sample remains widely representative for a range of variables including education level, employment status, income, marital status, number of offspring, hours worked and occupation. The 22 year follow-up data collection ran between March 2012 and July 2014.[1] Ethics approval for the Raine Study Cohort 22 year follow up was obtained from the University of Western Australia (UWA) (RA/4/1/5202).

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[1] Further detail on full measures collected can be found at:
http://www.rainestudy.org.au/for-researchers/cohort-follow-ups/ (37)

4.2.2   Recruitment, sampling and data collection

All data used in this study were obtained at the 22 year follow-up. Data were collected as part of 4 hours of testing followed by an overnight sleep study. For this follow up, 1065 individuals participated in pressure pain and cold pain threshold testing. Of the 970 participants who had pressure and cold pain threshold data, and completed questionnaire and physical assessment data on nominated correlates, 617 (280 female and 337 male) were classified as pain free and were included for analysis. Participants were considered pain free if they answered "no" to the question "do you have any current body pain?" from the Orebrö Musculoskeletal Pain Questionnaire (OMPQ).

Questionnaires were filled in before physical assessments and were checked for completion. Anthropometry measures and pressure and cold pain threshold testing were part of the physical assessment protocol conducted by twelve Raine research staff, all of who were thoroughly trained in the data collection procedures and used standardised protocols.

4.2.3   Quantitative sensory testing

Due to time constraints allowed for collecting data and to minimise the already significant participant burden, the sensitivity measures considered most clinical relevant were collected. A standardised protocol for QST consistent with current best practice recommendations (12, 17), was used to measure PPT and CPT. All QST measurements were taken from the right side of the body, as side to side consistency in pain threshold measurements have been shown in people with (38) and without pain (12) . All testing was done in the early evening minimising the influence of circadian rhythms on pain sensitivity (39) and the order of testing was PPT, followed by CPT, as applying cold first has been found to increase the risk of mechanical hyperalgesia (40). This testing sequence has been used previously (23). Both PPT and CPT have demonstrated inter-examiner and intra-subject reliability with reasonable levels of standard error of measurement (41-43). Excellent interrater and intrarater reliability for PPT testing by the Raine research staff has been demonstrated, with the caveat that an absence of any confounding of study estimates by rater should be checked due to a systematic rater bias identified (44).

4.2.4   Pressure pain thresholds

Pressure pain threshold (PPT) was established using a pressure algometer (Somedic AB, Sweden) with a contact area of 1 cm^2 applied perpendicularly to the skin with a ramp rate of 50kPa/s. The ramp rate varies across studies and it is acknowledged slower ramp rates may be appropriate for the study of clinical pain populations (45). PPT was defined as the moment the sensation of pressure became one of pressure and pain. Standardised instructions were read to participants: "The moment the pressure increases to a point where it first feels uncomfortable or painful, press and release the button. This means the very first onset of discomfort or pain and not the most pressure that you can bear". A cut-off pressure value of 1000kPa was set for safety purposes (46). Four trials were performed with a minimum 10 second rest between trials. The mean threshold was calculated for each site from the last three trials.

In order to capture widespread sensitivity data, four standardised sites were tested in the following sequence; the wrist, upper leg, upper trapezius and lumbar spine. These sites have been previously documented (2). The wrist was tested at the middle of the dorsal aspect of the wrist joint line. The leg was tested at the muscle belly of tibialis anterior, approximately 2.5 cm lateral and 5 cm distal to the tibial tubercle. The upper trapezius was tested at the mid-point between the C7 spinous process and the lateral acromion. The lumbar spine was tested at the erector spinae, 2 cm lateral to the L4/L5 interspinous space.

4.2.5   Cold pain threshold

To obtain the cold pain threshold, a thermal stimulator (Modular Sensory Analyzer (MSA), Somedic AB, Sweden) with a 12.5cm^2 (25mm x50mm) probe was used at one standardised body site. This site was the middle of the dorsal aspect of the wrist joint line, consistent with the test site for PPT. The baseline temperature was set as 32°C with a cut off temperature of 5°C. The temperature decreased at 1°C/s until the participant first perceived pain and pressed the control switch to terminate the test. For CPT, the following instructions were given to participants "Allow the temperature to drop until the moment it reaches a point where it feels uncomfortably or painfully cold, and then press the button. This means the very first onset of discomfort or pain and not the most cold that you can bear". Four trials were performed with a 10 second rest period between trials. The mean threshold was calculated from the last three trials.

4.2.6   Other variables

In order to investigate for possible associations with QST measures, a number of other variables were collected.

4.2.7   Physical Measures

With shoes removed, height (meters) was measured with a stadiometer and body mass (kilograms) was measured with digital scales (47). BMI (kg/m^2) was calculated from these measures. BMI was further categorised into underweight ($<18.5 kg/m^2$), normal ($18.5-24.9\ kg/m^2$), over-weight ($25.0-29.9\ kg/m^2$) or obese ($\geq30.0\ kg/m^2$). Waist and hip circumference were measured using a metric tape measure and a standardised protocol, to calculate the waist/hip ratio (WHR).

4.2.8   Smoking

Subjects were asked, 'Do you currently smoke cigarettes/cigars?' and were classified accordingly, as smokers or non-smokers.

4.2.9   Health-related quality of life

Health-related quality of life was measured using the Short Form-12, version 2 (SF-12)(48), a validated and reliable measure of health related quality of life. Twelve questions produce two summary measures: a Mental Component Summary (MCS); and Physical Component Summary (PCS) (49). Each SF-12 scale is a norm-based score with a mean of 50 and standard deviation of 10, with higher scores indicating less disability(48). The MCS and PCS of the SF12 were categorised into those with a score $\geq$50 and <50, to allow comparison with the study by Neziri et al.(6), in which SF36 scores were dichotomised.

4.2.10   Psychological Data

The Depression Anxiety Stress Scale 21 (DASS-21) was used to evaluate the severity of depression, anxiety and stress related symptoms. It is a valid and reliable questionnaire where a higher score indicates greater severity of symptoms (50), with established cut-off scores for mild, moderate, severe and extremely severe levels of each sub-scale (51).

4.2.11   Activity measures

Sedentary behaviour and physical activity were objectively measured over an eight day period using the Actigraph GT3X+ accelerometer (Actigraph, Pensacola, FL, USA) worn on the right hip continuously, except during bathing or aquatic activities. Data were recorded at 30Hz and vertical axis movement counts 'per 60 second epoch' used in current analyses. Accelerometer data were downloaded and processed in SAS (version 9.3, SAS Institute, Cary, NC, USA) (52). Common thresholds (53) were used to class each minute as sedentary (<100 counts per minute (cpm)), light intensity (100-1951 cpm), moderate intensity (1952-5724 cpm) or vigorous intensity (>5724 cpm). Minutes spent in moderate and vigorous physical activity (MVPA) per day; and sedentary time as percentage of non-MVPA time were calculated for each participant based on their valid days (≥10 hours of waking wear time) (54).

4.2.12   Statistical analysis

To provide reference values for pain hypersensitivity, quantile regression analyses were conducted to determine the 5th, 10th and 25th for PPT (6), and 95th, 90th and 75th percentiles for CPT, estimated with bootstrapped standard errors (1000 replications). Reference values for pain hyposensitivity were determined using the 75th, 90th and 95th percentiles for PPT and 25th, 10th and 5th for CPT.

Multivariable independent correlates of PPT were determined with linear regression utilising generalised estimating equations, with an exchangeable correlation structure (r=0.76) to account for the non-independence of the data due to repeated measures by site. Although the PPT was slightly right-skewed, logarithmic transformation did not significantly improve fit of the models and untransformed measures were used to facilitate clinical interpretation of regression coefficients. Multivariable independent correlates of CPT were determined using tobit regression, which was left-censored due to the lower limit of the testing equipment being 5°C. For both PPT and CPT, a series of univariable analyses were initially performed for sex, site (PPT only), rater, ethnicity, height, weight, smoking, activity, quality of life and psychological measures. Sex interactions were tested for all correlates. Sex, and variables with sex-adjusted associations of p<0.15, were entered into multivariable regression models, using a purposeful selection of covariates approach, to ensure no important confounding

variables were omitted (55). Covariates significant at p<0.05 were retained. Univariable associations were made using all cases available, candidate models were evaluated using cases with available data on all candidate variables, and final multivariable models were estimated using all cases with available data on variables included in final models. Each model was examined to ensure absence of influential observations and collinearity of variables, and linearity of associations and normality and homoscedasticity of residuals. Due to nonlinearity of association with PPT and CPT, BMI was parameterised as underweight, normal, overweight and obese in statistical models. Systematic differences between the 12 research personnel performing the tests in this study were checked. Although some testers' values were significantly different from others, inclusion of testers in our models confirmed a lack of confounding of the estimates of associations between PPT and covariates by differences between testers (55), and therefore testers were not adjusted for in final models. Stata/IC Version13.1 for Windows (StataCorp LP, College Station TX USA) was used for all analyses.

4.3   Results

The demographic, quality of life, physical and psychological data of the 617 participants are summarised in Table 4.1. The mean (SD) age of participants was 22.2 (0.6) years with a range of 21.0 to 24.4, and 280 (45.4%) were female. The SF-12 PCS and MCS mean (SD) values were 55.2 (5.1) and 47.9 (9.6), respectively. Depression, anxiety and stress symptoms were reported as mild by 9.2%, 5.8% and 6.7% and moderate-severe by 14.3%, 12.7% and 8.5%, respectively. The high numbers of subjects with missing activity data (n=173, 28.0%) represents poorer compliance with wearing the accelerometer. The participants' number of valid days wearing the accelerometer ranged from 1 to 15 with an average (SD) of 5.3(2.4).

Table 4.1   Demographic, quality of life and psychological data summary statistics (n=617)

Variable	Mean (SD or %)	Range
Age (years)	22.2 (0.6)	21.0 – 24.4
Sex (female)	280 (45.4%)	
Ethnicity (both parents Caucasian)	525 (85%)	
Height (cm)[a]	173 (9.6)	154 – 201
Weight (kg)[a]	75.9 (17.7)	42.4 – 147.5
Hip/waist ratio[b]	0.83 (0.07)	0.65 – 1.08
BMI (kg/m^2)[a]	25.2 (5.4)	15.4 - 49.3
Underweight (<18.5)	13 (2.1%)	15.4 – 18.3
Normal (18.5-24.9)	374 (60.7%)	18.5 – 25.0
Overweight(25.0-29.9)	136 (22.1%)	25.1 – 30.0
Obese (<30.0)	93 (15.1%)	30.1 – 49.3
SF-12[f]		
PCS≥50	471 (84.7)	24.6 – 67.3
MCS≥50	280 (50.5)	11.7 – 68.5
Smoking[c] (yes)	90 (14.7%)	
DASS-21		
Depression[d]	5.9 (7.7)	0 – 40
Anxiety[e]	3.9 (5.0)	0 – 36
Stress[e]	7.9 (7.4)	0 – 42
Activity		
MVPA (minutes/day)[g]	37.5 (28.8)	0 – 243.2
Sedentary time (% of non-MVPA during wake time)[g]	63.7 (9.7)	28.6 – 87.4

[a]Missing data : [a]=1, [b]=2, [c]=3, [d]=49, [e]=51, [f]=62, [g]= 173, BMI: body mass index, DASS-21: depression anxiety stress scale 21, PCS: physical component summary, MCS: mental component summary MVPA: moderate-vigorous physical activity.

References values for PPT stratified by sex and site and CPT stratified by sex are shown in Table 4.2. For PPT and CPT, reference values for hypersensitivity are reported from the most sensitive to least sensitive, while reference values for hyposensitivity are reported from the least insensitive to most insensitive. For CPT, reference values for hyposensitivity are reported at the 5th, 10th and 25th percentile in females only. Values were unable to be estimated for males, as 38.8% of male participants reached the 5°C minimum cut off.

Univariable and multivariable regression models for PPT are shown in Table 4.3. Variables with a p-value of <0.15 for univariable association with PPT were site, sex, BMI,

WHR, SF12-MCS, smoking, DASS stress and sedentary time. In the multivariable model for PPT measures, site, sex, WHR and SF12-MCS were retained as statistically significant, independent correlates of PPT. The neck was the most sensitive PPT test site (i.e. lowest PPT), and both the neck and the wrist sites were significantly more sensitive than the back and leg PPT test site. The neck was significantly more sensitive than the wrist, and there was no significant difference between the back and leg sites. Males were significantly less sensitive (i.e. higher PPT) than females (mean difference=+141.6KPa, 95%CI: 109.0, 174.3). WHR was associated with increasing pressure pain sensitivity (i.e. lower PPT) with PPT estimated to decrease by 28.2 KPa (95%CI: 5.6-50.8) with each 0.1 increase in WHR. Poorer mental health was associated with increased pressure pain sensitivity (i.e. lower PPT), those with MCS≥50 were estimated to have 33.0KPa (95%CI: 2.9-63.0) higher PPT values than those with MCS<50.

Univariable and multivariable regression models for CPT are shown in Table 4.4. Variables with a p-value of <0.15 for univariable association with CPT were sex, SF12-MCS, smoking, DASS stress, DASS depression and sedentary time. In the multivariable model for CPT measures, sex, SF12-MCS and smoking were retained as statistically significant, independent correlates of CPT. Males were significantly less sensitive to cold pain (i.e. CPT was elicited at a lower temperature) than females (difference= -3.5°C, 95%CI: -5.4, -1.6). Better mental health (MCS≥50) was associated with less sensitivity to cold pain (i.e. lower CPT temperature), those with MCS≥50 were estimated to have -2.5°C (95%CI: -4.4, -0.6) lower CPT values than those with MCS<50. Smoking was associated with less sensitivity to cold pain (i.e. lower CPT temperature) with CPT estimated to be 3.5°C lower (95%CI: -6.5, -0.8) in smokers compared to non-smokers.

Table 4.2   Reference values for pain threshold stratified by sex and site (n=617)

Pain Threshold (PPT=kPa)	Females				Males			
	Number	Mean (SD)	Hypersensitivity (PPT: P^5, P^{10}, P^{25})	Hyposensitivity (PPT: P^{75}, P^{90}, P^{95})	Number	Mean (SD)	Hypersensitivity (PPT: P^5, P^{10}, P^{25})	Hyposensitivity (PPT: P^{75}, P^{90}, P^{95})
PPT Back	275	382 (179)	135, 174, 250	475, 629, 726	334	541 (241)	194, 248, 346	717, 916, 999
PPT Leg	277	394 (189)	156, 183, 246	506, 669, 779	334	520 (234)	218, 255, 344	665, 933, 998
PPT Neck	277	245 (121)	92, 110, 155	319, 411, 488	334	353 (200)	125, 150, 214	434, 635, 793
PPT Wrist	276	360 (144)	162, 194, 256	448, 568, 942	336	492 (217)	197, 244, 340	617, 825, 940
Pain Threshold (CPT=°C)	Number	Mean (SD)	Hypersensitivity (CPT: P^{95}, P^{90}, P^{75})	Hyposensitivity (CPT: P^{25}, P^{10}, P^5)	Number	Mean (SD)	Hypersensitivity (CPT: P^{95}, P^{90}, P^{75})	Hyposensitivity (CPT: P^{25}, P^{10}, P^5)
CPT Wrist	274	13.7 (8.3)	26.9, 25.6, 22.0	5.2, 5.0, 5.0	328	10.8 (7.3)	25.7, 23.6, 16.0	Not estimated[a]

[a]38.8% of males reached the 5°C cut off for CPT; CPT=cold pain threshold; PPT=pressure pain threshold; P^5=5th percentile; P^{10}=10th percentile; P^{25}=25th percentile; P^{75}=75th percentile; P^{90}=90th percentile; P^{95}=95th percentile

Table 4.3   Univariable and multivariable regression model for pressure pain thresholds (kPa)

Variable	Univariable		Multivariable	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Site				
Back	REF	<0.001[d]	REF	
Leg	-4.7 (-15.5, 6.06)	0.390	-5.7 (-19.9, 5.5)	0.321
Neck	-164.8 (-175.6, -154.0)	<0.001	-165.2 (-176.4, -154.0)	<0.001
Wrist	-36.6 (-47.4, -25.8)	<0.001	-36.8 (-48.0, -25.6)	<0.001
Sex				
Females	REF		REF	
Males	131.6 (103.1, 160.2)	<0.001	141.6 (109.0, 174.3)	<0.001
Ethnicity				
Caucasian	REF			
Non-Caucasian	4.5 (-37.8, 46.7)	0.837		
Waist/hip ratio[a]	12.7 (-8.5, 34.0)	0.240[e]	-28.2 (-50.8, -5.6)	0.014
BMI				
Under	-53.3 (-158.2, 51.5)	0.319		
Normal	REF	0.050[f]		
Overweight	41.6 (4.2, 79.0)	0.029		
Obese	-17.6 (-60, -25.5)	0.424		
SF12				
PCS≥50	-2.1 (-5.2, 1.1)	0.196		
MCS≥50	2.2 (0.6, 3.9)	0.007	33.0 (2.9, 63.0)	0.032

	Univariable		Multivariable	
Variable	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Smoke				
No	REF			
Yes	35.3 (-7.1, 77.7)	0.102		
DASS21				
Depression	-1.2 (-3.2, 0.9)	0.260		
Anxiety	-1.1 (-4.3, 2.0)	0.483		
Stress	-2.8 (-4.9, -0.7)	0.009		
Activity				
MVPA (mins/day)[b]	3.0 (-3.0, 9.0)	0.375		
Sedentary time[c]	-1.421 (-3.26, 0.417)	0.130		

[a]Coefficient represents the expected change in PPT for a 0.1 change in Waist/hip ratio, [b]coefficient represents the expected change for a 10 minute change in MVPA, [c]coefficient represents the expected change for a 1% change in sedentary time, [d]omnibus p-value for group difference =0.000, and after adjustment for sex p=0.000, [e]Waist/hip ratio coefficient (95% CI) and p-value after adjusting for sex= -25.0 (-46.5, -3.6), p= 0.022, [f]overall p-value for group difference =0.050, and after adjustment for sex p=0.577 , CI: confidence interval, BMI: body mass index, DASS-21: depression anxiety stress scale 21, PCS: physical component summary, MCS: mental component summary, MVPA: moderate-vigorous physical activity, sedentary time=percentage of non-MVPA during wake-time.

Table 4.4   Non-linear Tobit regression table for cold pain threshold (°C)

Variable	Univarible		Multivariable	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Sex				
Female	REF			
Male	-4.2 (-5.9, - 2.4)	<0.001	-3.5 (-5.4, -1.6)	<0.001
Ethnicity				
Caucasian	REF			
Non-caucasian	0.5 (-2.1, 3.0)	0.722		
Waist/hip ratio[a]	-2.0 (-3.3, - 0.7)	0.002		
BMI				
Under	1.4 (-4.7 ,7.6)	0.651		
Normal	REF	0.241d		
Overweight	-2.3 (-4.5, 0.1)	0.054		
Obese	-0.9 (-3.5, 1.7)	0.502		
SF12				
PCS≥50	0.2 (-0.4, 0.3)	0.120		
MCS≥50	-0.1 (-0.2, 0.0)	0.013	-2.5 (-4.4, -0.6)	0.011
Smoke				
No	REF			
Yes	-3.0 (-5.6, -0.4)	0.022	-3.6 (-6.5, -0.8)	0.013

Variable	Univarible		Multivariable	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
DASS21				
Depression	0.1 (0.0, 0 2)	0.090		
Anxiety	0.0 (-0.2, 0.2)	0.949		
Stress	0.1 (0.0, 0.2)	0.060		
Activity				
MVPA (mins/day)[b]	0.1 (-0.2, 0.5)	0.462		
Sedentary time[c]	0.1 (0.0, 0.2)	0.050		

[a]Coefficient represents the expected change for a 0.1 change in Waist/hip ratio, [b]coefficient represents the expected change for a 10 minute change in MVPA, [c]coefficient represents the expected change for a 1% change in sedentary time, [d]overall p-value for group difference =0.241, and after adjustment for sex p=0.505, CI: confidence interval, BMI: body mass index, DASS-21: depression anxiety stress scale 21, PCS: physical component summary, MCS: mental component summary, MVPA: moderate-vigorous physical activity, sedentary time=percentage of non-MVPA during wake-time.

4.4   Discussion

The study has provided reference pressure and cold pain threshold data for a 'healthy' young adult population. The reference values reported here are currently the most comprehensive and robust data available for young adults aged 21-24. A major strength of this study is the consideration of the independent associations of a comprehensive number of potential known correlates of pressure and cold pain sensitivity, findings consistent with those previously reported in response to QST (56-58).

Comparing our data against current normative reference data highlights the most relevant comparison dataset as Neziri (6) who reported PPT data on 20-49 year olds for the same back and neck sites, using the same approach to data with percentiles for hypersensitivity and hyposensitivity (Table 4.5 shows a comparison with previously existing age, sex, site, and test specific reference data). In contrast, Magerl (9) using a moving average analysis, had an overall number of participants in each sex group of 90 resulting in small numbers in each of five decadal groups (age range 20-70), and did not report percentile values for hypersensitivity and hyposensitivity. Comparison with Neziri (6) shows our data consistently has a wider range of values and higher standard deviations. For example, the male PPT neck values ranged from 125 (P^5) to 793 (P^{95}, SD=200) compared with Neziri (6) who reported values from 150 (P^5) to 451 (P^{95}, SD=94). This discrepancy may reflect the larger numbers sampled for the current study, or differences in participants due to correlates known or unknown to be associated with pain sensitivity, including geographic location and ethnicity (59). This largely Caucasian cohort from a southern hemisphere, Mediterranean-style climate may differ in pain sensitivity from other cohorts due to ethnicity, lack of exposure to cold temperatures, sunlight exposure and inflammatory status (60). Further comparison with other reference data testing similar sites is not appropriate, as these previous studies have included participants from the general population (8, 61), without reporting pain status, thereby complicating interpretation. Including participants with musculoskeletal pain introduces variability into results and limits the post-hoc use of data for reference purposes (5). Screening for pain status here used the question "do you have any current body pain?" Therefore, we cannot exclude that some participants may have experienced pain at another time.

Table 4.5   Reference value comparison

	Females				Males			
Pain Threshold *(PPT=kPa)*	**Number**	**Mean (SD)**	**Hypersensitivity** *(PPT: P^5)*	**Hyposensitivity** *(PPT: P^{95})*	**Number**	**Mean (SD)**	**Hypersensitivity** *(PPT: P^5)*	**Hyposensitivity** *(PPT: P^{95})*
PPT Back								
Waller[a]	275	382 (179)	135	726	334	541 (241)	194	999
Neziri[b]	75	260 (121)	119	528	75	398 (141)	200	653
PPT Neck								
Waller[a]	277	245 (121)	92	488	334	353 (200)	125	793
Neziri[b]	75	212 (74)	118	360	75	313 (94)	150	451
PPT Wrist/Hand								
Waller[a]	276	360 (144)	162	942	336	492 (217)	197	940
Neziri[b]	90[c]	255 (106)	Not reported	Not reported	90[c]	263 (175)	Not reported	Not reported
Pain Threshold *(CPT=°C)*	**Number**	**Mean (SD)**	**Hypersensitivity** *(CPT: P^{95})*	**Hyposensitivity** *(CPT: P^5)*	**Number**	**Mean (SD)**	**Hypersensitivity** *(CPT: P^{95})*	**Hyposensitivity** *(CPT: P^5)*
CPT Wrist								
Waller[a]	274	13.7 (8.3)	26.9	5.0	328	10.8 (7.3)	25.7	Not estimated[e]
Neziri[b]	90[d]	15.6 (7.2)	Not reported	Not reported	90[d]	11.2 (8.2)	Not reported	Not reported

[a]Age range 21.0-24.4, [b]age range 20-49, [c]age range 20-30, [d]number of all female or male subjects aged 15-75, decade 20–30 years: calculated from subjects between > 15 and 35 years of age.
[e]38.8% of males reached the 5°C cut off for CPT; PPT: pressure pain threshold; CPT: cold pain threshold

4.4.1   Pain Sensitivity vs Site

The multivariable analysis for PPT measures showed the neck and wrist site to be significantly more sensitive than the back site. Pressure stimulates deep tissue nociceptors (62) and the variation seen in PPT between sites will reflect, at least in part, peripheral nervous system sensitivity that is also influenced by local anatomical variations in density of nociceptors and receptive fields (63). Neziri (6) did not report testing for site differences for PPT, but comparing their back and neck site mean values suggests a smaller gap than our study, possibly reflecting the smaller sample size. The significant site variations support the need for site specific reference values from large cohorts.

4.4.2   Pain Sensitivity vs Sex

The univariable and multivariable regression models for both PPT and CPT (tables 3 and 4) show females being significantly more pain sensitive than males supporting the need for sex adjusted reference data. PPT and CPT regression models respectively shows PPT 141.6 kPa lower in females and CPT 3.5 higher in females. Higher pressure pain sensitivity in females is consistent with previous studies in pain free populations (6, 9, 64), mixed pain status populations (7, 10, 65), and pain populations (66, 67). Greater sensitivity to cold pain in females is consistent with previous studies in both pain free (6, 9) and pain populations (66, 68). Systematic reviews have found females are consistently more pain sensitive to experimental pain than males across most pain modalities (19, 69). Studies investigating sex differences in pain sensitivity indicate reasonable evidence that psychological factors, social factors, coping strategies and differences in endogenous pain inhibition might partly explain these differences (70, 71).

4.4.3   Pain sensitivity vs BMI and WHR

In the univariable models unadjusted for sex, there was a non-linear association between BMI categories and PPT, however, this association attenuated when adjusting for sex (p=.577) and BMI categories were not considered for further multivariable modelling, consistent with previous findings from others regarding BMI and PPT (6). In the current study, no association between CPT and BMI was identified, before or after adjustment for sex (p=0.241 and 0.506 respectively), in contrast to a previous study (6) which demonstrated an association between less cold pain sensitivity and increasing BMI.

Although there was no univariable significant association between PPT and WHR, when adjusted for sex, higher WHR was significantly associated with increasing pressure pain sensitivity (p=0.022) and the association remained significant in the multivariable model (Table 4.3). Conversely, increasing WHR was significantly associated with less cold pain sensitivity in the univariable model, but there was no significant association in the multivariable model. The association between PPT and WHR in this study controls for site differences, sex and psychological status and suggests increasing pain sensitivity as WHR increases. The significant association of WHR but not BMI with sensitivity to pressure maybe due to WHR being a better measure of central adiposity, whereas BMI does not take into account the distribution of body fat (72). There is a strong association between WHR and metabolic risk, independent of BMI, which reflects central obesity (73, 74). Current evidence also demonstrates central obesity increases levels of circulating pro-inflammatory cells, and this finding suggests shared underlying mechanisms that could modulate both pain sensitivity and metabolic health (75, 76).

4.4.4   Pain sensitivity vs smoking

In our study, smoking was associated with less cold, but not pressure, pain sensitivity. In the multivariable model accounting for sex and mental well-being (SF12 MCS), the CPT of smokers was an estimated 3.6°C lower (i.e.; less sensitive) than non-smokers. Findings from human studies investigating the association of smoking and pain sensitivity have been mixed, probably reflecting small sample sizes, different ages and health status of participants, and mixed methods (8, 77, 78). Anti-nociceptive properties of nicotine on the central nervous system have been demonstrated (79) and combined with the human studies demonstrate that nicotine can have a significant but variable association with pain sensitivity. This highlights the need to include smoking as a confounder when investigating associations with pain sensitivity.

4.4.5   Pain sensitivity vs psychological health

Regarding DASS-21 scores, the only significant univariable association identified was for the stress sub-scale with both PPT and CPT, however neither association was significant after adjustment for sex, in the multivariable model. In multivariable models, better mental wellbeing as measured by the SF12 MCS was associated with less pressure

and cold pain sensitivity. Neziri (6) also reported a better SF-36 score was associated with less pain sensitivity. However, a systematic review found the association of depression and anxiety symptoms with pain sensitivity to be ambiguous, consistent with the current findings of different associations with different measures of psychological health (70). The severity of symptoms may be important, with depressive disorder having an association with increased cold pain sensitivity (22). Catastrophizing has also been shown to be associated with greater thermal pain sensitivity (68, 80). While there is some evidence of an association with psychological health and pain sensitivity, it may depend on the measure used, construct considered and level of symptoms.

4.4.6   Pain sensitivity vs activity

There was no significant association of MVPA and sedentary time with pain sensitivity. Physical activity has been proposed to elicit exercise induced hypoalgesia via recruitment of endogenous pain modulatory systems (81). The association of activity measured via accelerometry and pain sensitivity has only been investigated in one other small (n=21) study. Here, evidence was demonstrated in female participants of an association between meeting activity recommendations and lower pain sensitivity, whereas sedentary time had no association (82). Other studies (83, 84) have used subjective self-report activity questionnaires, with lower pain sensitivity found in participants doing more vigorous activity. Investigations using specific laboratory based exercise interventions have found an immediate association between high level activity and reduced pain sensitivity in healthy participants (24, 85, 86). Despite a large sample and valid activity measurement, our study did not find significant associations between activity and pain sensitivity. The variables MVPA and sedentary time used here might not be optimal to capture how physical activity is associated with pain sensitivity.

In conclusion, this study currently provides the most comprehensive sex specific reference value data for young adults aged 21-24 years of pressure pain threshold at four body sites and cold pain threshold at the dorsal wrist. This large cohort provides more robust values than existing, smaller studies and further, the population-based, non-clinical cohort provides generalisability and limits participant selection bias. These data will provide an important research resource to enable more accurate profiling and interpretation of pain sensitivity in clinical pain disorders in young adults. The robust

and comprehensive data can assist interpretation of future clinical pain studies and provide further insight into the complex associations of pain sensitivity that can be used in future research.

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Author contributions

Significant contributions to this work were made by all authors listed:

- conception and design (RW, AS, POS, MS, LS)
- literature review (RW, AS, POS, HS, JMcV, LS)
- data collection (RW, AS, LS)
- statistical analysis (RW, AS, HS, LS)
- writing design (RW, AS, POS, HS, JMcV, LS)

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Chapter 5　Associations Between Musculoskeletal Pain Experience and Pressure and Cold Pain Sensitivity: A Community Based Cross-Sectional Study of Young Adults in the Raine Study

ORIGINAL ARTICLE

Associations Between Musculoskeletal Pain Experience and Pressure and Cold Pain Sensitivity
A Community-based Cross-sectional Study of Young Adults in the Raine Study

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Objectives: To investigate the cross-sectional associations between musculoskeletal pain experience and measures of pressure and cold pain sensitivity in young adults from the Western Australian Pregnancy Cohort (Raine) Study.

Participants and Methods: In total, 917 participants were eligible for analysis if they provided data pertaining to musculoskeletal pain status at the 22-year follow-up and had data for at least 1 valid pain sensitivity test. Standardized protocols were used to assess pressure pain threshold (4 sites: lumbar spine, tibialis anterior, upper trapezius, and wrist) and cold pain threshold (wrist). Four pain experience groups ("No pain" [n = 562, 61.3%], "Low" [n = 84, 9.2%], "Medium" [n = 147, 16.0%], "High" [n = 124, 13.5%]) were determined by latent class analysis using parameters of pain chronicity, frequency, intensity, and number of pain areas. Variables considered as confounders included sex, age, ethnicity, waist-hip ratio, psychological symptoms, sleep quality, physical activity, sedentary behavior, smoking, and income.

Results: There were no associations between pain experience and pressure pain sensitivity after adjusting for confounders. The "Medium" and "High" pain experience groups demonstrated heightened cold pain sensitivity compared with the "No pain" group ($P = 0.023$), adjusted for sex and smoking.

Discussion: This study provides the most extensive investigation of the relationship between musculoskeletal pain experience and pressure and cold pain sensitivity in young adults. Heightened cold pain sensitivity in those classified as "Medium" and "High" pain experience may suggest altered nociceptive processing and has implications for clinical management.

Key Words: pain experience, pain sensitivity, quantitative sensory test, musculoskeletal, Raine Study

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There is a large burden of musculoskeletal pain worldwide with low back pain and neck pain the leading global cause of disability in 2015.[1] A poor correlation between pathology measured by imaging techniques and severity of pain has been shown in peripheral[2] and spinal[3] musculoskeletal pain disorders suggesting aspects other than structure are important to pain experience. There is substantial literature describing changes in nociceptive processing of various stimuli, typically reflecting heightened pain sensitivity, in clinical populations with musculoskeletal pain disorders including knee osteoarthritis,[4] low back pain,[5,6] whiplash-associated disorders,[7] elbow pain,[8] and widespread pain conditions such as fibromyalgia.[9,10] In addition, increased pressure and cold pain sensitivity have been identified in multisite pain disorders compared with localized pain disorders.[11,12] Collectively these studies suggest that changes in nociceptive processing are an important mechanism in persistent clinical pain states.[13–15]

Recent studies have contributed to improving the understanding of the association between pain experience and pain sensitivity by using multiple pain parameters to provide a better characterization of the pain experience.[16–18] Pain sensitivity, as measured by quantitative sensory testing (QST), is a psychophysical construct influenced by many factors[19] and typically alters across the lifespan including decreasing with age.[17,20,21] Although both age and pain experience are important correlates of pain sensitivity, associations reported to date have not been adequately adjusted for potential confounding. Potential confounders include sex,[18,22,23] psychological factors,[23–25] sleep,[26] physical activity and sedentary behavior,[23,27] anthropometrics,[21,23] ethnicity,[28] and socioeconomic status.[28]

While knowledge of the relationship between pain experience and pain sensitivity in the adult population is expanding, there is a lack of large population-based studies to assist our understanding of pain mechanisms specifically in young adults adjusting associations for potential confounders.[17] Current literature is often limited by using pain intensity alone to define the pain experience;[29] however, other parameters such as pain frequency, number of pain locations, and chronicity are important aspects of the pain experience in terms of impacts on quality of life and disability.[30] The Western Australian Pregnancy Cohort (Raine) Study provides an opportunity to explore the relationship between pain experience and pain sensitivity in young adults, while adjusting for a broad range of clinical correlates. Understanding the relationship between a person's pain experience and pain sensitivity can provide insight to inform underlying mechanisms to better inform interventions for young people with chronic musculoskeletal pain conditions. This relationship may be especially

Abstract

Objectives: To investigate the cross-sectional associations between musculoskeletal pain experience and measures of pressure and cold pain sensitivity in young adults from the Western Australian Pregnancy Cohort (Raine) Study.

Methods: Participants (n=917) were eligible for analysis if they provided data pertaining to musculoskeletal pain status at the 22-year follow up and had data for at least one valid pain sensitivity test. Standardised protocols were used to assess pressure pain threshold (4 sites: lumbar spine, tibialis anterior, upper trapezius and wrist) and cold pain threshold (wrist). Four pain experience groups ("No pain" (n=562, 61.3%), "Low" (n=84, 9.2%), "Medium" (n=147, 16.0%), "High" (n=124, 13.5%)) were determined by latent class analysis using parameters of pain chronicity, frequency, intensity and number of pain areas. Variables considered as confounders included sex, age, ethnicity, waist-hip ratio, psychological symptoms, sleep quality, physical activity, sedentary behaviour, smoking and income.

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Key Words: pain experience; pain sensitivity; quantitative sensory test; musculoskeletal; Raine Study

5.1   Introduction

There is a large burden of musculoskeletal pain worldwide with low back pain and neck pain the leading global cause of disability in 2015 [57]. A poor correlation between pathology measured by imaging techniques and severity of pain has been shown in peripheral [1] and spinal [5] musculoskeletal pain disorders suggesting aspects other than structure are important to pain experience. There is substantial literature describing changes in nociceptive processing of various stimuli, typically reflecting heightened pain sensitivity, in clinical populations with musculoskeletal pain disorders including knee osteoarthritis (OA) [53], low back pain [36; 40], whiplash associated disorders [56], elbow pain [47] and widespread pain conditions such as fibromyalgia [12; 25]. Additionally, increased pressure and cold pain sensitivity have been identified in multisite pain disorders compared with localised pain disorders [4; 15]. Collectively these studies suggest that changes in nociceptive processing are an important mechanism in persistent clinical pain states [8; 26; 63].

Recent studies have contributed to improving the understanding of the association between pain experience and pain sensitivity by using multiple pain parameters to provide a better characterisation of the pain experience [39; 46; 54]. Pain sensitivity, as measured by quantitative sensory testing (QST), is a psychophysical construct influenced by many factors [9] and typically alters across the lifespan including decreasing with age [30; 35; 46]. While both age and pain experience are important correlates of pain sensitivity, associations reported to date have not been adequately adjusted for potential confounding. Potential confounders include sex [3; 54; 59], psychological factors [27; 49; 59], sleep [45], physical activity and sedentary behaviour [34; 59], anthropometrics [35; 59], ethnicity [38] and socioeconomic status [38].

While knowledge of the relationship between pain experience and pain sensitivity in the adult population is expanding, there is a lack of large population-based studies to assist our understanding of pain mechanisms specifically in young adults adjusting associations for potential confounders [46]. Current literature is often limited by using pain intensity alone to define the pain experience [24], however other parameters such as pain frequency, number of pain locations and chronicity are important aspects of the pain experience in terms of impacts on quality of life and disability [22]. The Western Australian Pregnancy Cohort (Raine) Study provides an opportunity to explore the

relationship between pain experience and pain sensitivity in young adults, while adjusting for a broad range of clinical correlates. Understanding the relationship between a person's pain experience and pain sensitivity can provide insight to inform underlying mechanisms to better inform interventions for young people with chronic musculoskeletal pain conditions. This relationship may be especially important for young adults who are at a critical life transition stage where trajectories of musculoskeletal pain become established and can continue into later adulthood [22; 28; 37; 48].

Therefore, the aim of this study was to explore the relationship of pain experience (using parameters of pain chronicity, frequency, intensity and number of pain areas), with pain sensitivity, (as measured by pressure pain thresholds (PPT) and cold pain thresholds (CPT)), in young community-based adults of the Raine Study, adjusting for potential confounders. The hypothesis was that a higher pain experience will be associated with increased pain sensitivity.

5.2   Materials and methods

5.2.1   Recruitment and sampling

Cross-sectional data for this study were obtained from the Western Australian Pregnancy Cohort (Raine) Study (http://www.rainestudy.org.au). This is an ongoing birth cohort study that commenced with 2900 women who enrolled in the study before the 18th gestation week with 2868 children born entering the initial birth cohort. Data has been collected at 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22 years. The current study used data obtained at the 22-year follow up that ran between March 2012 and July 2014, 2086 were still 'active' and contacted for participation. Of these, 1234 took part in some aspect of the 22-year follow up [51]. The characteristics of the participants were compared with census data collected in 2011 on all similarly aged young adults in Western Australia and showed that the sample remains widely representative on a range of variables including education level, employment status, income, marital status, number of offspring, hours worked and occupation [51]. The ethnicity of the participants was 85.0% Caucasian, 0.9% Aboriginal and Torres Strait Islander, and 14.1% non-Caucasian. Ethics approval for the Raine Study Cohort 22-year follow up was obtained from Curtin University (HR 23/2013) and the University of Western Australia (UWA) (RA/4/1/5202).

5.2.2   Data collection

Data for this study were collected as part of 4 hours of testing followed by an overnight sleep study [52]. Questionnaires were completed before physical assessments and were checked for completion by a research assistant. Anthropometry measures and pressure and cold pain threshold testing were part of the physical assessment protocol conducted by twelve Raine Study research staff, all of whom were thoroughly trained in the data collection procedures and used standardised protocols. Participants were eligible for analysis if they had completed relevant aspects of the Örebro Musculoskeletal Pain Questionnaire (ÖMPQ) and had data for at least one valid pain sensitivity test (n=917).

5.2.3   Quantitative sensory testing

Due to the already significant time burden required of the participants in the broader Raine Study, pain sensitivity measures were limited to PPT and CPT. A standardised protocol ('method of limits') consistent with current best practice recommendations [2] was used to measure PPT and CPT at a constant room temperature. All pain threshold measurements were taken from the right side of the body as it has been shown there is side to side consistency in pain sensitivity measurement [44]. PPT was tested prior to CPT, as cold exposure has been shown to increase the risk of mechanical hyperalgesia [19]. Both PPT and CPT have demonstrated inter-examiner and intra-subject reliability with reasonable levels of standard error of measurement [61]. Excellent interrater and intrarater reliability for PPT testing by the Raine Study research staff have been demonstrated [60].

5.2.4   Pressure pain thresholds

Pressure pain threshold was established using a pressure algometer (Somedic AB, Sweden) with a contact area of 1 cm^2 applied perpendicularly to the skin with a ramp rate of 50kPa/s. PPT was defined as the moment the sensation of pressure becomes one of pressure and pain. Standardised instructions were read to participants: "The moment the pressure increases to a point where it first feels uncomfortable or painful, press and release the button. This means the very first onset of discomfort or pain and not the most pressure that you can bear". A cut-off pressure value of 1000kPa was set for safety

purposes. Four trials were performed with a minimum 10 second rest between trials. The mean threshold was calculated for each site from the last three trials. Four standardised sites were tested in the following sequence; the dorsal wrist, tibialis anterior, upper trapezius and lumbar spine. The wrist was tested at the middle of the dorsal aspect of the wrist joint line. The leg was tested at the muscle belly of tibialis anterior, approximately 2.5 cm lateral and 5 cm distal to the tibial tubercle. The upper trapezius was tested at the mid-point between the C7 spinous process and the lateral acromion. The lumbar spine was tested at the erector spinae, 2 cm lateral to the L4/L5 interspinous space.

5.2.5   Cold pain threshold

A Modular Sensory Analyzer (MSA) thermal stimulator (Somedic AB, Sweden) using a $12.5cm^2$ (25mm x50mm) probe was used to obtain the CPT at one standardised body site, on the skin at the middle of the dorsal aspect of the wrist joint line. The starting temperature was set as 32°C with a cut off temperature of 5°C. The temperature decreased at 1°C/s until the participant first perceived pain and pressed the control switch to terminate the test. For CPT, the following instructions were given to participants "Allow the temperature to drop until the moment it reaches a point where it feels uncomfortably or painfully cold, and then press the button. This means the very first onset of discomfort or pain and not the most cold that you can bear". Four trials were performed with a 10 second rest period between trials. The mean threshold was calculated from the last three trials.

5.2.6   Pain experience

Pain experience groupings were determined using items from the ÖMPQ. Participants who answered no to the ÖMPQ question "Do you currently have any body pain?" were re-directed away from answering further ÖMPQ questions and assigned to a 'No pain' group. Participants who answered yes were classified into groups by latent class analysis using ÖMPQ [29] items on pain chronicity, frequency, intensity and number of pain areas as indicator variables. Pain chronicity was categorized using the ÖMPQ question "How long have you had your current pain problem?" into less than 2 months, 3-6 months, 6-12 months and > 12 months. Pain frequency was determined using the ÖMPQ question "How often would you say that you have experienced pain episodes, on

average, during the past three months?", using a numerical rating scale (NRS) with 1 indicating "never" and 10 indicating "always". Pain intensity was calculated from the mean of two ÖMPQ questions "How would you rate the pain that you have had during the past week?" and "In the past three months, on average, how bad was your pain on a 0-10 scale?", using an NRS with 1 indicating "no pain" and 10 indicating" pain as bad as it could be". A count of pain sites (maximum 10) was calculated from the number of endorsed response options to a list of predefined body sites from the ÖMPQ question "Where do you have pain?".

5.3   Other variables

To investigate for possible confounding of associations between pain experience and QST measures, several other variables were collected. Waist and hip circumference were measured using a metric tape measure and a standardised protocol, to calculate the waist-hip ratio (WHR). The Depression Anxiety Stress Scale 21 (DASS-21) was used to evaluate the severity of depression, anxiety and stress related symptoms. It is a valid and reliable questionnaire where a higher score indicates greater severity of symptoms [21]. The Pittsburgh Sleep Quality Index (PSQI) is a questionnaire which assesses perceived sleep quality and disturbance over a 1-month period. It is considered a reliable and valid measure of sleep quality which is scored on a 0-21 scale with a score greater than 5 indicative of poor sleep quality [7]. Sedentary behaviour and physical activity were objectively measured over an eight-day period following the overnight sleep study using the Actigraph GT3X+ accelerometer (Actigraph, Pensacola, FL, USA) worn on the right hip continuously, except during bathing or aquatic activities. Data were recorded at 30Hz and vertical axis movement counts 'per 60 second epoch' used in current analyses. Accelerometer data were downloaded and processed in SAS (version 9.3, SAS Institute, Cary, NC, USA) [32]. Common thresholds [31] were used to class each minute as sedentary (<100 counts per minute (cpm)), light intensity (100-1951 cpm), moderate intensity (1952-5724 cpm) or vigorous intensity (>5724 cpm). Minutes spent in moderate and vigorous physical activity (MVPA) per day and sedentary time as percentage of non-MVPA time during wake time were calculated for each participant based on their valid days (≥10 hours of waking wear time) [43]. Subjects were asked, 'Do you currently smoke cigarettes/cigars?' and were classified accordingly, as smokers or non-smokers. Income was assessed by total usual pay per week after tax and for statistical analysis was

categorised according to 2012 Australian tax brackets. The usual pay per week after tax categories were: less than $116, $116-604, $605-1076, $1077-2180 and greater than $2180. Ethnicity was determined as 'Caucasian' if both parents were Caucasian, or 'non-Caucasian' if parents had mixed ethnicity.

5.3.1   Statistical analysis

Subgroups with differing profiles of pain experience were determined using latent class analysis which is a statistical technique used to subgroup people according to their profile across several variables (indicators). For those participants reporting pain, this technique was used to identify subgroups with differing profiles across pain chronicity, frequency, intensity and number of pain areas as indicator variables. The resultant subgroups can be deemed to be a 'latent' variable representing the overall pain experience. One to six cluster models were estimated with 1000 random starts to ensure global rather than local solutions, and indicator variables were considered as ordinal. Log-likelihood-based Akaike's information criterion (AIC), Bayesian information criterion (BIC) and Consistent AIC (CAIC) were used to assess comparative fit of n-cluster models. Participants were assigned to the cluster for which they displayed the maximum posterior probability of membership. One to six cluster models were estimated with 1000 random starts to ensure global rather than local solutions. Log-likelihood-based Akaike's information criterion (AIC), Bayesian information criterion (BIC) and Consistent AIC (CAIC) were used to assess comparative fit of n-cluster models. Participants were assigned to the cluster for which they displayed the maximum posterior probability of membership. Resulting pain experience groups (including the group without pain) were assessed for differences across groups using linear regression for continuous normally distributed variables (age, PPT, waist-hip ratio, sleep, sedentary time), chi-squared analyses for nominal variables (sex, ethnicity, smoking), Tobit regression for CPT and Kruskall Wallis test for skewed continuous variables (DASS-21, income, MVPA).

To identify potential confounders of the association between pain experience groups and pain sensitivity measures, a series of univariable regression analyses adjusted for sex were performed to assess the strength of association of each potential confounding variable with PPT and CPT. As sex is strongly associated with PPT and CPT [59], confounders were only considered after sex adjustment. For PPT, linear regression models

utilising generalised estimating equations were used with an exchangeable correlation structure to account for the non-independence of the data due to repeated measures by site. For CPT Tobit regression models were used, as CPT was left-censored due to the lower limit of the thermal stimulator being 5°C. Potential confounders assessed in addition to sex were age, test site (PPT only), ethnicity, waist-hip ratio, psychological symptoms, sleep quality, physical activity, sedentary behaviour, smoking and income.

To analyse the relationship between pain experience and pain sensitivity measures of PPT and CPT, a series of linear and tobit regression models respectively were performed [23]. Firstly, models for PPT and CPT were adjusted for sex and those potential confounders identified to have sex-adjusted univariable associations of $p<0.15$. In a second step using only those cases used in Step 1, potential confounding variables were sequentially removed if they were not significant in the model ($p>.05$) and their removal did not alter the coefficients for pain experience subgroup membership by more than 20%. In Step 3, a final model was estimated using those cases with no missing data on those variables identified in Step 2. Using the final models for PPT and CPT, interaction between sex and pain experience group was tested to explore the possibility that differences over pain experience subgroups were sex-dependent. Stata/IC Version 15 for Windows (Statacorp LP, College Station, TX, USA) was used for all analysis.

5.4   Results

There were 1058 participants with at least one valid pain sensitivity test, of which 917 had data pertaining to musculoskeletal pain. Of these, 562 (61.3%) did not report any current pain and were assigned to a 'No pain' group and not included in subsequent latent class analysis. A three-class solution was determined as the best fit according to the BIC, AIC and CAIC fit statistics (Table 5.1). 'Low', 'Medium' and 'High' pain experience groups were determined from latent class analysis and were used for further analysis. The number (percentage) of participants in the 'Low', 'Medium' and 'High' pain experience groups were 84 (9.2%), 147 (16.0%) and 124 (13.5%) of participants respectively. The profiles of the three pain experience groups on the indicator variables pain chronicity, frequency, intensity and number of pain areas are presented in Table 5.2, with profiles indicative of increasing severity for all indicators moving from 'Low to 'High' groups. The mean Short Form ÖMPQ scores (standard deviation, range) for the 'Low',

'Medium' and 'High' pain experience groups respectively were 24.1 (9.6, 7.1 – 52.6), 31.7 (9.0, 11.4 – 52.8) and 43.3 (10.0, 25.6 – 71.2).

The mean (SD) age of all participants was 22.1 (0.7) years with a range of 21.3 to 24.4 and 475 (51.8%) were female. The demographic, psychological, sleep and activity data summary statistics of the 917 participants, reported by pain experience, are summarised in Table 5.3. There was a significant difference in sex across pain experience groups with the percentage of females in the 'Medium' and High' pain experience groups higher at 57.1% and 75.0% respectively. The DASS and PSQI scores varied significantly between pain experience groups, with higher psychological symptoms and poorer sleep quality reported as pain experience worsened (Table 5.3). There was no significant difference in age, ethnicity or waist-hip ratio between pain experience groups

The mean MVPA levels across pain experience groups ranged from 31.8 to 36.2 mins/day and there was no significant difference across pain experience groups (Table 5.3). Mean sedentary time, as a percentage of non-MVPA time during wake time, ranged from 63.3 to 65.3% across pain experience groups without significant variance between pain experience groups (Table 5.3). The mean (SD) of valid days wearing the accelerometer was 5.4 (2.4) with a range of 1 to 15. There was a high number of participants (n=228) who did not comply with wearing the accelerometer, however this did not vary across pain groups.

The mean (SD) PPT values across pain experience groups via test site are reported in Table 5.3. Not accounting for sex, PPT values varied significantly between pain experience groups, with increased pressure pain sensitivity in the higher pain experience groups. Table 5.4 reports univariable associations between PPTs and potential confounders, adjusted for sex. Variables found to have sex-adjusted associations with PPT of $p<0.15$ were site, waist-hip ratio, sedentary time and income. Table 5.5 reports the association of PPT with pain experience group membership adjusted for sex only and adjusting for potential confounders from final model resulting from Step 3 of the analysis. There was no association between pain experience group and PPT univariably (adjusted for sex) or when adjusted for additional confounders (site, waist-hip ratio and sedentary time). There was no significant interaction between sex and pain experience group ($p=0.158$), meaning the degree of difference in PPT between pain experience groups was similar between males and females. PPT was estimated to be 158.5kPa higher in males

compared to females (i.e. less pressure pain sensitivity) (95% CI: 129.1, 187.9, p=0.001). PPT was estimated to be significantly lower (i.e. more pressure pain sensitivity) at the neck (-153.8kPa, 95% confidence interval (CI): -163.9, -143.7, p=0.001) and wrist (-28.5kPa, 95% CI: -38.6, -18.4, p=0.001) compared to the lumbar spine test site. For a 0.1 increase in waist-hip ratio, PPT was estimated to be 25.3kPa lower (95% CI: -44.8, -5.7, p=0.011). For an increase in sedentary time by 10%, PPT was estimated to be 14.2kPa lower (95% CI: -28.1, -0.3 p=0.045).

The mean (SD) CPT values across pain experience groups are reported in Table 5.3. Not accounting for sex, CPT values varied significantly between pain experience groups, with increased cold pain sensitivity in the higher pain experience groups. Table 5.4 reports univariable associations between CPTs and potential confounders adjusted for sex. Variables found to have sex-adjusted associations with CPT of p<0.15 were sedentary time, smoking and income. Table 5.6 reports the association of CPT with pain experience group membership adjusted for sex only and adjusting for potential confounders from Step 3 of the analysis. There was a significant overall association between pain experience group and CPT (p=0.023) adjusted for sex and smoking, with the 'Medium' pain experience group and 'High' pain experience group demonstrating more cold pain sensitivity than the 'No pain' experience group (2.1°C, 95% confidence interval (CI): 0.1-4.2, p=0.038 and 2.3°C, 95% CI: 0.1-4,5, p=0.037, respectively). The 'Medium' pain experience group and 'High' pain experience group also displayed significantly more cold pain sensitivity than the 'Low' pain experience group (3.3°C, 95% CI: 0.2-6.3, p=0.024 and 3.3°C, 95% CI: 0.2-6.4, p=0.022 respectively) (Table 5.5). There was no significant interaction (p=0.666) between sex and pain experience group. The CPT of males was estimated to be 4.8°C lower (i.e. less cold pain sensitivity) than females (95% CI: -3.3, -6.3, p=0.001). Smokers, compared with non-smokers, were estimated to have 2.1°C lower CPT (95% CI: -4.1, -0.1, p=0.043).

Table 5.1   Latent class analysis

Number of classes	BIC	AIC	CAIC
1	6383	6232	6420
2	6146	5975	6188
3	6109	5918	6156
4	6134	5922	6186
5	6153	5921	6210
6	6173	5921	6235

BIC: Bayesian Information Criterion
AIC: Akaike Information Criterion
CAIC: Consistent Akaike Information Criterion

Table 5.2   Profiles of pain experience subgroups on indicator pain variables (number of sites, chronicity, frequency and intensity)

	Pain experience group		
Variable	Low (n=84)	Medium (n=147)	High (n=124)
Number of sites (median, (p25, p75))	1.0 (1,1)	2.0 (1,2)	2.3 (2,4)
Chronicity (n, %)			
<=2 months	67.0 (79.8%)	52.0 (35.4%)	10.0 (8.1%)
3- 6 months	5.0 (6.0%)	22.0 (14.7%)	16.0 (12.9%)
6-12 months	2.0 (2.4%)	17.0 (11.6%)	12.0 (9.7%)
> 12 months	10.0 (11.9%)	56.0. (38.1%)	86.0 (69.4%)
Frequency (mean, (SD))	1.9 (0.7)	4.2 (1.1)	7.6 (1.2)
Intensity (mean, (SD))	2.9 (1.0)	4.1 (1.1)	6.0 (1.4)

Table 5.3   Demographic, pain sensitivity, psychological, sleep and activity data summary statistics via pain experience (n=917)

Variable	No pain (n=562) Mean (SD) or Number (%)	Range	Low (n=84) Mean (SD) or Number (%)	Range	Medium (n=147) Mean (SD) or Number (%)	Range	High (n=124) Mean (SD) or Number (%)	Range	P value diff across groups
Age *(years)*	22.2 (0.7)	21.0, 24.4	22.1 (0.6)	21.2, 24.0	22.1 (0.7)	20.6, 24.2	22.1 (0.7)	20.9, 24.3	0.662[k]
Sex *(female)*	260 (46.3%)[d]		38 (45.2%)[d]		84 (57.1%)[a]		93 (75.0%)[a,b,c]		0.001[l]
Ethnicity *(both parents Caucasian)*	478 (85.1%)		69 (82.1%)		130 (88.4%)		106 (85.5%)		0.603[l]
Waist-hip ratio[e]	0.83 (0.07)	0.65, 1.085	0.83 (0.08)	0.61, 1.02	0.83 (0.08)	0.67, 1.11	0.82 (0.08)	0.69, 1.09	0.231[k]
DASS-21 total score *(0-63)*[f]	8.6 (8.7)[d]	0, 56.0	10.1 (9.5)[d]	0, 42.0	12.8 (11.4)[a,b]	0, 57.0	15.1 (10.3)[a,b,c]	0, 47.0	0.001[n]
PSQI *(0-21)*[g]	4.3 (2.1)[d]	0, 13	4.2 (1.9)[d]	0, 10	5.2 (2.8)[a,b]	0, 16	6.2 (2.8)[a,b,c]	1, 15	0.001[k]
Accelerometry[h]									
Awake wear time *(mins/day)*	897.8 (92.8)	612, 1101.1	885.5 (86.6)	650, 1046	898.6 (93.4)	619, 1105.7	914.7 (86.9)	623, 1134	0.217[k]
MVPA *(mins/day)*	36.2 (27.8)	0, 243.2	34.7 (23.7)	2.3, 101.3	31.8 (21.0)	1, 150	35.5 (28.6)	2.5, 175.5	0.734[n]
Sedentary time *(%)*	63.9 (9.7)	28.7, 88.9	65.3 (8.3)	45.5, 80.3	64.5 (9.8)	39.9, 83.8	63.3 (10.4)	23.0, 82.5	0.565[k]
Smoking *(yes)*[i]	76 (13.5%)		12 (14.3%)		33 (22.4%)		21 (17.2%)		0.063[l]
Income[j]	2.5 (0.9)	1, 5	2.5 (0.8)	1, 5	2.5 (0.8)	1, 5	2.6 (0.8)	1, 5	0.924[n]
PPT lumbar spine *(kPa)*	468.5 (228.8)[d]	69.3, 1000	462.2 (263.7)[d]	90, 1000	454.7 (228.6)[d]	85.3, 1000	376.5 (211.7)[a,b,c]	82.0, 1000	0.001[k]
PPT tibialis anterior *(kPa)*	463.2 (224.7)[d]	74.0, 1000	449.4 (236.0)[d]	98.7, 1000	454.2 (206.5)[d]	86.7, 1000	395.6 (203.0)[a,c]	84.0, 1000	0.024[k]
PPT upper trapezius *(kPa)*	306.0 (181.2)[d]	44.3, 1000	314.3 (222.7)[d]	61.0, 1000	276.1 (131.6)[d]	75.0, 702.7	254.6 (147.2)[a,b]	25.0, 1000	0.009[k]
PPT wrist *(kPa)*	432.3 (196.5)[d]	91.7, 1000	434.3 (210.1)[d]	137.3, 1000	422.7 (180.4)[a,b]	105.3, 1000	371.5 (171.3)[a,b]	40.3, 1000	0.016[k]
CPT *(°C)*	12.1 (7.9)[d]	5, 29.7	11.2 (7.6)[d]	5, 27.6	14.0 (8.6)[a,b]	5, 30.3	14.5 (8.6)[a,b]	5, 29.1	0.001[m]

[a] Significant difference with 'No pain' group; [b] Significant difference with 'Low' group; [c] Significant difference with 'Medium' pain group; [d] No significant difference between groups; Missing data (for all participants): [e] =2, [f] =22, [g] =66, [h] =228, [i] =5, [j] =64; [k] =Linear regression, [l] =Chi-squared, [m] =Tobit regression; [n] =Kruskal-Wallis; SD: standard deviation; DASS-21: depression anxiety stress scale 21; PSQI: Pittsburgh sleep quality index; MVPA: moderate-vigorous physical activity; Sedentary time = as a percentage of non-MVPA time during wake time; Income: total usual pay per week after tax (categorised according to 2012 Australian tax brackets)

Table 5.4   Univariable regression model for pressure pain thresholds (kPa) and cold pain thresholds (°C)

Variable	Regression coefficient Pressure Pain Threshold (95% CI) [e]	p-value	Regression coefficient Cold Pain Threshold (95% CI) [e]	p-value
Site				
Back	Ref	0.001 [f]		
Leg	-1.8 (-10.7, 7.0)	0.680		
Neck	-158.2 (-167.1, -149.3)	0.001		
Wrist	-30.5 (-39.3, -21.6)	0.001		
Age (years)	16.1 (-1.1, 3.3)	0.067	-0.6 (-1.7, 0.5)	0.307
Sex				
Female	Ref		Ref	
Male	144.9 (122.3, 167.6)	0.001	-5.3 (-3.9, -6.8)	0.001
Ethnicity				
Both parents Caucasian	Ref		Ref	
Non-Caucasian	8.4 (40.3, -23.6)	0.607	1.4 (3.5, -0.6)	0.178
Waist-hip ratio [a]	-21.0 (-37.5, -4.5)	0.012	-0.7 (-1.7, 0.4)	0.192
DASS-21 total score (0-63)	-0.4 (-1.5, 0.8)	0.560	0.0 (-0.1, 0.1)	0.650
PSQI total score (0-21)	-2.6 (-7.5, 2.2)	0.289	0.0 (-0.4, 0.3)	0.795

Variable	Regression coefficient Pressure Pain Threshold (95% CI) [e]	p-value	Regression coefficient Cold Pain Threshold (95% CI) [e]	p-value
Activity				
MVPA (mins/day) [b]	-0.2 (-5.3, 4.8)	0.923	0.2 (-0.1, 0.5)	0.295
Sedentary time (%) [c, d]	-13.0 (-27.0, 0.9)	0.067	0.9 (0.0, 1.8)	0.039
Smoking				
No	Ref		Ref	
Yes	12.0 (-18.3, 44.0)	0.417	-1.8 (-3.8, 0.2)	0.080
Income (pay/week after tax)	17.9 (6.3, 29.6)	0.002	-0.9 (-1.7, -0.1)	0.020

[a] Coefficient represents the expected change in PPT for a 0.1 change in waist-hip ratio; [b] Coefficient represents the expected change in CPT for an increase in MVPA of 10 minutes/day; [c] Adjusted for awake wear time; [d] Coefficient represents the expected change in CPT for a 10% increase in sedentary time; [e] Adjusted for sex; [f] Omnibus p-value for group difference; DASS-21: depression anxiety stress scale 21; PSQI: Pittsburgh sleep quality index; MVPA: moderate-vigorous physical activity; Sedentary time = as a percentage of non-MVPA time during wake time; Income: total usual pay per week after tax (categorised according to 2012 Australian tax brackets)

Table 5.5   Multivariable regression model for the association of pressure pain threshold (kPa) with Pain experience (n=685)

Variable	Regression coefficient (95% CI) [a]	p-value	Regression coefficient (95% CI) [b]	p-value
Pain experience				
No pain	Ref	0.493 [c]	Ref	0.405 [c]
Low	26.4 (-19.5, 72.3)	0.259	28.0 (-17.6, 73.7)	0.228
Medium	7.4 (-29.7, 44.5)	0.697	9.3 (-27.5, 46.2)	0.619
High	-15.8 (-55.1, 23.5)	0.431	-17.7 (-56.8, 21.4)	0.376
Sex				
Female	Ref		Ref	
Male	146.7 (119.6, 173.8)	0.001	158.5 (129.1, 187.9)	0.001
Site				
Back			Ref	0.001 [c]
Leg			-1.4 (-11.6, 8.7)	0.780
Neck			-153.8 (-163.9, -143.7)	0.001
Wrist			-28.5 (-38.6, -18.4)	0.001
Waist-hip ratio [d]			-25.3 (-44.8, -5.7)	0.011
Activity				
Sedentary time (%) [c, d]			-14.2 (-28.1, -0.3)	0.045

[a] Adjusted for sex and only for participants without any missing data for confounding variables; [b] Adjusted for sex, site, waist-hip ratio, sedentary time, awake wear time; [c] Omnibus p-value for group difference; [d] Coefficient represents the expected change in PPT for a 0.1 change in waist-hip ratio; [e] Coefficient represents the expected change in PPT for a 10% increase in sedentary time; [f] Coefficient represents the expected change in PPT for a 10 min increase in accelerometer awake wear time

Table 5.6   Tobit regression models for the association of cold pain threshold (°C) with pain experience (n=894)

Variable	Regression coefficient (95% CI) [a]	p-value	Regression coefficient (95% CI) [b][e]	p-value
Pain experience				
No pain	Ref [c]	0.036 [d]	Ref [e]	0.023 [d]
Low	-1.3 (-3.9, 1.3)	0.313	-1.3 (-3.8, 1.3)	0.319
Medium	1.9 (-0.1, 4.0)	0.060	2.1 (0.1, 4.2)	0.038
High	2.2 (0.0, 4.4)	0.048	2.3 (0.1, 4.5)	0.037
Sex				
Female	Ref		Ref	
Male	-5.0 (-3.5, -6.4)	0.001	-4.8 (-3.3, -6.3)	0.001
Smoking				
Yes			Ref	
No			-2.1 (-4.1, -0.1)	0.043

[a] Adjusted for sex, reporting only participants not missing smoking data; [b] Adjusted for sex, smoking; [c] Contrast of Medium vs Low: 3.3 (0.3, 6.3), p=0.033 and High vs Low: 3.5 (0.4, 6.6), p=0.026; [d] Omnibus p-value for group difference; [e] Contrast of Medium vs Low: 3.4 (0.5, 6.4), p=0.024 and High vs Low: 3.6 (0.5, 6.7), p=0.022

5.5   Discussion

This study is the most extensive investigation to date of the relationship between pain experience, and pressure and cold pain sensitivity in young adults. When subgrouped, 'Medium' and 'High' pain experience groups had heightened cold pain sensitivity when compared with 'Low' and 'No pain' groups, after adjusting for sex and smoking. The significant differences between pain experience groups were estimated to be between 2.1 and 3.6°C. There were no associations between pain experience and pressure pain sensitivity before or after adjusting for confounders. The implications of these findings are discussed considering pain mechanisms that might be present in young adults with musculoskeletal pain.

5.5.1   Pain mechanisms

Using large, community-based non-clinical cohorts such as the Raine Study to investigate the association between cold and pressure pain sensitivity and the pain experience allows for better interpretation and generalizability of data compared with smaller clinical studies. Surprisingly there are few larger scale population-based pain sensitivity data sets identified. A community-based study on 941 adolescents, with 197 classified as having chronic pain, revealed increased pressure pain sensitivity at the trapezius for those with chronic pain versus without chronic pain [54]. However, there was no association between cold-pressor pain ratings and pain. This finding may differ from the current study due to the modality used for cold stimuli (cold-pressor pain ratings) or the categorisation of pain groups (expert judgement to form a dichotomous grouping). Another large population-based study [46] reported normative data for conditioned pain modulation and pressure pain sensitivity in an adult Danish general population sample (n=2,199) while controlling for pain intensity recorded from multiple body areas but did not investigate the association of pain sensitivity with pain experience. The limited community-based studies in this area highlights the need for more research.

Females consistently have greater cold pain sensitivity than males [30; 35; 59] and subsequently the heightened cold pain sensitivity in the 'Medium" and 'High' pain experience groups might be expected to be explained by the significantly higher female membership of those groups (Table 5.3). However, the significant association

of higher pain experience with heightened cold pain sensitivity remained after adjusting for sex (Table 5.6). Additionally, there was no interaction between sex and pain experience, meaning the difference in CPT across pain experience groups was similar for males and females.

This study was cross-sectional and therefore it is not known if cold pain sensitivity is causal to the pain experience or if the pain experience drives pain sensitivity. However, pain experience group membership might be partially explained by cold pain sensitivity, suggesting heightened nociceptive mechanisms are potentially associated with the higher pain experience. CPT was tested at the wrist only, which is likely to be distal from common pain sites in most participants and supports the hypothesis that central nociceptive mechanisms are at least partly contributing to the pain experience in the 'Medium' and 'High' pain experience groups. The association of increased cold pain sensitivity, but not pressure pain sensitivity, with pain experience may reflect disruption of thermosensation and thermoregulation which are modulated by central systems [49; 58]. In young female adults of the Raine Study (22-year follow-up) with severe menstrual pain (VAS 8-10) or 'mixed' menstrual pain (VAS 4-7), increased cold pain sensitivity (measured at the dorsal wrist, i.e. distant from the pelvis) was suggested to reflect altered central nociceptive pain processing [49]. Altered nociceptive processing, including heightened pain sensitivity to pressure and cold, is proposed to be causal in the development of chronic pain in adult populations [18; 62; 64]. A systematic review found support for heightened cold pain sensitivity as a prognostic factor for ongoing pain and disability in Whiplash Associated Disorders [17]. Increased pain sensitivity in knee osteoarthritis patients pre-operatively has also been associated with chronic pain after total knee replacement [55; 64].

The determination of pain experience groups by latent class analysis allowed consideration of a broader pain experience in a single measure rather than using only pain intensity or unidimensional aspects of the pain experience. A meta-analysis investigated whether lower pain thresholds were associated with higher intensity of spinal pain, with a pooled correlation coefficient estimate of -0.15 (95% CI: -0.18 to -0.11) indicating a very weak association [24]. This isolated pain measure (intensity) may not capture the broader pain experience and hence be the reason for lack of identification of stronger associations with pain thresholds. The authors further hypothesized that pain intensity alone is unlikely

to reflect dominant central pain mechanisms and therefore the potential for identifying stronger associations with pain thresholds was limited as many participants in the included studies may not have dominant central nociceptive processes [24]. For example, using a comprehensive clinical examination only 23% of 464 chronic low back pain participants were identified as having dominant central pain mechanisms [50]. In support of the utility of multidimensional consideration of the pain experience when considering associations with pain thresholds, a smaller study of chronic low back pain participants used clinical examination and pain behaviour to classify participants into either 'mechanical' or 'non-mechanical' pain profiles, finding heightened cold pain sensitivity at the dorsal wrist in the 'non-mechanical' pain profile group consistent with augmented nociceptive processing, whereas the 'mechanical' pain profile group had similar pain threshold to controls [36]. Consideration of both the extent of pain areas using single-site versus multisite pain, and only including participants with chronic pain, two studies found sensory testing profiles in chronic back pain were distinct from those with fibromyalgia [4; 15]. The findings from this study are consistent with the previous research, the 'High' pain experience group had more pain sites and pain sensitivity when compared with the 'Low' pain experience group, highlighting the utility of recording the number of pain sites to assist in profiling the pain experience. Questionnaire measures, even when considering the broader pain experience, cannot fully characterise and differentiate nociceptive mechanisms. While a clinical examination allows a more individualised characterisation of each pain experience this is impractical in larger cohort studies.

The relationship between a person's pain experience and psychological factors is complex and potentially bidirectional [14]. While the DASS-21 scores varied significantly between pain experience groups, with higher psychological symptoms reported as pain experience worsened, there was no association between the DASS-21 score and PPT or CPT. This may reflect the relatively low mean (10.3, SD 9.7) DASS-21 scores recorded by our cohort. However, our results reflect the variation reported in the literature, where some previous investigations have found a significant association between poorer psychological function and pain sensitivity [10; 54], while others have reported no significant association [8; 27; 35].

5.5.2   Strengths and limitations

A major strength of this study is the large age-specific sample, as best practice requires age specific pain sensitivity data [16] to inform a better understanding of potential pain mechanisms in younger populations [54]. Other strengths include collection of a broad range of data allowing for consideration of potential confounders, and investigation in a community-based, non-clinical cohort that is representative of the Western Australian population, providing generalizability to the general young adult population of Australia. Limitations of the study include the cross-sectional design, no control for pain medication and, due to issues of participant burden, capture of only two QST measures. The Raine study participants live in a temperate climate which potentially influences cold pain sensitivity, and this may be considered a limitation of the study when generalizing results to other regions of the world [42]. However, these limitations are unlikely to invalidate the association between the pain experience and cold pain sensitivity identified in this study.

5.5.3   Implications for clinical practice

Examining the relationship between pain experience and pain sensitivity is important for young adults as this is an important window of development where prevalence for musculoskeletal pain is reaching adult rates. In this study a substantial number of young adults had a 'Medium' or 'High' pain experience which included frequent, intense, long lasting pain in multiple body areas. For young adults describing a higher pain experience, the potential presence of heightened nociceptive processing should be a consideration, suggesting more targeted clinical assessment of pain mechanisms is appropriate [36; 50]. Incorporating the clinical assessment of pain mechanisms augmented via QST has been advocated and has potential benefit in guiding choice of treatment by identifying subgroups of patients based on underlying pathophysiological mechanisms [9]. However better bedside QST protocols and further research in this area are required to improve the clinical utility and cost of pain sensitivity assessment [17]. The current evidence, including this study, while nascent suggests mechanism-based management consider a wider spectrum including interventions which help normalise nociceptive processing. Strategies to improve heightened nociceptive processing could include prescription of appropriate pharmaceuticals [20], physical activity [11], advice on improving sleep health [45] and consideration of psychological factors [6; 13; 33; 41].

5.6   Conclusion

This comprehensive investigation of community-based young adults found increased cold pain sensitivity to be associated with a heightened pain experience, potentially suggesting augmented central nociceptive processing. The findings support the clinical assessment of pain mechanisms, along with considering the pain experience, to assist in providing individualised, mechanism-based, musculoskeletal pain management approaches for young adults. The study is one of only a few community-based studies exploring the relationship between the pain experience and pain sensitivity highlighting the need to expand current knowledge to improve interpretation of QST findings and develop management approaches that help address the worldwide burden of musculoskeletal pain.

Acknowledgments

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Chapter 6   Associations Between Physical Activity and Sedentary Behaviour with Pain Sensitivity in Young Adults of the Raine Study

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Associations of physical activity or sedentary behaviour with pain sensitivity in young adults of the Raine Study

Abstract

Background and aims: There is high level evidence for physical activity (PA) improving outcomes in persistent pain disorders and one of the mechanisms proposed is the effect of exercise on central nociceptive modulation. Although laboratory studies and small field intervention studies suggest associations between physical activity and pain sensitivity, the association of objectively measured, habitual PA and sedentary behaviour (SB) with pain sensitivity requires further investigation. Current evidence suggests PA typically lowers pain sensitivity in people without pain or with single-site pain, whereas PA is frequently associated with an increase in pain sensitivity for those with multisite pain. The aim of this study was to explore the relationships of PA and SB with pain sensitivity measured by pressure pain thresholds and cold pain thresholds, considering the presence of single-site and multisite pain and controlling for potential confounders.

Methods: Participants from the Western Australian Pregnancy Cohort (Raine) Study ($n = 714$) provided data at age 22-years. PA and SB were measured via accelerometry over a 7-day period. Pain sensitivity was measured using pressure pain threshold (4 sites) and cold pain threshold (wrist). Participants were grouped by number of pain areas into "No pain areas" ($n = 438$), "Single-site pain" ($n = 113$) and "Multisite pain" ($n = 163$) groups. The association of PA and SB variables with pain sensitivity was tested separately within each pain group by multivariable regression, adjusting for potential confounders.

Results: For those with "Single-site pain", higher levels (>13 min/day) of moderate-vigorous PA in ≥10 min bouts was associated with more pressure pain sensitivity ($p = 0.035$). Those with "Multisite pain" displayed increased cold pain sensitivity with greater amounts of vigorous PA ($p = 0.011$). Those with "No pain areas" displayed increased cold pain sensitivity with decreasing breaks from sedentary time ($p = 0.046$).

Conclusions: This study was a comprehensive investigation of a community-based sample of young adults with "No pain areas", "Single-site pain" and "Multisite pain" and suggests some associations of measures of PA and SB with pain sensitivity.

Implications: The findings suggest that the pattern of accumulation of PA and SB may be important to inform improved clinical management of musculoskeletal pain disorders. This study provides a baseline for follow-up studies using the Raine Study cohort. Future research should consider temporal influences of PA and SB on pain sensitivity, pain experience and consider using a broader range of pain sensitivity measures.

Keywords: pain sensitivity; accelerometry; musculoskeletal; Raine Study; physical activity; sedentary behaviour.

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1 Introduction

There is high level evidence for increased levels of physical activity (PA) reducing disability and associated costs for persistent musculoskeletal disorders including lower limb osteoarthritis [1], chronic low back pain [2] and fibromyalgia syndrome [3]. Longitudinal general population

Abstract

Background and aims: There is high level evidence for physical activity (PA) improving outcomes in persistent pain disorders and one of the mechanisms proposed is the effect of exercise on central nociceptive modulation. Although laboratory studies and small field intervention studies suggest associations between physical activity and pain sensitivity, the association of objectively measured, habitual PA and sedentary behaviour (SB) with pain sensitivity requires further investigation. Current evidence suggests PA typically lowers pain sensitivity in people without pain or with single-site pain, whereas PA is frequently associated with an increase in pain sensitivity for those with multisite pain. The aim of this study was to explore the relationships of PA and SB with pain sensitivity measured by pressure pain thresholds and cold pain thresholds, considering the presence of single-site and multisite pain and controlling for potential confounders.

Methods: Participants from the Western Australian Pregnancy Cohort (Raine) Study (n=714) provided data at age 22-years. PA and SB were measured via accelerometry over a 7-day period. Pain sensitivity was measured using pressure pain threshold (4 sites) and cold pain threshold (wrist). Participants were grouped by number of pain areas into 'No pain areas' (n=438), 'Single-site pain' (n=113) and 'Multisite pain' (n=163) groups. The association of PA and SB variables with pain sensitivity was tested separately within each pain group by multivariable regression, adjusting for potential confounders.

Results: For those with 'Single-site pain', higher levels (>13mins/day) of moderate-vigorous PA in ≥10min bouts was associated with more pressure pain sensitivity (p=0.035). Those with 'Multisite pain' displayed increased cold pain sensitivity with greater amounts of vigorous PA (p=0.011). Those with 'No pain areas' displayed increased cold pain sensitivity with decreasing breaks from sedentary time (p=0.046).

Conclusions: This study was a comprehensive investigation of a community-based sample of young adults with 'No pain areas', 'Single-site pain' and 'Multisite pain' and suggests some associations of measures of PA and SB with pain sensitivity.

Implications: The findings suggest the pattern of accumulation of PA and SB may be important to consider in the clinical management of musculoskeletal pain disorders. This study provides a baseline for follow-up studies using the Raine Study cohort. Future research should consider temporal influences of PA and SB on pain sensitivity, pain experience and consider using a broader range of pain sensitivity measures.

Keywords: Pain sensitivity; Accelerometry; Musculoskeletal; Raine Study; Physical activity; Sedentary behaviour

6.1   Introduction

There is high level evidence for increased levels of physical activity (PA) reducing disability and associated costs for persistent musculoskeletal disorders including lower limb osteoarthritis (1), chronic low back pain (2) and fibromyalgia syndrome (3). Longitudinal general population studies further suggest higher PA may reduce the risk for the onset of persistent musculoskeletal pain (4, 5). Additionally, young adults spend much of their awake time sedentary (6), and links between sedentary behaviour (SB) and increased risk of musculoskeletal pain have been reported in adolescents (7) and adults (8). One of the mechanisms proposed for PA improving outcomes in musculoskeletal pain disorders, is the effect of exercise on efficient central nociceptive modulation (9). Measurement of pain sensitivity maybe important to improve the understanding of the relationship between physical activity and sedentary behaviour with pain disorders. Understanding this relationship in young adulthood is of particular importance as this life stage is a transition period when trajectories for persistent pain become established (10, 11) and there is already a significant burden from persistent musculoskeletal pain (12, 13).

Alterations in pain sensitivity in response to laboratory-based, acute bouts of exercise is variable, with evidence of transient decreases in pressure and cold pain sensitivity in pain-free, healthy participants (14), and both increases and decreases in participants with persistent pain (14-16). This variability in participants with persistent pain may reflect different central nociceptive modulatory responses to exercise (9, 16). Importantly, increased pressure pain sensitivity following exercise is more prevalent in people with persistent, multisite pain disorders, such as fibromyalgia, consistent with evidence of the presence of augmented central nociceptive processing (15, 17). Based on laboratory studies, the optimal dose of prescribed exercise to improve pain sensitivity is inconclusive for persistent pain conditions (14).

While laboratory based exercise studies have measured immediate changes in pain sensitivity in response to single exercise sessions, the association of exercise interventions and habitual PA with pain sensitivity may provide more insight into the longer-term associations of PA with pain sensitivity in both clinical and community-based settings. Findings from a limited number of short to medium term (1 to 10 weeks) exercise intervention field studies, suggest the potential for increased PA to produce a medium term beneficial reduction of pressure pain sensitivity (18-20). In healthy people,

when habitual PA was measured via self-report, evidence suggests an association between higher levels of PA and decreased pressure and cold pain sensitivity (21, 22). Observational studies using objective measurement of PA via accelerometry to investigate the association of habitual PA and pain sensitivity have inconclusive findings with either very limited participant numbers (n=21) (23) or only using participants without pain (24).

There is little investigation of the association of objectively measured, habitual PA and SB with pain sensitivity in community based cohorts. The aim of this study was to explore the relationships of PA and SB with pain sensitivity measured by pressure pain thresholds (PPT) and cold pain thresholds (CPT), considering the presence of single-site and multisite pain and controlling for potential confounders.

6.2   Methods

6.2.1   Participants

Cross-sectional data for this study were obtained from the Western Australian Pregnancy Cohort (Raine) Study (http://www.rainestudy.org.au). This is an ongoing birth cohort study that commenced with 2900 women who enrolled in the study before the 18th gestation week with 2868 children born entering the initial birth cohort. Data has been collected at 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22-years. The current study used data obtained at the 22-year follow up that ran between March 2012 and July 2014, 2086 were still 'active' and contacted for participation. Of these, 1234 took part in some aspect of the 22-year follow up that included an extensive range of questionnaires and physical assessments (25, 26). The characteristics of the active participants were compared with census data collected in 2011 on all similarly aged young adults in Western Australia and showed that the sample remains widely representative on a range of variables including education level, employment status, income, marital status, number of offspring, hours worked and occupation (25). The ethnicity of the active participants was 85.0% Caucasian, 0.9% Aboriginal and Torres Strait Islander, and 14.1% non-Caucasian.

6.2.2 Recruitment, sampling and data collection

Data for this study were collected as part of 4 hours of testing followed by an overnight sleep study (27). Questionnaires were completed before physical assessments and were checked for completion by a research assistant. Anthropometry measures, and pressure and cold pain threshold testing were part of the physical assessment protocol conducted by twelve Raine research staff, all of who were thoroughly trained in the data collection procedures and used standardised protocols. For this follow up, 773 (389 female and 384 male) participants wore Actigraph GT3X+ monitors 24 h/day over a one-week period. Participants were eligible for analysis if they had data for at least one 'valid' day (≥10 h of waking wear time) and completed the Orebro Musculoskeletal Pain Questionnaire. The minimum of one 'valid' day was chosen in order to maximize statistical power and to minimize selection bias. Of these, 714 individuals had valid PPT data and 702 individuals had valid CPT data.

6.2.3 Physical activity and sedentary behaviour

Physical activity and sedentary behaviour were objectively measured over a one-week period using the Actigraph GT3X+ accelerometer (Actigraph, Pensacola, FL, USA) worn continuously on the right hip, except during bathing or aquatic activities. The GT3X+ was programmed to record raw data at a frequency of 30Hz which were later reduced to vertical axis movement counts 'per 60 second epoch' for the purpose of the current analyses. Accelerometer data were downloaded and processed in SAS (version 9.3, SAS Institute, Cary, NC, USA). The protocol and measured patterns of PA and SB in the Raine Study have previously been comprehensively described (6). The '60 second epoch' was used as cut points in this age group have been validated for this length of epoch and this allows comparisons with other accelerometer data also processed using a 60 second epoch (28). Common thresholds were used to class each minute as sedentary (<100 counts per minute (cpm)), light intensity (100-1951 cpm), moderate intensity (1952-5724 cpm) or vigorous intensity (>5724 cpm) (6, 29). All minutes in continuous periods of ≥90 minutes of zero cpm, allowing for <3 minutes with counts 1 to 50 cpm, were classed as non-wear. The algorithm used for identifying waking wear time has been reported as mostly good, and better than evaluated published alternatives (28). Variables representing moderate PA, vigorous PA, combined moderate/vigorous PA (MVPA),

sedentary time in minutes per day and sedentary time as a percentage of non-MVPA time during wake time were derived from these classifications. A further five variables captured the pattern of accumulation PA and SB as follows; MVPA mins/day in ≥10 min bouts (allowing for two minutes below the cut-point), sedentary mins/day in ≥20 min bouts and ≥30 min bouts, proportion of sedentary time per day accumulated in ≥20 min bouts and number of breaks from sedentary time per day.

6.2.4   Quantitative sensory testing

Due to the already significant time burden required of the participants in the broader Raine Study, pain sensitivity measures were limited to PPT and CPT. A standardised protocol ('method of limits') consistent with current best practice recommendations (30) was used to measure PPT and CPT at a constant room temperature. The protocol has been published previously and is also described below (24). All testing was done in the early evening, minimising the influence of circadian rhythms on pain sensitivity (31). All pain threshold measurements were taken from the right side of the body as it has been shown there is side to side consistency in pain sensitivity measurement in people with (32) and without pain (33). PPT was tested first, followed by CPT, to minimise the risk of mechanical hyperalgesia (34). Both PPT and CPT have demonstrated inter-examiner and intra-subject reliability with reasonable levels of standard error of measurement (35). Excellent interrater and intrarater reliability for PPT testing by the Raine research staff has been demonstrated (36).

6.2.5   Pressure pain thresholds

Pressure pain threshold was established using a pressure algometer (Somedic AB, Sweden) with a contact area of 1 cm^2 applied perpendicularly to the skin with a ramp rate of 50kPa/s. PPT was defined as the moment the sensation of pressure becomes one of pressure and pain. Standardised instructions were read to participants: "The moment the pressure increases to a point where it first feels uncomfortable or painful, press and release the button. This means the very first onset of discomfort or pain and not the most pressure that you can bear". A cut-off pressure value of 1000kPa was set for safety purposes. Four trials were performed with a minimum 10 second rest between trials. The mean threshold was calculated for each site from the last three trials. Four standardised

sites were tested in the following sequence; the dorsal wrist, tibialis anterior, upper trapezius and lumbar spine. The wrist was tested at the middle of the dorsal aspect of the wrist joint line. The leg was tested at the muscle belly of tibialis anterior, approximately 2.5 cm lateral and 5 cm distal to the tibial tubercle. The upper trapezius was tested at the mid-point between the C7 spinous process and the lateral acromion. The lumbar spine was tested at the erector spinae, 2 cm lateral to the L4/L5 interspinous space.

6.2.6   Cold pain threshold

A Modular Sensory Analyzer (MSA) thermal stimulator (Somedic AB, Sweden) using a 12.5cm^2 (25mm x50mm) probe was used to obtain the CPT at one standardised body site, on the skin at the middle of the dorsal aspect of the wrist joint line. The starting temperature was set as 32°C with a cut off temperature of 5°C. The temperature decreased at 1°C/s until the participant first perceived pain and pressed the control switch to terminate the test. For CPT, the following instructions were given to participants "Allow the temperature to drop until the moment it reaches a point where it feels uncomfortably or painfully cold, and then press the button. This means the very first onset of discomfort or pain and not the most cold that you can bear". Four trials were performed with a 10 second rest period between trials. The mean threshold was calculated from the last three trials.

6.2.7   Musculoskeletal pain status

Pain experience was determined using items from the Örebro Musculoskeletal Pain Questionnaire (ÖMPQ). The number of musculoskeletal pain areas was determined from an individual question asking "Where do you have pain?" with instruction to select appropriate sites from the options of neck, shoulder, arm, upper back, lower back, leg and other ('please state'). In the Örebro questionnaire, pain was defined as "musculoskeletal (muscle and bone) aches or pains, such as back, shoulder or neck pain". Participants were classified by number of pain areas endorsed into 'No pain areas', 'Single-site pain' and 'Multisite pain' (i.e. two or more pain areas) groups. Pain chronicity was categorized from the ÖMPQ question "How long have you had your current pain problem?" into less than 3 months, 3-12 months and > 12 months. Pain frequency was determined using the ÖMPQ question "How often would you say that you have

experienced pain episodes, on average, during the past three months?", using a numerical rating scale (NRS) with 1 indicating "never" and 10 indicating "always". Pain intensity was calculated from the mean of two ÖMPQ questions "How would you rate the pain that you have had during the past week?" and "In the past three months, on average, how bad was your pain on a 0-10 scale?", using an NRS with 1 indicating "no pain" and 10 indicating "pain as bad as it could be".

6.2.8 Other variables

A number of other variables were collected at 22-years to provide a profile of participants and to control for confounders of pain sensitivity. Potential confounders of the association between pain sensitivity and PA/SB measures were considered based on a previous investigation of correlates of PPT and CPT in the Raine cohort at the 22-year follow-up (24). Statistically significant, known, independent correlates of increased pressure pain sensitivity measures were test site, sex (female), higher waist-hip ratio (WHR) and poorer mental health (as measured by the Mental Component Summary (MCS) of the Short Form-12, version 2 (SF-12)) (24). Statistically significant, known, independent correlates of increased cold pain sensitivity measures were sex (female), poorer mental health and smoking (24).

Waist and hip circumference were measured using a metric tape measure and standard protocol, to calculate the WHR. Health-related quality of life was measured using the SF-12 (37), a validated and reliable measure of health related quality of life. Twelve questions produce two summary measures: a MCS; and Physical Component Summary (PCS) (37). Each SF-12 scale is a norm-based score with a mean of 50 and standard deviation of 10, with higher scores indicating better quality of life (37). The MCS and PCS of the SF12 were categorised into those with a score ≥50 and <50. Subjects were asked, "Do you currently smoke cigarettes/cigars?" and were classified accordingly as smokers or non-smokers

6.2.9 Statistical analysis

Multivariable regression models were used to examine the association between PPT and CPT measures (outcome variable) with each of the 10 PA and SB measures (independent variables). For these models, PA and SB measures were parameterised as

continuous variables with the exception of moderate PA and MVPA which were categorized into deciles due to left-skew distribution, and vigorous PA and MVPA accumulated in ≥10 min bouts, which were categorized into three groups with one-third of participants registering zero activity and the remaining values split at the median of the non-zero values (1.75 and 13 mins/day respectively). The analyses for all variables were adjusted for waking wear time per day (mean of daily totals on valid days, mins/day, except for 'Proportion of sedentary time≥20mins') and number of days of valid wear time (>10 hours/day). The analysis of breaks from sedentary time was adjusted for total sedentary time to reflect a break rate based on total sedentary time per day. All models were stratified by pain area groups in keeping with the aim of the study to estimate associations between PA and SB with pain sensitivity separately for people with 'no pain areas', 'single-site pain' and 'multisite pain'. The sample size of smallest of these groups ('single-site pain', n=112) gave 80% power to detect increases in R^2 of at least 0.05 due to addition of a PA or SB variable to a base model of relevant covariates with R^2 of 0.15 at α=0.05. Estimates are presented with 95% confidence intervals and p-values. All models were examined for linearity of effects and absence of influential outliers, and with non-linearity modelled by addition of a quadratic term. For PPT models, linear regression models utilising generalized estimating equations with an exchangeable correlation structure to account for the repeated measures over four sites were used. PPT models were adjusted for potential confounders (24) of sex, test site, waist-hip ratio and MCS. For CPT models, Tobit regression models were used as measures were left-censored due to the lower limit of the testing equipment being 5°C. CPT models were adjusted for potential confounders (24) of sex, smoking and MCS. A sensitivity analysis was performed, to test if results of the main analysis were potentially biased by atypical activity levels as some participants with only a few valid days of accelerometer wear were included. Thus, the sensitivity analysis included only data from those participants with at least 3 valid weekdays and 1 valid day of weekend data in PPT and CPT regression models.

6.3   Results

The demographic, pain, physical, quality of life and psychological data of the 714 participants (by pain groups) are summarised in Table 6.1. Summary statistics for PA and SB are presented in Table 6.2 and for PPT (by site) and CPT in Table 6.3. The participants'

were asked to wear the accelerometer for one week, but the number of valid days wearing the accelerometer ranged from 1 to 15 with a mean (SD) of 5.3 (2.4).

Multivariable regression models for the association of PA and SB measures with PPT stratified by number of pain areas are shown in Table 6.4. For the 'Single-site pain', those categorized with median amounts of MVPA accumulated in ≥10min bouts greater than 13mins/day were associated with more pressure pain sensitivity (p=0.035), with PPT estimated to be 95.0kPa (95%CI: -171.0, -19.9, p=0.013) lower compared with participants with a value between >0 and ≤13mins/day and 75.3kPa (95%CI: -160.8, 10.3, p=0.085) lower than those subjects with 0 mins/day. There were no other associations observed between PA and SB and PPT. A sensitivity analysis including only those participants with at least 3 valid weekdays and 1 valid day of weekend data (n=460, 'No pain areas': n=281, n=157 excluded, 'Single-site pain: n=69, n=44 excluded, 'Multisite pain': n=110, n=53 excluded) returned similar strength and direction of regression coefficients (Appendix 1).

Multivariable regression models for the association of PA and SB with CPT stratified by number of pain areas are shown in Table 6.5. In the 'Multisite pain group', higher levels of vigorous PA was associated with higher cold pain sensitivity (p=0.011) with CPT of participants with ≥1.75mins/day estimated to be 5.1°C (95%CI: 0.7, 9.4, p=0.022) higher (more cold pain sensitivity) compared with participants with zero mins/day, and 7.2°C (95%CI: 2.4, 12.2, p=0.004) higher that those participants with <1.75mins/day. In the 'No pain areas' group, more breaks from sedentary time (adjusted for minutes of sedentary time per day) were significantly associated with lower cold pain sensitivity, with CPT estimated to be 0.8°C (95%CI: -1.5, -0.1, p=0.046) less (i.e. less cold pain sensitivity) for each 10-break increment per day. There were no other associations observed between PA and SB and CPT. A sensitivity analysis including only those participants with at least 3 valid weekdays and 1 valid day of weekend data (n=454, 'No pain areas': n=277, n=153 excluded, 'Single-site pain: n=68, n=54 excluded, 'Multisite pain': n=109, n=51 excluded)) returned similar strength and direction of regression coefficients (Appendix 2).

Table 6.1   Summary statistics for demographic, pain, physical, quality of life, psychological and smoking measures

Variable	No pain areas (n=438) Mean (SD) or Number (%)	Range	Single-site pain (n=113) Mean (SD) or Number (%)	Range	Multisite pain (n=163) Mean (SD) or Number (%)	Range
Age (years)	22.1 (0.6)	21.0 – 24.4	22.1 (0.6)	20.7 – 24.3	22.1 (0.7)	21.0 – 24.2
Sex (female)	187 (42.7%)		57 (50.5%)		119 (73.0%)	
Pain chronicity						
<3 months			54 (47.8%)		46 (28.2%)	
3-12 months			23 (20.4%)		30 (18.3)	
>12 months			36 (31.8%)		87 (53.4)	
Pain frequency			4.2 (2.3)		5.4 (2.4)	
Pain intensity			4.1 (1.9)		4.8 (2.0)	
Waist-hip ratio	0.83 (0.07)	0.66 – 1.09	0.83 (0.07)	0.65 – 1.00	0.81 (0.08)	0.68 – 1.09
SF-12[a]						
PCS	55.3 (4.9)	24.6 – 66.5	52.07 (6.0)	34.80 – 65.40	51.10 (8.2)	14.6 – 70.9
PCS≥50	343 (86.8%)		73 (70.0%)		104 (65.8%)	
MCS	50.0 (9.5)	11.7 – 62.5	47.7 (9.2)	24.40 – 62.40	43.0 (11.4)	-0.8 – 62.2
MCS≥50	201 (50.9%)		55 (50.4%)		51 (32.3%)	
Smoking[b] (yes)	66 (15.1%)		20 (17.9%)		29 (17.9%)	

Missing data (all participants): [a] 52, [b] 4, PCS: physical component summary, MCS: mental component summary.

Table 6.2   Summary statistics for physical activity and sedentary behaviour measures

Variable	No pain areas (n=438)		Single-site pain (n=113)		Multisite pain (n=163)	
	Mean (SD) or Median (IQR)	Range	Mean (SD) or Median (IQR)	Range	Mean (SD) or Median (IQR)	Range
Valid days	5.3 (2.5)	1 – 15	5.3 (2.3)	1 – 10	5.4 (2.5)	1 - 9
Moderate PA (mins/day)	28.5 (17.8, 46)	0.0 – 214.0	31.8 (19.0, 49.1)	2.3 - 175.0	25.6 (14.5, 37.8)	1.0 - 112.9
Vigorous PA (mins/day)	0.3 (0, 2.5)	0.0 – 31.2	0.3 (0, 1.4)	0.0 – 33.0	0.0 (0.0, 1.4)	0.0 - 25.0
MVPA (mins/day)	30.4 (19.0, 48.9)	0.0 – 243.2	35.0 (19.5, 53)	2.3 - 175.5	28.0 (15.2, 41.5)	1.0 - 114.3
MVPA in ≥10 min bouts (mins/day)	9.2 (1.3, 20.0)	0.0 – 170.7	9.3 (1.5, 23.2)	0.0 - 99.5	6.6 (0.0, 14.7)	0.0 - 77.6
Sedentary time per day (mins)	547.4 (94.0)	201.0 – 775.6	553.0 (99.9)	112.5 – 794.0	562.4 (96.1)	279.8 – 815.0
Sedentary time as percentage of non-MVPA time	63.6 (9.7)	28.7 – 87.4	63.8 (10.0)	23.0 - 82.5	64.6 (9.4)	29.2 - 83.8
Sedentary time ≥ 20 mins (mins/day)	185.3 (80.2)	0.0 – 480.0	203.0 (85.4)	30.5 - 445.6	193.5 (81.8)	41.0 – 488.0
Sedentary time ≥ 30 mins (mins/day)	115.3 (66.9)	0.0 – 406.0	130.1 (72.4)	10.3 - 364.6	120.5 (68.0)	0.0 – 389.0
Proportion of Sedentary time≥20mins (percent)	32.9 (11.6)	0.0 – 80.3	35.8 (11.6)	10.8 - 64.8	33.6 (11.1)	11.0 - 73.7
Number of breaks from sedentary time per day	96.8 (18.7)	27.0 – 152.5	93.8 (17.6)	34.0 - 139.1	97.8 (18.4)	42.0 – 138.0

PA: physical activity; MVPA: moderate vigorous physical activity

Table 6.3 Summary statistics for pressure and cold pain threshold measures

Variable	No pain areas (n=438)		Single-site pain (n=113)		Multisite pain (n=163)	
	Median (IQR)	Range	Median (IQR)	Range	Median (IQR)	Range
PPT lumbar spine (kPa)	421.7 (288.7, 606.0)	69.3 – 1000.0	389.3 (280.3, 600.3)	85.3 – 1000.0	338.0 (247.2, 511.2)	82.0 – 1000.0
PPT tibialis anterior (kPa)	415.5 (284.0, 577.0)	74.0 – 1000.0	392.3 (325.0, 566.0)	86.6 – 1000.0	362.7 (275.7, 528.3)	84.0 – 1000.0
PPT upper trapezius (kPa)	261.0 (185.7, 384.3)	44.3 – 1000.0	260.3 (179.0, 392.7)	61.0 – 1000.0	228.7 (165.7, 332.7)	25.0 – 1000.0
PPT wrist (kPa)	390.7 (281.3, 530.3)	91.7 – 1000.0	398.3 (288.3, 527.0)	105.3 – 1000.0	363.0 (274.3, 532.3)	40.3 – 1000.0
CPT (°C)	9.2 (5.0, 20.3)	5.0 – 28.9.0	9.2 (5.0, 22.7)	5.0 – 30.3	11.5 (5.0, 22.7)	5.0 – 29.8.0

PPT: pressure pain threshold; CPT: cold pain threshold

Table 6.4   Multivariable regression models for PPT (kPa) measures

Variable	No pain areas (n=438) Regression coefficient (95% CI)[d]	p-value	Single-site pain (n=113) Regression coefficient (95% CI)[d]	p-value	Multisite pain (n=163) Regression coefficient (95% CI)[d]	p-value
Moderate PA (mins/day)[a, b]						
Linear term	0.7 (-23.7, 25.1)	0.998[e]	10.7 (-35.8, 57.2)	0.179[e]	-18.6 (-48.1, 10.8)	0.121[e]
Quadratic term	-0.1 (-2.6, 2.5)		-2.2 (-7.0, 2.6)		3.0 (-0.5, 6.5)	
Vigorous PA (mins/day)[a, b]						
Zero	Ref	0.669[e]	Ref	0.854[e]	Ref	0.543[e]
<1.75mins/day	-17.7 (-64.4, 28.9)	0.455	-23.6 (-109.0, 61.8)	0.588	28.1 (-32.9, 89.2)	0.367
≥1.75mins/day	--19.4 (-66.1, 27.4)	0.417	-15.7 (-99.7, 68.2)	0.713	28.5 (-32.6, 89.5)	0.361
MVPA (mins/day)[a, b]						
Linear term	-5.6 (29.8, 18.5)	0.897[e]	10.4 (-35.4, 56.2)	0.204[e]	-16.4 (-46.1, 13.3)	0.172[e]
Quadratic term	0.6 (-1.9, 3.1)		-2.1 (-6.9, 2.6)		2.7 (-0.9, 6.3)	
MVPA in ≥10 min bouts (mins/day)[a, b]						
Zero	Ref	0.607[e]	Ref[f]	0.035[e]	Ref	0.536[e]
≤13mins/day	16.6 (-32.8, 66.1)	0.509	20.1 (-67.0, 107.3)	0.650	-0.9 (-59.8, 57.9)	0.976
>13mins/day	-3.3 (-53.0, 46.3)	0.895	-75.3 (-160.8, 10.3)	0.085	29.3 (-35.2, 93.9)	0.373
Sedentary time per day (mins)[a, b]	-1.2[g] (-3.3, 0.9)	0.264	-0.4[g] (-4.3, 3.5)	0.847	-1.5[g] (-4.3, 1.3)	0.287
Sedentary time as percentage of non-MVPA time [a, b]	-12.0[h] (-31.0, 7.1)	0.217	-4.6[h] (-38.3, 29.0)	0.787	-9.7[h] (-35.1, 15.7)	0.453
Sedentary time ≥ 20 mins (mins/day)[a, b]	-1.2[g] (-3.4, 1.1)	0.298	-0.3[g] (-4.3, 3.6)	0.865	-2.5[g] (-5.4, 0.4)	0.094

Variable	No pain areas (n=438)		Single-site pain (n=113)		Multisite pain (n=163)	
	Regression coefficient (95% CI)[d]	p-value	Regression coefficient (95% CI)[d]	p-value	Regression coefficient (95% CI)[d]	p-value
Sedentary time ≥ 30 mins (mins/day)[a, b]	-1.2[g] (-3.9, 1,5)	0.375	0.0[g] (-4.7, 4.7)	0.996	-2.6[g] (-6.1, 0.9)	0.150
Proportion of sedentary time≥20mins (percent)[b]	-8.1[i] (-23.5, 7.3)	0.302	4.0[i] (-24.6, 32.5)	0.786	-18.1[i] (-39.6, 3.4)	0.100
Number of breaks from sedentary time/day[a, b, c]	1.1[j] (-14.1, 11.9)	0.867	-4.7[j] (-30.2, 20.8)	0.718	0.2[j] (-18.5, 18.0)	0.982

[a] Adjusted for awake wear time; [b] adjusted for number of days of valid wear time; [c] adjusted for sedentary time per day; [d] Adjusted for sex, site, waist-hip ratio, SF12-mental component summary; [e] Overall p-value; [f] Contrast of group 2 vs 1: -95.4 (-171.0, -19.9), p=0.013; [g] Difference estimate represents the expected change for a 10min change in sedentary or sitting time; [h] Difference estimate represents the expected change for a 10% change in sedentary time as % of non-MVPA time; [i] Difference estimate represents the expected change for a 10% change in proportion of sedentary time≥20mins; [j] Difference estimate represents the expected change for 10 breaks in sedentary time; CI: confidence interval; PA: physical activity; MVPA: moderate vigorous physical activity

Table 6.5   Multivariable Tobit regression models for CPT (°C) measures

Variable	No pain areas (n=430)		Single-site pain (n=112)		Multisite pain (n=160)	
	Regression coefficient (95% CI)[d]	p-value	Regression coefficient (95% CI)[d]	p-value	Regression coefficient (95% CI)[d]	p-value
Moderate PA (mins/day)[a, b]						
Linear term	0.4 (0.0, 0.8)	0.073	0.0 (-0.8, 0.8)	0.978	-0.1 (-0.7, 0.6)	0.783
Vigorous PA (mins/day)[a, b]						
Zero	Ref	0.199[e]	Ref	0.146[e]	Ref[f]	0.011[e]
<1.75mins/day	2.4 (-0.4, 5.1)	0.092	1.5 (-3.7, 6.6)	0.577	-2.2 (-6.6, 2.2)	0.320
≥1.75mins/day	2.0 (-0.8, 4.7)	0.162	-3.9 (-9.0, 1.2)	0.133	5.1 (0.7, 9.4)	0.022
MVPA (mins/day)[a, b]						
Linear term	0.4 (0.0, 0.8)	0.059	-0.1 (-0.9, 0.6)	0.756	0.0 (-0.7, 0.6)	0.966
MVPA in ≥10 min bouts (mins/day)[a, b]						
Zero	Ref	0.118[e]	Ref	0.835[e]	Ref	0.383[e]
≤13mins/day	1.9 (-1.1, 4.8)	0.216	1.6 (-3.9, 7.2)	0.560	0.2 (-4.1, 4.5)	0.930
>13mins/day	3.1 (0.1, 6.1)	0.040	1.3 (-4.1, 6.6)	0.642	2.8 (-1.9, 7.4)	0.241

Variable	No pain areas (n=430)		Single-site pain (n=112)		Multisite pain (n=160)	
	Regression coefficient (95% CI)[d]	p-value	Regression coefficient (95% CI)[d]	p-value	Regression coefficient (95% CI)[d]	p-value
Sedentary time per day (mins)[a, b]	0.0[g] (0.0, 0.2)	0.472	0.1[g] (-0.2, 0.3)	0.569	0.1[g] (-0.1, 0.3)	0.596
Sedentary time as percentage of non-MVPA time[a, b]	0.7[h] (-0.4, 1.9)	0.226	0.7[h] (-1.4, 2.9)	0.503	0.4[h] (-1.5, 2.2)	0.704
Sedentary time ≥ 20 mins (mins/day)[a, b]	0.1[g] (-0.1, 0.2)	0.267	0.0[g] (-0.3, 0.2)	0.931	0.0[g] (-0.2, 0.3)	0.742
Sedentary time ≥ 30 mins (mins/day)[a, b]	0.1[g] (-0.1, 0.2)	0.287	0.0[g] (-0.3, 0.3)	0.854	0.0[g] (-0.3, 0.3)	0.963
Proportion of sedentary time≥20mins (percent)[b]	0.6[i] (-0.3, 1.4)	0.215	0.0[i] (-1.8, 1.9)	0.968	0.0[i] (-1.6, 1.6)	0.996
Number of breaks from sedentary time/day[a, b, c]	-0.8[j] (-1.5, -0.0)	0.046	0.4[j] (-1.2, 2.0)	0.595	0.3[j] (-1.1, 1.6)	0.684

[a] Adjusted for awake wear time; [b] adjusted for number of days of valid wear time; [c] adjusted for sedentary time per day; [d] adjusted for sex, smoking, SF12-mental component summary; [e] Overall p-value; [f] Contrast of group 2 vs 1: 7.2 (2.4, 12.2), p=0.004: [g] Difference estimate represents the expected change for a 10min change in sedentary or sitting time; [h] Difference estimate represents the expected change for a 10% change in sedentary time as % of non-MVPA time; [i] Difference estimate represents the expected change for a 10% change in proportion of sedentary time≥20mins; [j] Difference estimate represents the expected change for an additional 10 breaks in sedentary time; CI: confidence interval; PA: physical activity; MVPA: moderate vigorous physical activity

6.4   Discussion

To our knowledge, this study is the largest community-based, comprehensive investigation into the association of objectively measured, habitual PA and SB with tissue sensitivity to noxious pressure and cold stimuli in young adults. Overall, little was detected in the way of associations between PA and SB with pressure and cold pain sensitivity. However, there were some interesting associations of note for the 'Single-site pain' group between PA and pressure pain sensitivity, for the 'Multisite pain' group for PA and cold pain sensitivity and for the 'No pain areas' group for more breaks from sedentary time and cold pain sensitivity.

6.4.1   Strengths and limitations

Strengths of the study include sample size, age specific population, consideration of number of pain sites, control for potential correlates of pressure and cold pain sensitivity and the use of accelerometry to objectively measure PA and SB, including intensity, frequency, duration and pattern of accumulation over time (6). The large sample at one age results in good power to estimate associations at this particular age, but the limitation is that the results may not be generalizable across age groups. Importantly, PA as measured in this study reflects habitual activity, providing a different capture of associations between pain sensitivity and PA when compared to laboratory controlled exercise protocols (14). While previous studies using self-report measurement of PA suggest an association between higher levels of PA and decreased pressure and cold pain sensitivity (21, 22), they are limited by small participant numbers (n<72), recall bias of activity by using self-report measurement (38), and the poor correlation of self-report with objective measurement of PA (39). Previously, only one study considered objective measurement of SB and this only included pain-free participants (n=444), finding no association between pressure and cold pain sensitivity and total daily sedentary time (24).

Affective factors potentially influence the relationship between PA and pain sensitivity, however a previous study reported that major depression did not moderate this relationship (40). The multivariable regression models in our study were adjusted for mental health as previous investigations of the Raine cohort have reported an association of the MCS with PPT and CPT (24).

There were limitations in this study. Accelerometers were worn on the hip, therefore not measuring arm movement, were not worn while swimming and were insensitive to cycling and gradients while walking or running (41). The authors acknowledge the limitations of an inclusion criteria of at least 1 valid day of wear time, however the sensitivity analysis including only participants with more valid days of wear time returned similar strength and direction of regression coefficients. Therefore, the inclusion criteria for wear time did not limit the results of this study.

The pressure and cold pain threshold measures used in this study may not be ideal to specifically capture the relationship of habitual PA and SB with pain sensitivity. PA can result in exercise induced hypoalgesia, with potential underlying mechanisms including acute recruitment of descending inhibitory control systems (42). In this context, the use of dynamic quantitative sensory testing measures such as conditioned pain modulation or temporal summation may be more appropriate to capture evoked sensitivity modulation associated with PA (43). However, conditioned pain modulation and exercise induced hypoalgesia have been found to be partially impaired in chronic pain patients with high versus low pressure pain sensitivity (16).

The literature suggests the number of pain sites is an important factor to consider when investigating the relationship between PA and pain sensitivity (15, 17), hence in the current study, participants were categorized according to their current pain status, so chronicity of pain was not considered, meaning the 'Single-site pain' and 'Multisite pain' groups contained participants with pain of varying duration. Table 6.1 reports the 'Multisite pain' group contained participants with higher levels of pain chronicity, pain frequency and pain intensity when compared to the 'Single-site pain' group.

Numerous statistical contrasts were performed without adjustment of the type I error rate, adopting the philosophy of Sterne et al (44) of the unadjusted p-value as strength of evidence against the null hypothesis, and the 95% confidence interval as the range of credible values for the population parameter. It is possible that the few associations observed in this study occur by chance only, and the confidence intervals for these estimates indicate that differences may not be of a meaningful magnitude. Furthermore, the associations detected are only cross-sectional, and give us no information as to how PA and SB behaviours might temporally heighten or lower pressure and cold pain sensitivity. The following discussion of the associations identified by this study is therefore presented with this caveat in mind.

6.4.2 Pain sensitivity, physical activity and sedentary behaviour

With respect to findings regarding pressure pain sensitivity, for the 'Single-site pain' group, participants with higher levels of MVPA accumulated in ≥10min bouts (>13 mins/day) demonstrated greater pressure pain sensitivity compared with those participants with ≤13 mins/day MVPA accumulated in ≥10min bouts, but not compared to those with no MVPA accumulated in ≥10min bouts. These findings suggest that for participants with 'single site pain', how MVPA is accumulated (mins accumulated in longer bouts of MVPA) may be important in the context of heightened pressure pain sensitivity. The mechanisms underlying heightened pressure pain sensitivity and PA in the 'single site pain' group are likely complex, potentially involving both neuronal (45) and non-neuronal factors (e.g. immune) (46). Given pressure pain sensitivity was measured across four sites and models were adjusted for site, this association might plausibly reflect changes in central nociceptive processing or modulation (for example, altered endogenous descending control system efficiency) (14) or facilitated spatial/temporal summation in response to PA (16), rather than primarily peripheral sensitisation (as this would manifest in a more localised site sensitivity). However, it is unclear why this association would be detected for the single-site pain group, but not multisite pain. Variable effects of PA on pressure pain sensitivity in both clinical and experimental pain populations have been reported (15), but interpretation is complicated by differences in study quality, design, exercise protocols, measurement tools, clinical populations and outcomes (14).

With respect to findings on cold pain sensitivity, for those with 'multisite pain', participants falling within the highest tertile of vigorous PA (VPA) had greater cold pain sensitivity when compared with participants with lower or no vigorous PA. It is unclear what this association might reflect, as in this 'multisite pain group', similar differences between VPA levels for pressure sensitivity would also be expected, given the potential for facilitated (temporal and spatial) nociception from deep tissues following exercise in multisite pain (for example in chronic widespread pain, or fibromyalgia (16, 17). Notwithstanding this point, differences in cold sensitivity levels have been demonstrated previously in a non-clinical cohort drawn from the Raine Study (young females), with heightened cold pain sensitivity evident in those females reporting moderate to severe menstrual pain (47) and an association between low cortisol response to stress and

musculoskeletal pain in females with heightened cold pain sensitivity (13). These authors suggest that cold hypersensitivity may reflect changes in central regulatory systems linked to homeostasis (including thermosensation and thermoregulation). It is also possible that VPA in this group may differentially influence cold and pressure pain sensitivity, as these psychophysical tests are designed for nociceptors located in skin and muscle tissue, respectively (33). Collectively, these findings allude to potentially important dose-relationships between PA/exercise and pain sensitivity, suggesting that higher amounts of VPA may not be ideal for all musculoskeletal pain conditions, particularly for clinical populations with two or more pain areas (15, 17).

The association of lower cold pain sensitivity with an increase in the number of breaks from sedentary time for participants in the 'No pain areas' group also suggests the way sedentary time is accumulated may be related to pain sensitivity. Increased breaks in sedentary time, independent of total sedentary time, have demonstrated associations with lower waist circumference (48, 49), lower inflammatory marker concentration (48) and improved plasma glucose levels (48, 49). These physiological effects may suggest mechanisms whereby more breaks from sedentary time could be associated with lower cold pain sensitivity partly through mechanisms including improved energy metabolism and lower circulating inflammatory markers. Young adults spend most of the waking day being sedentary (6) and targeted interventions for pain prevention and also for improving other life-course health trajectories, should consider the accumulation patterns of sedentary time.

6.5   Conclusions

This study was a comprehensive investigation into the association of pressure and cold pain sensitivity with habitual, objectively measured PA and SB in young adults. In this community-based sample of young adults with 'No pain areas', 'Single-site pain' and 'Multisite pain' few associations between PA and SB with pressure and cold pain sensitivity were demonstrated. These findings suggest that consideration of patterns of accumulation of PA and SB are important for future research, and highlight the need for high quality longitudinal studies that would enable better characterisation of the pain sensitivity of cohorts over time, and related temporal influences of PA and SB on tissue sensitivity.

Research funding

Conflicts of interest

There are no actual or potential conflicts of interest for any of the authors.

Informed consent

Informed consent has been obtained from all individuals included in this study

Ethical approval

The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, Ethics approval for the Raine Study Cohort 22-year follow up was obtained from the University of Western Australia (UWA) (RA/4/1/5202).

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Appendix 1

Univariable regression model for pressure pain thresholds (kPa) and cold pain thresholds (°C)

Variable	No pain areas (n=281) Regression coefficient (95% CI)[d]	p-value	Single-site pain (n=69) Regression coefficient (95% CI)[d]	p-value	Multisite pain (n=110) Regression coefficient (95% CI)[d]	p-value
Moderate PA (mins/day)[a, b]						
Linear term	4.0 (-36.6, 28.7)	0.721[e]	37.6 (-16.6, 91.9)	0.091[e]	-12.2(-49.2, 4.7)	0.441[e]
Quadratic term	0.0 (-3.4, 3.4)		-5.1 (-10.7, 0.5)		2.1 (-2.2, 6.5)	
Vigorous PA (mins/day)[a, b]						
Zero	Ref	0.582[e]	Ref	0.527[e]	Ref	0.544[e]
<1.75mins/day	-30.1 (-87.3, 27.1)	0.302	-55.3 (-43.1, 153.6)	0.271	38.1 (-30.0, 106.3)	0.273
≥1.75mins/day	-21.5 (-80.5, 37.6)	0.541	-19.6 (-83.2, 122.4)	0.709	20.7 (-53.7, 95.1)	0.586
MVPA (mins/day)[a, b]						
Linear term	-10.2 (-42.9, 22.5)	0.560[e]	52.5 (-0.5, 105.5)	0.038[e]	-7.2 (-44.5, 30.2)	0.170[e]
Quadratic term	0.6 (-2.7, 3.9)		-6.5 (-12.0, -1.0)		1.3 (-3.1, 5.7)	
MVPA in ≥10 min bouts (mins/day)[a, b]						
Zero	Ref	0.630[e]	Ref	0.084[e]	Ref	0.897[e]
≤13mins/day	-0.9 (-70.7, 69.1)	0.980	83.1 (-28.4, 194.7)	0.144	-12.8 (-60.8, 86.3)	0.734
>13mins/day	-22.8 (-93.5, 47.9)	0.527	-9.7 (-118.3, 98.6)	0.858	19.3 (-62.6, 101.2)	0.644

Variable	No pain areas (n=281)		Single-site pain (n=69)		Multisite pain (n=110)	
	Regression coefficient (95% CI)[d]	p-value	Regression coefficient (95% CI)[d]	p-value	Regression coefficient (95% CI)[d]	p-value
Sedentary time per day (mins)[a, b]	-0.6[f] (-3.4, 2.3)	0.702	-1.1[f] (-4.2, 6.3)	0.694	-0.5[f] (-4.2, 3.1)	0.770
Sedentary time as percentage of non-MVPA time[a, b]	-7.7[g] (-34.0, 18.6)	0.568	-2.2[g] (-43.9, 48.3)	0.926	-1.1[g] (-35.2, 33.1)	0.951
Sedentary time ≥ 20 mins (mins/day)[a, b]	-1.2[f] (-4.1, 1.8)	0.432	-0.2[f] (-5.0, 5.5)	0.928	-0.9[f] (-4.9, 3.2)	0.677
Sedentary time ≥ 30 mins (mins/day)[a, b]	-1.8[f] (-5.4, 1.7)	0.315	0.4[f] (-5.4, 6.1)	0.892	-1.4[f] (-6.5, 3.6)	0.574
Proportion of sedentary time≥20mins (percent)[b]	-12.8[h] (-34.0, 8.4)	0.237	4.3[h] (-34.2, 42.7)	0.828	-9.9[h] (-39.4, 19.5)	0.508
Number of breaks from sedentary time/day[a, b, c]	2.4[i] (-14.3, 19.1)	0.779	-7.7[i] (-40.3, 25.0)	0.645	-1.8[i] (-25.1, 21.5)	0.878

[a] Adjusted for awake wear time; [b] adjusted for number of days of valid wear time; [c] adjusted for sedentary time per day; [d] Adjusted for sex, site, waist-hip ratio, SF12-mental component summary; [e] Overall p-value; [f] Difference estimate represents the expected change for a 10min change in sedentary or sitting time; [g] Difference estimate represents the expected change for a 10% change in sedentary time as % of non-MVPA time; [h] Difference estimate represents the expected change for a 10% change in proportion of sedentary time≥20mins; [i] Difference estimate represents the expected change for 10 breaks in sedentary time; CI: confidence interval; PA: physical activity; MVPA: moderate vigorous physical activity

Appendix 2

Multivariable Tobit regression models for CPT (°C) measures (min 3 valid weekdays, 1 valid weekend day)

Variable	No pain areas (n=277) Regression coefficient (95% CI)[d]	p-value	Single-site pain (n=68) Regression coefficient (95% CI)[d]	p-value	Multisite pain (n=109) Regression coefficient (95% CI)[d]	p-value
Moderate PA (mins/day)[a, b]						
Linear term	0.4 (-0.1, 1.0)	0.112	-0.3 (-1.3, 0.7)	0.548	-0.1 (-1.0, 0.7)	0.800
Vigorous PA (mins/day)[a, b]						
Zero	Ref	0.405[e]	Ref	0.819[e]	Ref[f]	0.004[e]
<1.75mins/day	2.4 (-1.1, 5.8)	0.180	-0.7 (-7.0, 5.5)	0.819	-2.9 (-8.0, 2.2)	0.267
≥1.75mins/day	1.6 (-2.0, 5.1)	0.394	-2.0 (-8.5, 4.7)	0.534	6.5 (1.0, 11.9)	0.020
MVPA (mins/day)[a, b]						
Linear term	0.5 (-0.1, 1.0)	0.085	-0.4 (-1.3, 0.6)	0.451	0.0 (-0.8, 0.9)	0.954
MVPA in ≥10 min bouts (mins/day)[a, b]						
Zero	Ref	0.364[e]	Ref	0.725[e]	Ref	0.438[e]
≤13mins/day	1.5 (-2.9, 5.8)	0.500	1.7 (-5.7, 9.1)	0.651	0.1 (-5.5, 5.7)	0.962
>13mins/day	2.9 (-1.5, 7.3)	0.190	-0.6 (-7.6, 6.5)	0.873	3.2 (-3.0, 9.3)	0.306

Variable	No pain areas (n=277) Regression coefficient (95% CI)[d]	p-value	Single-site pain (n=68) Regression coefficient (95% CI)[d]	p-value	Multisite pain (n=109) Regression coefficient (95% CI)[d]	p-value
Sedentary time per day (mins)[a, b]	0.0[g] (-0.1, 0.2)	0.506	0.1[g] (-0.3, 0.4)	0.764	0.0[g] (-0.3, 0.3)	0.951
Sedentary time as percentage of non-MVPA time[a, b]	0.9[h] (-0.7, 2.6)	0.261	0.8[h] (-2.9, 3.0)	0.956	-0.1[h] (-2.6, 2.5)	0.991
Sedentary time ≥ 20 mins (mins/day)[a, b]	0.1[g] (-0.1, 0.3)	0.176	0.0[g] (-0.2, 0.4)	0.622	-0.1[g] (-0.4, 0.2)	0.591
Sedentary time ≥ 30 mins (mins/day)[a, b]	0.2[g] (-0.1, 0.4)	0.143	0.1[g] (-0.3, 0.5)	0.604	-0.2[g] (-0.5, 0.2)	0.427
Proportion of sedentary time≥20mins (percent)[b]	1.0[i] (-0.3, 2.3)	0.119	1.1[i] (-1.5, 3.6)	0.402	-0.8[i] (-3.0, 1.5)	0.494
Number of breaks from sedentary time/day[a, b, c]	-1.1[j] (-2.1, -0.1)	0.032	-0.3[j] (-2.4, 1.8)	0.798	0.8[j] (-0.9, 2.5)	0.355

[a] Adjusted for awake wear time; [b] adjusted for number of days of valid wear time; [c] adjusted for sedentary time per day; [d] adjusted for sex, smoking, SF12-mental component summary; [e] Overall p-value; [f] Contrast of group 2 vs 1: 9.3 (3.8, 14.9), p=0.001: [g] Difference estimate represents the expected change for a 10min change in sedentary or sitting time; [h] Difference estimate represents the expected change for a 10% change in sedentary time as % of non-MVPA time; [i] Difference estimate represents the expected change for a 10% change in proportion of sedentary time≥20mins; [j] Difference estimate represents the expected change for an additional 10 breaks in sedentary time; CI: confidence interval; PA: physical activity; MVPA: moderate vigorous physical activity

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Chapter 7   The Association of Early Life Stressors with Pain Sensitivity and Pain Experience at 22 Years

The association of early life stressors with pain sensitivity and pain experience at 22 years

Robert Waller[a,*], Anne J. Smith[a], Peter B. O'Sullivan[a], Helen Slater[a], Michele Sterling[b], Leon M. Straker[a]

Abstract

Early life stress (ELS) can significantly influence biological pathways associated with nociception, increasing vulnerability to future heightened pain sensitivity and subsequent risk of pain events. However, very little human research has investigated the association of ELS, measured across multiple domains, with future pain sensitivity. Data from Gen1 and Gen2 of the Raine Study were used to assess the association between a wide range of early life stressors, including antenatally, and pressure and cold pain sensitivity at young adulthood. Participants were classified into 2 groups according to their cold pain sensitivity. In addition, the interaction between ELS, pain sensitivity, and pain experience (based on Örebro Musculoskeletal Pain Questionnaire) at age 22 years was examined. Analysis was performed using both a complete case and multiple imputation approach, adjusting for contemporaneous 22-year correlates, with comparable results in each model. More problematic behaviour at age 2 years was associated with less pressure pain sensitivity at 22 years (13.7 kPa, 95% CI: 1.0-27.0, $P = 0.037$), with no interaction between problematic behaviour and pain experience at 22 years. For those reporting a moderate/high pain experience at 22 years, poor family functioning increased the odds ratio for high cold pain sensitivity (3.0, 95% CI: 1.6-5.6), but for those reporting no/low pain experience, it did not (OR:1.2, 95% CI: 0.8-1.8). This study provides the most comprehensive investigation of the relationship between ELS and pressure and cold pain sensitivity in young adults supporting early life as a critical period of development influencing future nociceptive processing.

Keywords: Early life stress, Pain sensitivity, Longitudinal, Pain experience, The Raine Study

1. Introduction

Early life, antenatally and in the first 3 years postnatally, is a critical developmental period when biological systems undergo maturation and associated changes can become enduring.[4,26] During this time, various stressors can significantly influence biological pathways associated with nociception, increasing vulnerability to future pain sensitivity and pain events, and potentially increasing the risk of poorer health outcomes.[4,14,15] Early life stress (ELS) can influence hypothalamic pituitary adrenal (HPA) function,[7,69] and this is possibly consequential given that a hyporesponsive HPA stress response is associated with heightened pain sensitivity.[23,30,37] Early life stress is likely important given that heightened pain sensitivity is associated with persistent or recurrent musculoskeletal pain disorders,[16,35,52,56] and future pain is partially predicted by heightened pain sensitivity.[2,14,15,17,44,66,68]

Early life stress represents any threat to an organism's homeostasis, in early life, which induces a physiological response in biological systems.[26] Multiple factors could manifest as ELS, and these can increase risk of future heightened pain sensitivity through biological, psychological, and social pathways.[31] Findings from both basic animal studies, human experimental pain studies, and clinical studies provide some insights into the role of ELS on pain sensitivity. Data from animal studies on the effect of early life social stressors reveal alterations in adult biological processes mediated through complex interactions between epigenetic, endocrine, and immune systems.[69] Both animal and human studies suggest the effect of ELS is potentially partially mediated by maternal care giving.[29,31,69] Data from human studies demonstrate higher pain sensitivity in adolescence and early adulthood after exposure to a significant neonatal pain experience, findings consistent with augmented nociceptive processing.[38,55] However, other human pain studies report reduced pain sensitivity after significant neonatal pain experience, probably reflective of whether sensory testing occurred at a pain-naive site or site previously exposed to pain.[39,45,61]

Some socioenvironmental conditions during early life in humans can be considered as ELS, such as exposure to smoking, multiple stressful events, financial stress, poor family functioning, and less breastfeeding, and these are all associated with poorer health outcomes into adolescence and adulthood.[18,36,40,41] Early life stress may also manifest as problematic behaviours.[40,41] There is very little human research investigating the association of ELS (including in utero) with pain sensitivity. A comprehensive consideration of multiple factors that could manifest as ELS directly, are proxies for ELS (eg, income) or are consequences of ELS (eg, child behaviour), would advance the understanding of the role for ELS in future pain sensitivity.

The literature suggests early life is a critical period of development, and therefore, the aims of this study were to (1)

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Abstract

Early life stress (ELS) can significantly influence biological pathways associated with nociception, increasing vulnerability to future heightened pain sensitivity and subsequent risk of pain events. However, very little human research has investigated the association of ELS, measured across multiple domains, with future pain sensitivity. Data from Gen1 and Gen2 of the Raine Study were used to assess the association between a wide range of early life stressors, including antenatally, and pressure and cold pain sensitivity at young adulthood. Participants were classified into two groups according to their cold pain sensitivity. Additionally, the interaction between ELS, pain sensitivity and pain experience (based on Örebro Musculoskeletal Pain Questionnaire) at age 22 years was examined. Analysis was done using both a complete case and multiple imputation approach, adjusting for contemporaneous 22 year correlates, with comparable results in each model. More problematic behaviour at age two was associated with less pressure pain sensitivity at 22 years (13.7kPa, 95%CI:1.0 to 27.0, p=0.037), with no interaction between problematic behaviour and pain experience at 22 years. For those reporting a moderate/high pain experience at 22 years, poor family functioning increased the odds ratio for high cold pain sensitivity (3.0, 95%CI: 1.6 to 5.6), but for those reporting no/low pain experience it did not (OR:1.2, 95%CI: 0.8 to 1.8). This study provides the most comprehensive investigation of the relationship between ELS and pressure and cold pain sensitivity in young adults supporting early life as a critical period of development influencing future nociceptive processing.

7.1   Introduction

Early life, antenatally and in the first 3 years postnatally, is a critical developmental period when biological systems undergo maturation and associated changes can become enduring [4,26]. During this time, various stressors can significantly influence biological pathways associated with nociception, increasing vulnerability to future pain sensitivity and pain events, and potentially increasing the risk of poorer health outcomes [4,14,15]. Early life stress (ELS) can influence hypothalamic pituitary adrenal (HPA) function [7,69], and this is possibly consequential given that a hypo-responsive HPA stress response is associated with heightened pain sensitivity [23,30,37]. ELS is likely important given that heightened pain sensitivity is associated with persistent or recurrent musculoskeletal pain disorders [16,35,52,56] and future pain is partially predicted by heightened pain sensitivity [2,17,44,66,68].

ELS represents any threat to an organism's homeostasis, in early life, which induces a physiological response in biological systems [26]. Multiple factors could manifest as ELS and these can increase risk of future heightened pain sensitivity through biological, psychological and social pathways [31]. Findings from both basic animal studies, human experimental pain studies and clinical studies provide some insights into the role of ELS on pain sensitivity. Data from animal studies on the effect of early life social stressors, reveal alterations in adult biological processes mediated via complex interactions between epigenetic, endocrine and immune systems[69]. . Both animal and human studies suggest the effect of ELS is potentially partially mediated by maternal care giving [29,31,69]. Data from human studies demonstrate higher pain sensitivity in adolescence and early adulthood following exposure to a significant neonatal pain experience, findings consistent with augmented nociceptive processing [38,55]. However, other human pain studies report reduced pain sensitivity following significant neonatal pain experience, probably reflective of whether sensory testing occurred at a pain naive site or site previously exposed to pain [39,45,61].

Some socioenvironmental conditions during early life in humans can be considered as ELS, such as exposure to smoking, multiple stressful events, financial stress, poor family functioning and less breastfeeding, and these are all associated with poorer health outcomes into adolescence and adulthood [18,36,40,41]. ELS may also manifest as problematic behaviours [40,41]. There is very little human research investigating the

association of ELS (including in utero) with pain sensitivity. A comprehensive consideration of multiple factors that could manifest as early life stress directly, are proxies for ELS (for example income) or are consequences of ELS (for example child behaviour), would advance the understanding of the role for ELS in future pain sensitivity.

The literature suggests early life is a critical period of development, therefore, the aims of this study were to: (1) investigate whether a range of factors potentially contributing to ELS, measured antenatally and in the first three years postnatally, are associated with pressure and cold pain sensitivity at young adulthood (22 years of age); (2) examine the interaction between early life stressors, pressure and cold pain sensitivity and pain experience at young adulthood.

7.2   Methods

7.2.1   Study population

Data for this longitudinal study were obtained from the Raine Study (http://www.rainestudy.org.au). The study commenced with 2900 women (Gen1) who enrolled before the 18th gestation week [32], with 2868 children (Gen2) born entering the initial birth cohort. Initial measures from Gen1 were collected at 16-20 weeks gestation, with a follow-up at 34 weeks gestation. For Gen2, data has been collected at 1, 2, 3, 5, 8, 10, 14, 17, 20 and 22 year follow-ups. The current study used data obtained during gestation, from 1 to 3 years and from the Gen2-22 year follow-up. Description of participation rates at follow-up, representativeness of the cohort and detail of follow-up measures have been reported [50]. The Gen2-22 year follow-up ran between March 2012 and July 2014, with 2086 participants still 'active' and contacted for participation. Of these, 1234 took part in some aspect of the Gen2-22 year follow-up [50]. A comparison of the characteristics of the active participants with census data from all similarly aged young adults in Western Australia collected in 2011 showed that the sample remains widely representative on a range of variables including education level, employment status, income, marital status, number of offspring, hours worked and occupation [50]. The ethnicity of the active participants was 85.0% Caucasian, 0.9% Aboriginal and Torres Strait Islander, and 14.1% non-Caucasian. Ethics approval for the 22-year follow-up was obtained from the University of Western Australia Human Research Ethics Committee (RA/4/1/5202).

7.2.2   Data Collection at Gen2-22 year follow-up

Data for the Gen2-22 year follow-up were collected as part of 4 hours of testing followed by an overnight sleep study [51]. Questionnaires were completed before physical assessments and were checked for completion by a research assistant. Anthropometry measures, and pressure and cold pain threshold testing were part of the physical assessment protocol conducted by twelve Raine research staff, all of who were thoroughly trained in the data collection procedures and used standardised protocols. Participants were eligible for analysis if they had data for at least one valid pain sensitivity test.

7.2.3   Quantitative sensory testing

Due to the already significant time burden required of the participants in the broader Raine Study, pain sensitivity measures were limited to pressure pain threshold (PPT) and cold pain threshold (CPT). A standardised protocol ('method of limits') consistent with current best practice recommendations [5] was used to measure PPT and CPT at a constant room temperature. All pain threshold measurements were taken from the right side of the body as it has been shown there is side to side consistency in pain sensitivity measurement [42]. PPT was tested first, followed by CPT, to minimise the risk of mechanical hyperalgesia, consistent with previous investigations that have reported this protocol [47,62]. Both PPT and CPT have demonstrated inter-examiner and intra-subject reliability with reasonable levels of standard error of measurement [65]. Excellent interrater and intrarater reliability for PPT testing by the Raine Study research staff has been demonstrated [64].

7.2.4   Pressure pain thresholds

Pressure pain threshold was established using a pressure algometer (Somedic AB, Sweden) with a contact area of 1 cm^2 applied perpendicularly to the skin with a ramp rate of 50kPa/s. PPT was defined as the moment the sensation of pressure becomes one of pressure and pain. Standardised instructions were read to participants: "The moment the pressure increases to a point where it first feels uncomfortable or painful, press and release the button. This means the very first onset of discomfort or pain and not the most pressure that you can bear". A cut-off pressure value of 1000kPa was set for safety

purposes. Four trials were performed with a minimum 10 second rest between trials. The mean threshold was calculated for each site from the last three trials. Four standardised sites were tested in the following sequence; the dorsal wrist, tibialis anterior, upper trapezius and lumbar spine. The wrist was tested at the middle of the dorsal aspect of the wrist joint line. The leg was tested at the muscle belly of tibialis anterior, approximately 2.5 cm lateral and 5 cm distal to the tibial tubercle. The upper trapezius was tested at the mid-point between the C7 spinous process and the lateral acromion. The lumbar spine was tested at the erector spinae, 2 cm lateral to the L4/L5 interspinous space.

7.2.5   Cold pain threshold

A Modular Sensory Analyzer (MSA) thermal stimulator (Somedic AB, Sweden) using a $12.5cm^2$ (25mm x50mm) probe was used to obtain the CPT at one standardised body site, on the skin at the middle of the dorsal aspect of the wrist joint line. The starting temperature was set as 32°C with a cut off temperature of 5°C. The temperature decreased at 1°C/s until the participant first perceived pain and pressed the control switch to terminate the test. For CPT, the following instructions were given to participants "Allow the temperature to drop until the moment it reaches a point where it feels uncomfortably or painfully cold, and then press the button. This means the very first onset of discomfort or pain and not the most cold that you can bear". Four trials were performed with a 10 second rest period between trials. The mean threshold was calculated from the last three trials.

7.2.6   Pain experience

Pain experience was determined using items from the Örebro Musculoskeletal Pain Questionnaire (ÖMPQ). Participants who answered no to the ÖMPQ question "Do you currently have any body pain?" were re-directed away from answering further ÖMPQ questions and assigned to a 'No pain' group. Participants who answered 'yes' were classified into pain experience groups by latent class analysis. This statistical technique is used to subgroup people according to their profile across several variables (indicators), specifically here, the ÖMPQ [25] items on pain chronicity, frequency, intensity and number of pain areas. Pain chronicity was categorized using the ÖMPQ question "How long have you had your current pain problem?" into less than 2 months, 3-6 months, 6-

12 months and > 12 months. Pain frequency was determined using the ÖMPQ question "How often would you say that you have experienced pain episodes, on average, during the past three months?" using a numerical rating scale (NRS) 1 indicating never and 10 indicating always scale. Pain intensity was calculated from the mean of two ÖMPQ questions "How would you rate the pain that you have had during the past week?" and "In the past three months, on average, how bad was your pain on a 0-10 scale?", using a NRS with 1 indicating no pain and 10 indicating pain as bad as it could be. A count of pain sites (maximum 10) was calculated from the number of endorsed response options to a list of predefined body sites from the ÖMPQ question "Where do you have pain?" Previous study in this cohort reported a 3-class solution was the best fit determining "Low", "Medium" and "High" pain experience groups [63]. To ensure adequate statistical power for the current study, two pain experience groups were formed, "Low" (combining the "No pain" and "Low" pain experience participants, n=646 (70.4%)) and "High" (combining the "Medium" and "High" pain experience participants, n=271 (29.6%)).

7.2.7   Other Gen2-22 year variables

To enable control for possible confounding of associations between early life stressors and QST measures, several other variables collected at the Gen2-22 year follow-up were included. Inclusion was based on findings of previous QST investigations using Raine Study Gen2-22 year data [62,63]. Waist and hip circumference were measured using a standardized protocol and a metric tape measure, to calculate the waist-hip ratio (WHR). Participants were classified as smokers or non-smokers based on the answer to the question "Do you currently smoke cigarettes/cigars?" Income was measured by total usual pay per week after tax and for statistical analysis was categorized (coded from 1 to 5) according to 2012 Australian tax brackets [63]. The 5 usual pay per week after tax categories were: <$116 (1), $116 to 604 (2), $605 to 1076 (3), $1077 to 2180 (4), and >$2180 (5).

7.2.8   Early life stressors

7.2.8.1   Early life stress events

The number of life stress events was measured using a validated and reliable 11-item questionnaire selecting questions from the life stress inventory developed by Tennant and

Andrews [53]. The questions included problems with pregnancy, death of a close relative, death of a friend, marital problems, separation or divorce, problems with children, involuntary loss of own job, involuntary loss of partners job, financial hardship, residential move, and "other" stressful events. Mothers answered the questionnaire, whether the selected life stress events had been experienced since pregnancy at 18 weeks gestation. The questionnaire was repeated at 34 weeks gestation and referred to the prior 4 months. Antenatal life stress was determined from the combined total of the two antenatal life stress events questionnaire scores. At the Gen2-1, -2- and -3 year follow-ups, the primary caregiver reported on the whether the same 11 life stress were experienced in the previous 12 months. An average count of life stress events was calculated from the 3 follow-up measures when there was data from at least one time point.

7.2.8.2   Family functioning

Family functioning was measured at the Gen2-3 year follow-up using the general functioning subscale of the McMaster Family Assessment questionnaire completed by the primary caregiver, with scores ranging from 12 to 48 and higher scores indicating poorer family functioning [8]. The reliability and validity has been demonstrated [8].

7.2.8.3   Child Behaviour Checklist (CBCL)

Data on child behaviour was collected at the Gen2-2 year follow-up. The parent/guardian completed the CBCL for ages 2-3 (CBCL/2-3) which is a 99-item validated checklist measuring child behaviour during the previous six months [3]. The CBCL/2-3 raw scores were converted to sex-adjusted T-scores ranging from 24 to 83 for total behaviour with higher scores indicating more problematic behaviour.

7.2.8.4   Socioeconomic status

Family income, father's occupation, maternal education and whether the father was living with the family were considered. Yearly family income was measured at the Gen2-1, -2- and -3 year follow-ups and was categorized (coded from 1 to 5) according to Australian tax brackets at the time of data collection. These were: <$7,000 (1), $7,000 to $13,999 (2), $14,000 to $26,999 (3), $27,000 to $40,999 (4) and $\geq$ $41, 000 (5) per year. Categories over the 3 follow-ups were averaged when there was data from at least one

time point. At the Gen2-1 year follow-up, father occupation was categorized according to the Australian Standard Classification of Occupations, second edition [1], then dichotomized as either 'manager or professional' versus other. At the Gen1-18 week follow-up mothers were asked 'Since leaving school have you completed any further education?' Maternal education was dichotomized according to the response category with responses of 'none', 'trade certificate or apprenticeship' and 'other' versus 'professional registrations (non-degree)', 'college diploma or degree' and 'university degree'. A binary variable was created if the father was not living with the family at 1 or more of the Gen2-1, -2- and -3 year follow-ups.

7.2.8.5   Smoking

Exposure to smoking was determined during pregnancy and early life. If the mother was smoking at either the Gen1-18- or -34-week follow-up, the participant was classified as being exposed to smoke in utero. The participant was classified as being exposed to smoke in early life if the mother was smoking or if anyone living in the house smoked at the Gen2-1, -2- and -3 year follow ups.

7.2.8.6   Breastfeeding

At the Gen1-1 year follow-up, mothers were asked how long they breastfed their baby. Based on the responses, breastfeeding was dichotomized into either yes if breastfed at all or no if never breastfed.

7.2.9   Statistical analysis

Stata/IC version 15 for Windows (Statacorp LP, College Station, TX) was used for all analysis. PPT was analysed as a continuous outcome variable using linear mixed-effects regression models to account for the within-participant repeated measures of PPT across 4 body sites. CPT was bimodally distributed, which is potentially indicative of the emergence of two separate underlying populations of cold pain sensitivity [43]. Therefore, participants were classified into two groups according to their CPT, by means of latent class analysis of the CPT distribution using sex as an active covariate (Figure 7.1).
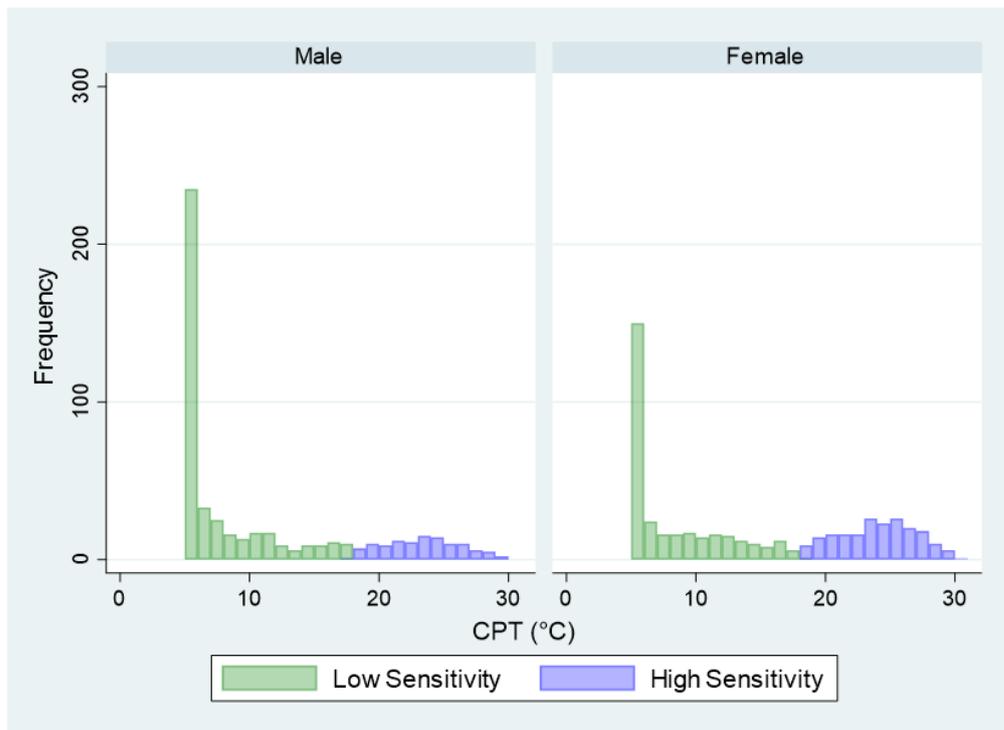
Figure 7.1 Cold pain threshold (CPT (°C)) distribution.

Subsequently, logistic regression models where used to estimate the differential odds for membership of the high cold sensitivity group according to levels of covariates of interest. These models accounted for relative uncertainty of membership of those close to the cut-off by weighting analyses by the estimated probability for membership for the allocated group for each individual. Due to the collection of data over six time points spanning 23 years, there was variation in patterns of missing data. The cumulative effect of missing data results in loss of precision and power when using a complete case analysis, potentially resulting in biased results [58]. Hence, analyses were performed both as complete case and using a multiple imputation approach [58].

Analysis proceeded according to the following steps:

Step 1: To identify early life variables potentially associated with pain sensitivity measures at age 22 years, a series of analyses were performed considering each candidate early life variable separately, using both complete case and multiple imputation analysis. Multiple imputation by chained equations in Stata was used to create 10 imputed copies of the dataset whereby missing covariate values were replaced by imputed ones [58]. Coefficients and standard errors adjusted for the variability between the 10 imputation sets using Rubin's combination rules [67]. Models in step 1

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were adjusted for previously reported contemporaneous correlates [62,63]: PPT was adjusted for sex, test site, income, pain experience and waist-hip ratio and CPT was adjusted for sex, income, pain experience and smoking.

Step 2: Early life variables with an adjusted association with PPT or CPT of p<0.200 from the complete case or multiple imputation analyses from step 1 were selected for further analysis. A bootstrapped backwards step-wise selection procedure with 2000 repetitions using a Wald test with a stopping rule of α=0.157 [58] was performed, using the selected early life variables, sex and Gen2-22 year correlates from step 1. The bootstrapped procedure provides internal validation of results guarding against sample specific, overly optimistic associations [58]. The overall percentage of times a variable was retained in the model was assessed [58]. This step was performed both as a complete case analysis and for each of the 10 imputed datasets (200 replications each dataset), and the overall percent of times a variable was retained from both the complete case (replications=2000) and multiply imputed datasets (replications = 2000) was calculated.

Step 3: Early life variables consistently retained across the bootstrapping samples at least 70% of the time were retained for final complete case and multiple imputation models, which were adjusted for sex and Gen2-22 year correlates. Due to nonlinearity of association with CPT, family functioning was further examined in this step for the form of the association with CPT, and subsequently dichotomised to contrast the upper tertile and combination of the lower two tertiles. In these final models, interaction between early life variables and pain experience group membership at age 22 were tested to explore the possibility that associations between early life factors and pain sensitivity outcomes were different in those with moderate to high pain experience versus those with no or low pain experience.

7.3   Results

There were 1065 participants with a least one valid pain sensitivity test, of which 537 were female. All variables are summarized in Table 7.1. Most variables had some missing data with a maximum missing of n=207 for an early life variable (CBCL) and n=190 for a Gen2-22 year variable (smoking).

Complete case and multiple imputation analyses of each early life variable separately (statistical analysis step 1) for the association with PPT adjusting for sex and Gen2-22 year correlates are reported in Table 7.2. Variables found to have an adjusted association (using complete case or multiple imputation) with PPT of p<0.200 were child behaviour, antenatal life stress events, biological father not living with the family and exposure to smoke in utero. In the bootstrapped stepwise selection models (statistical analysis step 2), child behaviour was retained 40.5% of the time in the complete case model and 85.9% of the time in the multiple imputation model. However, other early life candidate variables selected were below the 70% threshold (antenatal life stress events; 14.1% and 25.5% for complete case and multiple imputation respectively, biological father not living with the family 19.6% and 58.3% and exposure to smoke in utero 40.2% and 20.8%). In the final linear regression model (statistical analysis step 3, Table 7.3), for an increase in the CBCL total score of 10 (equal to 1 standard deviation), PPT was estimated to be 13.7kPa (95% CI, 1.0 to 27.0; p=0.037) higher (i.e. more problematic child behaviour was associated with less pressure pain sensitivity) in the complete case regression analysis and 15.3kPa (95% CI, 3.3 to 27.4; p=0.013) higher in the multiple imputation regression analysis. There was no evidence that this association differed according to pain experience at age 22 years, with no interaction detected between child behaviour and 22-year pain experience in either the complete case analysis (p=0.823) or the multiple imputation analysis (p=0.499). Other significant variables in the final linear regression model for the complete case and multiple imputation analysis were: females were estimated to be higher pressure pain sensitive (-128.8kPa, 95%CI:-157.8 to -99.8, p=0.001 and -148.2kPa, 95%CI: -172.1 to -124.4, p=0.001); higher taxable income at 22 years was associated with lower pressure pain sensitivity (24.3kPa, 95%CI: 8.7 to 39.9, p=0.002 and 23.4kPa, 95%CI:10.3 to 36.9, p=0.001); and for a 0.1 increase in waist-hip ratio at 22 years pressure pain sensitivity was estimated to be higher (-23.0kPa, 95%CI:-41.9 to -4.2, p=0.017 and -21.0kPa, 95%CI:-37.6 to -6.3).

Complete case and multiple imputation analyses of each early life variable separately for the association with CPT high sensitivity group membership, controlling for sex and Gen2-22 year correlates (statistical analysis step 1), are reported in Table 7.2. Variables found to have an adjusted complete case or multiple imputation association with CPT of p<0.200 were family functioning, family income and paternal occupation. In the bootstrapped stepwise selection models (statistical analysis step 2), family

functioning was retained 92.0% of the time in the complete case model and 82.1% of the time in the multiple imputation model. However, other early life candidate variables selected were below the 70% threshold (early life family income; 34.5% and 30.6% for complete case and multiple imputation respectively) and paternal occupation (28.2% and 40.0%). Using the complete case and multiple imputation data, there was a significant interaction between family functioning and 22-year pain experience (statistical analysis step 3, Table 7.4). For those in the moderate/high pain experience group, poor family functioning increased the odds of being in the high cold pain sensitivity group (OR: 3.0, 95%CI: 1.6 to 5.6, p=0.001 and 2.3, 95%CI: 1.3 to 3.9, p=0.004) whereas for those with no/low pain experience, there was no evidence of an association between family functioning and high cold pain sensitivity (OR:1.2, 95%CI: 0.8 to 1.8, p=0.445 and 1.2, 95%CI: 0.8 to 1.6, p=0.554). Female sex was associated with higher cold pain sensitivity in the final linear regression model in both the complete case and multiple imputation analysis (OR:2.3, 95%CI:1.6, p=0.001 to 3.2 and 2.1, 95%CI:1.5 to 2.8, p=0.001). The other significant Gen2-22 year variables associated with higher cold pain sensitivity in the multiple imputation analysis were smoking (OR:06, 95%CI:0.4 to 1.0, p=0.049) and higher pain experience (OR:1.5, 95%CI:1.1 to 2.0, p=0.017).

Table 7.1   Early life, 22-year and pain sensitivity variable summary statistics, case control

Variable	Number	Mean (SD), median (IQR) or Number (%)	Range
Early life			
Ethnicity (both parents Caucasian)	1065	905 (85.0%)	
Child behaviour (CBCL total score)	858	46.6 (10.0)	24 to 83
Early life family functioning	901	19.6 (5.6)	12 to 48
Lower two tertiles	574	16.3 (3.0)	12.0 to 21.8
Upper tertile	327	25.5 (4.0)	22.0 to 48.0
Antenatal life stress events (total)	968	2.0 (1.0 to 10.0)	0 to 12
Early life stress events (mean)	1038	1.3 (0.7 to 2.3)	0 to 6.25
Gestational weeks	1064	38.7 (2.2)	23 to 42
Gestational weight (grams)	1064	3314.3 (586.1)	750 to 5185
Early life Family income[*]	1043	2.1 (0.9)	1 to 5
Biological father not living with family	1050	162.0 (15.4%)	
Paternal occupation (not managerial or professional)	982	565.0 (57.5%)	
Maternal education (no college education or above)	1039	581.0 (45.9%)	
Exposed to smoke in utero (yes)	1039	229.0 (22.0%)	
Exposed to smoke in early life (yes)	1051	437.0 (41.6%)	
Breastfed (no)	1010	74.0 (7.7%)	

Variable	Number	Mean (SD), median (IQR) or Number (%)	Range
22-year variables			
Age at 22-year follow-up (years)	1065	22.2 (0.7)	21.0 to 24.4
Sex (female)	1065	537 (50.4%)	
22-year income[#]	875	2.5 (0.9)	1 to 5
22-year waist-hip ratio	1063	0.83 (0.07)	0.61 to 1.11
22-year smoking (yes)	972	157 (16.2%)	
22-year pain experience (medium and high)	917	271 (29.6%)	
Pain sensitivity measures			
PPT lumbar spine (kPa)	1049	461.3 (236.4)	69.3 to 1000
PPT tibialis anterior (kPa)	1055	457.3 (223.5)	74.0 to 1000
PPT upper trapezius (kPa)	1055	298.0 (179.0)	25.0 to 1000
PPT wrist (kPa)	1058	428.4 (197.1)	40.3 to 1000
PPT mean (kPa)	1060	411.1 (192.4)	66.75 to 1000
CPT all participants (°C)	1040	9.1 (5 to 20.5)	5.0 to 30.2
Low sensitivity group	727	5.7 (5.0 to 10.0)	5.0 to 18.2
High sensitivity group	313	23.8 (21.6 to 26.0)	18.0 to 30.3

SD: standard deviation; IQR: inter-quartile range; CBCL: child behaviour checklist total score; *Early life family income: average yearly family income (categorised according to Australian tax brackets at the time of data collection, <$7,000 (1), $7,000 to $13,999 (2), $14,000 to $26,999 (3), $27,000 to $40,999 (4) and ≥ $41, 000 (5)); PPT: pressure pain threshold; CPT: cold pain threshold; #Year-22 Income: total usual pay per week after tax (categorised according to 2012 Australian tax brackets, <$116 (1), $116 to 604 (2), $605 to 1076 (3), $1077 to 2180 (4), and >$2180 (5))

Table 7.2   Univariable regression for PPT (kPa) and CPT (°C): Complete case and multiple imputation models

Variables	PPT univariable analysis[#^]				CPT univariable analysis[#*]			
	Complete case		Multiple imputation		Complete case		Multiple imputation	
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
Child behaviour (CBCL total score)*	13.7 (1.0 to 27.0)	0.037	15.3 (3.3 to 27.4)	0.013	1.0 (1.0 to 1.0)	0.588	1.0 (1.0 to 1.0)	0.742
Family functioning	0.1 (-2.1 to 2.3)	0.915	1.4 (-0.8 to 3.5)	0.211	1.0 (1.0 to 1.1)	0.037	1.0 (1.0 to 1.0)	0.080
Antenatal life stress events (total)	6.6 (0.3 to 12.8)	0.039	4.2 (-1.2 to 9.6)	0.126	1.0 (0.9 to 1.1)	0.686	1.0 (0.9 to 1.0)	0.239
Early life stress events (mean)	-1.6 (-11.1 to 7.9)	0.737	3.0 (-6.6 to 12.6)	0.538	1.0 (0.9 to 1.2)	0.555	1.0 (0.9 to 1.2)	0.741
Gestational weeks	-1.2 (-6.7 to 4.2)	0.662	-1.3 (-6.2 to 3.5)	0.596	1.0 (0.9 to 1.1)	0.938	1.0 (0.9 to 1.1)	0.777
Gestational weight (grams)	0.0 (0.0 to 0.0)	0.423	0.0 (0.0 to 0.0)	0.297	1.0 (1.0 to 1.0)	0.461	1.0 (1.0 to 1.0)	0.926
Early life family income	0.0 (-13.1 to 13.1)	0.998	-4.3 (-16.5 to 7.9)	0.487	0.8 (0.7 to 1.0)	0.058	0.9 (0.8 to 1.0)	0.129
Biological father not living with family	13.6 (-19.8 to 46.9)	0.426	29.1 (-1.2 to 59.5)	0.060	1.2 (0.8 to 1.9)	0.390	1.0 (0.7 to 1.6)	0.812
Paternal occupation (not managerial or professional)	-9.9 (-34.8 to 14.9)	0.434	-5.8 (-28.3 to 16.6)	0.611	1.3 (0.9 to 1.8)	0.144	1.3 (1.0 to 1.8)	0.085
Maternal education (no college education or above)	0.2 (-24.1 to 24.6)	0.984	11.5 (-10.9 to 33.9)	0.315	1.1 (0.8 to 1.5)	0.525	1.0 (0.8 to 1.4)	0.893
Exposed to smoke in utero (yes)	24.8 (-4.1 to 53.7)	0.092	15.5 (-10.7 to 41.7)	0.247	1.2 (0.8 to 1.7)	0.406	1.2 (0.8 to 1.6)	0.340
Exposed to smoke in early life (yes)	1.4 (-22.8 to 25.6)	0.911	2.0 (-19.9 to 23.9)	0.857	0.9 (0.7 to 1.3)	0.628	1.0 (0.7 to 1.3)	0.959
Breastfed (no)	4.0 (-42.4 to 50.5)	0.865	10.0 (-32.9 to 52.9)	0.648	1.0 (0.5 to 1.8)	0.985	1.0 (0.6 to 1.7)	0.985

PPT: pressure pain threshold; CPT: cold pain threshold; CI: confidence interval; CBCL: child behaviour checklist total; *coefficient represents the expected change in PPT for a 10 point increase in CBCL total score; Early life family income: average yearly family income (categorised according to Australian tax brackets at the time of data collection, <$7,000 (1), $7,000 to $13,999 (2), $14,000 to $26,999 (3), $27,000 to $40,999 (4) and ≥ $41, 000 (5), coefficient represents expected change for a 1 category increment); [#]adjusted for sex, 22-year income: total usual pay per week after tax (categorised according to 2012 Australian tax brackets, <$116 (1), $116 to 604 (2), $605 to 1076 (3), $1077 to 2180 (4), and >$2180 (5)), 22-year pain experience; [^]Adjusted for 22-year waist-hip ratio, PPT test site; [*]Adjusted for 22-year smoking;

Table 7.3   Multivariable linear regression for PPT (kPa): complete case and multiple imputation models

| Variables | Linear mixed-effects regression | | | |
| | Complete case | | Multiple imputation | |
	Regression coefficient (95% CI)	p-value	Regression coefficient (95% CI)	p-value
Child behaviour (CBCL total score)*	13.7 (1.0 to 27.0)	0.037	15.3 (3.3 to 27.4)	0.013
Sex (female)	-128.8 (-157.8 to -99.8)	<0.001	-148.2 (-172.1 to -124.4)	<0.001
22-year income#	24.3 (8.7 to 39.9)	0.002	23.4 (10.3 to 36.9)	0.001
22-year waist-hip ratio¶	-23.0 (-41.9 to -4.2)	0.017	-21.9 (-37.6 to -6.3)	0.006
22-year pain experience (high)	-16.5 (-45.2 to 12.2)	0.259	-16.8 (-42.0 to 8.4)	0.192

PPT: pressure pain threshold; CI: confidence interval; CBCL: child behaviour checklist total score; *coefficient represents the expected change in PPT for a 10-point increase in CBCL total score; #22-year Income: total usual pay per week after tax (categorised according to 2012 Australian tax brackets, <$116 (1), $116 to 604 (2), $605 to 1076 (3), $1077 to 2180 (4), and >$2180 (5)), coefficient represents expected change for a 1 category increment); ¶Coefficient represents the expected change in PPT for a 0.1 change in waist-hip ratio

Table 7.4   Multivariable logistic regression for CPT (°C): complete case and multiple imputation models

	CPT logistic regression			
	Complete case		Multiple imputation	
Variables	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Early life family functioning (upper tertile)				
No/low pain experience	1.2 (0.8 to 1.8)	0.445	1.1 (0.8 to 1.6)	0.554
Moderate/high pain experience	3.0 (1.6 to 5.6)	<0.001	2.3 (1.3 to 3.9)	0.004
Sex (female)	2.3 (1.6 to 3.2)	<0.001	2.1 (1.5 to 2.8)	<0.001
22-year income[*]	0.9 (0.7 to 1.1)	0.201	0.9 (0.7 to 1.1)	0.260
22-year smoking (yes)	0.8 (0.5 to 1.3)	0.273	0.6 (0.4 to 1.0)	0.049
22-year pain experience (moderate/high)	1.4 (1.0 to 2.1)	0.058	1.5 (1.1 to 2.0)	0.017

CPT: cold pain threshold; CI: confidence interval; [*]22-year Income: total usual pay per week after tax (categorised according to 2012 Australian tax brackets, <$116 (1), $116 to 604 (2), $605 to 1076 (3), $1077 to 2180 (4), and >$2180 (5)), Odd ratio represents proportional change in odds per 1 category increment)

7.4 Discussion

7.4.1 Summary

This study is a unique, comprehensive investigation into the association of a wide range of factors representing early life stressors and young adult pressure and cold pain sensitivity. The results summarized below are from final linear regression models that had accounted for other ELS variables in the prior steps of the analysis. More problematic behaviour at age two was associated with less sensitivity to pressure pain at 22 years, after adjusting for sex and Gen2-22 year correlates. There was no interaction between problematic behaviour and 22-year pain experience. For those reporting a moderate/high pain experience at 22 years, poor family functioning increased the odds for more cold pain sensitivity.

7.4.2 Strengths and limitations

This rich longitudinal data set has allowed an investigation of a wide range of early life factors in a large, community-dwelling non-clinical cohort. While this study captured a wide range of early life factors, other influences known to result in long-term changes in pain sensitivity such as lived pain events (e.g.; experience of injections and/or early surgery) [60,61] and childhood trauma (e.g.; physical/sexual abuse) [4,34], have not been captured. The longitudinal nature of the study results in missing data from most variables, potentially biasing results [58]. However, this is partially mitigated by the robust statistical analysis with the inclusion of multiple imputation data sets thereby minimizing the risk of bias, provided data is missing at random or missing completely at random [58]. Additionally, the bootstrapped backwards step-wise selection procedure provided internal validation of results guarding against spurious associations and ensuring stability of the final multiple regression models [58]. Furthermore, a broad range of potential correlates of pressure and cold pain sensitivity have been investigated in the Raine Study cohort and the adjustment for previously reported contemporaneous correlates ensured more robust estimates.

7.4.3 How might early life stress be associated with pain sensitivity?

As a long period of time had elapsed between the early life stressors (captured antenatally to 3 years postnatally) and measures of pain sensitivity at young adulthood (22 years), our data must be interpreted with necessary caution as accurate and specific

developmental trajectories for this cohort and the related temporal pain sensitivity variance remain to be elucidated. Additionally, although this study identified associations, it is not possible to conclude a causal relationship between ELS and young adult pressure and cold pain sensitivity. Therefore, our findings are discussed in the context of how neurobiological mechanisms associated with ELS might influence future pain sensitivity.

During early life, including the antenatal period, neuronal connections are rapidly establishing memories and associations, with biological systems evolving accordingly [28]. ELS experienced during this period, including repetitive pain during neonatal hospitalization, may increase future vulnerability to pain, and in this context, both genetic and epigenetic factors play a major role in the embedding of ELS on neurobiological systems ([10] for a comprehensive review see [4]). Moreover, socioenvironmental conditions perceived as threatening, stressful, socially isolating or that create uncertainty, may trigger a molecular transcriptional response heightening pain sensitivity by up-regulating pro-inflammatory genes and down-regulating antibody and antiviral related genes [9,10,20].

Consequently, exposure to early life stressors can become entrenched in the life trajectory by modifying future responses to socioenvironmental exposures and subsequent gene transcription responses [12,15]. Such changes can affect enduring biologic system alterations and provide an understanding of why social stress could be associated with a predisposition to inflammatory-related common diseases including musculoskeletal, neoplastic, cardiovascular and metabolic [12,20]. A pro-inflammatory state can prime the nervous system (including the nociceptive apparatus) via immune activation, and is a key mechanism underlying heightened tissue sensitivity (for example, the cold pain sensitivity demonstrated in our findings). While not a prerequisite, these events may also ultimately increase the risk for persistent pain [9,14,21].

While the human brain develops rapidly after birth, it also continues to highly develop throughout adolescence [54]. Additionally, the physiological effects of early life stressors may be modified at later stages of human development depending on whether adverse social conditions are maintained or attenuated [11,12]. For example, for those in the moderate/high pain experience group, poor family functioning increased the odds of being in the high cold pain sensitivity group, whilst for those in the no/low pain experience group, it did not. This difference may represent cumulative and interactive

effects of multidimensional biopsychosocial and epigenetic factors relevant to pain sensitivity between 3 and 22 years. Life stress can result in chronic dysregulation of the HPA axis, with enduring hyper- or hypo-activation of stress response systems partially dependent on where in development stress events occur or accumulate, reflecting age-dependent differences in how the HPA axis responds to major stress events [4]. Of note however, not all individuals exposed to ELS develop pain, highlighting that differences likely relate to genetic makeup, resilience and the environment to which the individual is exposed across the lifespan.

Factors influencing pain sensitivity are known to vary across modalities that are distinct phenomena from an environmental and a genetic perspective [33]. Pressure and cold pain threshold quantitative sensory testing targets different nerve fibres that innervate the skin, muscle (and viscera) [13]. Pressure stimuli tests deep tissue sensitivity (muscle and viscera) [13], while cold stimulates superficial nociceptive fibres with evidence that cold pain in humans is mediated via nociceptors of cutaneous veins [22]. The divergent findings for pressure and cold may partially reflect different mechanisms driving somatosensory phenotypes.

The sympathetic nervous system is intimately involved in central nociceptive processing and can be sensitized by the stress regulation system, particularly by the HPA axis and subsequent alteration of circulating cortisol levels [27,30,46]. In our study, one effect of exposure to poor family functioning is potentially altered stress response systems sensitivity, which is reflected in the increased odds of high cold pain sensitivity. In young female adults of the Raine Study (Gen2-22 year follow-up, n=432), menstrual pain severity was associated with increased cold pain sensitivity (measured at the wrist, i.e., remote from the pelvis) after adjusting for potential confounding variables including musculoskeletal pain [47]. The changes in cold pain sensitivity reported were suggested to reflect altered central nociceptive processing due to disruption of thermosensation and thermoregulation, both modulated by central systems regulating homeostasis [47,59]. Increased cold pain sensitivity has been associated with sympathetic nervous system impairment in people with whiplash associated disorder, providing evidence for sympathetic nervous system disruption in the presence of cold hyperalgesia [48]

The mechanisms underlying the association of more problematic behaviour with less pressure pain sensitivity are unclear. Previous research on the Raine Study cohort has

reported significant risk factors for behaviour problems at age two including maternal stress and smoking during pregnancy [41]. At age five, significant risk factors were the experience of multiple life stress events, exposure to smoking, male gender and a short length of breastfeeding [41]. While the above factors were not associated with pain sensitivity in this study, other stressors not measured or inadequately captured in this study may be reflected by behaviour problems. As ELS has been linked with low reactivity of the stress response system, more problematic behaviour may be a reflection of this [7,37]. Low stress reactivity potentially manifests in less perceived threat to pressure stimuli (i.e. lower pressure pain sensitivity) supporting previous evidence that certain personality traits such as excitement seeking result in less experimental pain sensitivity [57]. Variable responses to pain stimuli can represent different pain coping strategies including behavioural distraction, affect, attentional focus and cognitive processing [6,24,49,57]. However, previous research in this area is limited with comparison of findings difficult due to variable methodology and small participant numbers.

7.4.4   Future directions

This study tested the hypothesis that early life represents a critical period of development, however, the Raine Study dataset also allows future testing of whether the accumulation or reduction of exposures to life stressors in childhood and adolescence influence pain sensitivity in young adulthood [28]. This may help to better understand distinct and common mechanisms associated with the effect of ELS on vulnerability to pain sensitivity and to pain events according to the timing of ELS exposures. Additionally, consideration of other measures, such as childhood trauma and pain events, in this and other cohorts during childhood and adolescence is required and could highlight other factors, that are associated with adult pain sensitivity.

7.4.5   Conclusion

This unique and comprehensive investigation, using robust statistical analysis, provides support for early life being a critical period of development, with results showing an association between ELS and future pain sensitivity. Specifically, more problematic behaviour at age two was associated with less pressure pain sensitivity at 22 years. ELS from poorer family functioning increased the odds for having high cold pain sensitivity at 22 years and for those reporting a moderate/high pain experience at 22 years, poor family

functioning further increased the odds of higher cold pain sensitivity. ELS may be a potential biomarker for future pain sensitivity and risk of pain, providing a potential target for early identification for risk of pain and timely management [11,19]. A better understanding of when during development and how early life socioenvironmental and biologic factors may influence pain sensitivity and the association between pain sensitivity with future pain, may offer opportunities to address and reduce the impact of pain from a broader public health and epidemiological perspective.

Acknowledgements

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Chapter 8 Discussion of Thesis

This thesis represents a comprehensive investigation of pain sensitivity in community-dwelling young-adults from the Raine Study, helping to provide a greater understanding of mechanisms relating to musculoskeletal pain disorders. The thesis comprised of five studies, the first being an assessment of the reliability of pressure pain threshold (PPT) measures as taken by Raine Study research assistants, and the next four integrating measures of pain sensitivity of Raine participants at 22 years of age with cross-sectional and existing longitudinal data. In this chapter, each of the studies will be summarised according to the aims of the thesis, followed by a discussion of the body of work as a whole, highlighting and integrating the findings, and their research and clinical significance. Finally, the strengths and limitations of the thesis and directions for future research will be discussed.

8.1 Summary of studies included in this thesis

8.1.1 Study 1: Pressure pain threshold testing reliability in young adults

The first study of this thesis aimed to (i) assess the intrarater and interrater reliability, including systematic bias, of pressure pain threshold (PPT) testing by the same method (handheld algometer) and at the same body sites (lumbar spine, tibialis anterior, neck and dorsal wrist) as in the larger cohort study; (ii) to calculate sample sizes required for parallel and cross-over studies for various effect sizes accounting for measurement error. Investigation of the multidimensional correlates of pain sensitivity, including PPT, requires the study of large cohorts, and thus the use of multiple raters, for sufficient statistical power. Although PPT testing has previously been shown to be reliable (Tunks, McCain et al. 1995, Chesterton, Sim et al. 2007, Walton, MacDermid et al. 2011), the reliability of multiple raters and investigation for systematic bias between raters has not been reported.

This study reported both intrarater reliability (intraclass correlation coefficient (ICC) = 0.81–0.99) and interrater reliability (ICC = 0.92–0.95) were excellent, and intrarater standard error of measurement (SEM) ranged from 79 to 100 kPa. There was systematic bias detected at three sites with no single rater tending to consistently rate higher or lower than others across all sites.

The key contribution to the literature from this study is that the observed excellent interrater ICCs support using multiple research assistants in large cohort studies. The excellent interrater reliability results were achieved via using standardised protocols and thorough training of raters. The results established that the measurement of PPT for the remaining studies in this thesis was reliable. A caveat is that an absence of any confounding of study estimates by rater is checked, due to systematic rater bias identified in this study.

8.1.2 Study 2: Pressure and cold pain threshold reference values in young adults

The second study in this thesis aimed to provide sex specific reference values of pressure and cold pain thresholds in young pain-free adults aged 21-24 years and examine the potential confounders of pressure and cold pain thresholds to inform research investigating associations with pain. Previously there was a lack of large population studies that had reported normal age and sex specific pain sensitivity distributions in healthy pain-free people. Additionally, prior studies did not adequately investigate or adjust for potential confounding variables (Rolke, Baron et al. 2006, Magerl, Krumova et al. 2010).

This study provided reference values for young adults for pressure pain threshold (lumbar spine, tibialis anterior, neck and dorsal wrist) stratified by sex and site, and cold pain threshold (CPT) (dorsal wrist) stratified by sex. Statistically significant, independent correlates of increased pressure pain sensitivity were site (neck, dorsal wrist), sex (female), higher waist-hip ratio and poorer mental health. Statistically significant, independent correlates of increased cold pain sensitivity measures were, sex (female), poorer mental health and smoking.

Study 2 provided the most comprehensive and robust sex specific reference values for PPT specific to four body sites, and CPT at the dorsal wrist for young adults aged 21–24 years. In addition, statistically significant, independent correlates of PPT and CPT were reported. These data provide an important resource to enable more accurate profiling and interpretation of pain sensitivity in musculoskeletal pain disorders in young adults. The independent associations of pain sensitivity provide insight into the complex associations of pain sensitivity that can be used in future research and to assist the interpretation of pain sensitivity in clinical practice.

8.1.3   Study 3: Pressure and cold pain sensitivity associations with musculoskeletal pain experience in young adults

The third study in this thesis investigated the cross-sectional associations between musculoskeletal pain experience and measures of pressure and cold pain sensitivity in Raine Study young adult participants. While knowledge of the relationship between pain experience and pain sensitivity in the adult population is expanding, there was a lack of large population-based studies to assist the understanding of pain mechanisms specifically in young adults (Skovbjerg, Jørgensen et al. 2017). Existing studies were also limited by not adequately adjusting associations for potential confounders. Often pain experience was captured by using only pain intensity and this may be the reason for the very weak associations reported in a meta-analysis between pain experience and pain sensitivity (Hübscher, Moloney et al. 2013). The pain experience is complex and capturing other parameters such as pain frequency, number of pain locations and chronicity are important in terms of impacts on quality of life and disability (Hoftun, Romundstad et al. 2011).

This study considered four aspects of the pain experience: pain chronicity, pain frequency, pain intensity, and number of pain areas. Potential confounders were based on those factors identified in Study 2. A substantial proportion of young adults (29.5%) were classified as having "Medium" or "High" pain experience with frequent, intense, long-lasting pain in multiple body areas. There were 61.3% of participants classified as "No pain" and 9.2% classified as having "Low" pain. This study identified associations between pain experience and cold, but not pressure, pain sensitivity. Participants in the "Medium" and "High" pain experience groups demonstrated heightened cold pain sensitivity compared with the "No pain" group, after adjusting for sex and smoking.

This study contributed to the literature by providing the most extensive investigation of the relationship between musculoskeletal pain experience and pressure and cold pain sensitivity in young adults. Membership to the "Medium" or "High" pain experience groups might be partially explained by cold pain sensitivity, suggesting augmented nociceptive mechanisms are potentially associated with the higher pain experience.

8.1.4   Study 4: Pressure and cold pain sensitivity associations with physical activity or sedentary behaviour in young adults

The fourth study of this thesis explored the relationships between pain sensitivity and physical activity (PA) and sedentary behaviour (SB) in the Raine Study young adult

participants. Prior laboratory-based evidence suggested PA transiently lowers pain sensitivity in people without pain or with single-site pain, whereas PA was frequently associated with a transient increase in pain sensitivity for those with multisite pain (Naugle, Fillingim et al. 2012, Daenen, Varkey et al. 2015). In contrast, the association between SB and pain sensitivity was largely unconsidered with no observational studies using objective measurement of SB reported. Although laboratory studies and small field intervention studies suggested associations between PA and pain sensitivity (Nielsen, Andersen et al. 2010, Geva and Defrin 2013), the association of objectively measured, habitual PA or SB with pain sensitivity required further investigation.

Based on evidence from previous laboratory based research, participants for this study were grouped by number of pain areas into "No pain areas", "Single-site pain" and "Multisite pain" groups. PA and SB were objectively measured using accelerometry over a 1-week period. Common thresholds were used to class each waking minute as sedentary, light intensity, moderate intensity or vigorous intensity. Ten PA and SB variables were derived for analysis to represent how PA and SB were accumulated. The association of PA and SB variables with pain sensitivity was tested separately within each pain group by multivariable regression, adjusting for potential confounders.

This study was the largest community-based, comprehensive investigation into the association of pain sensitivity with objectively measured, habitual PA and SB in young adults. Overall, little was detected in the way of associations between PA and SB with pressure and cold pain sensitivity. However, there were some interesting associations of note suggesting that the pattern of accumulation of PA and SB are important to consider for future research.

8.1.5 Study 5: The association of pressure and cold pain sensitivity and pain experience in young adults with early life stressors

The aim of the fifth and final study of this thesis was to evaluate a range of early life stressors (prenatal and 1st three years) for association with pressure and cold pain sensitivity in Raine Study participants at age 22, and to investigate if pain experience at age 22 moderated any associations. Early life is a critical developmental period when biological systems undergo maturation and associated changes can become enduring (Maniam, Antoniadis et al. 2014, Agorastos, Pervanidou et al. 2019) with stress and/or

pain experience significantly influencing biological pathways associated with nociception, increasing vulnerability to future pain sensitivity and pain events (Denk, McMahon et al. 2014, Denk and McMahon 2017, Agorastos, Pervanidou et al. 2019). No prior studies have comprehensively considered the relationship between multiple factors that could manifest as early life stress (including in utero) and future pain sensitivity.

A range of prenatal and 1-3 year measures of socioenvironmental stress investigated that could be considered as early life stress included exposure to smoking, multiple stressful events, financial stress, poor family functioning and no breastfeeding. Early life stress may also manifest as problematic behaviour (Robinson, Mattes et al. 2011) and was also considered. The study identified more problematic behaviour at age two was associated with less pressure pain sensitivity at 22 years and for those reporting a moderate/high pain experience at 22 years, poor family functioning increased the odds of higher cold pain sensitivity.

This study contributed to the literature by providing the most comprehensive investigation of the relationship between early life stressors and pressure and cold pain sensitivity in young adults with the findings providing some evidence for early life as a critical period of development influencing future nociceptive phenotypes.

8.2   Discussion on how thesis contributes to current knowledge?

8.2.1   Why is pain sensitivity important to understand?

There is substantial literature describing heightened pain sensitivity in clinical populations with persistent or recurrent localised musculoskeletal pain disorders (Slater, Arendt-Nielsen et al. 2005, Suokas, Walsh et al. 2012, Marcuzzi, Dean et al. 2015) and widespread musculoskeletal pain disorders (Gerhardt, Eich et al. 2016). Heightened pain sensitivity reflects altered nociceptive processing including peripheral and central nociceptive augmentation. Current evidence supports the use of PPT and CPT to assist with the identification and characterisation of somatosensory phenotypes in various localised (Slater, Arendt-Nielsen et al. 2005, Chien and Sterling 2010, Finan, Buenaver et al. 2013, Rabey, Slater et al. 2015) and widespread musculoskeletal pain disorders (Blumenstiel, Gerhardt et al. 2011). There is some emerging evidence that heightened pain sensitivity increases the risk for the development of musculoskeletal pain

(Greenspan, Slade et al. 2013) and persistence of musculoskeletal pain (Georgopoulos, Akin-Akinyosoye et al. 2019). Using quantitative sensory testing (QST) to help predict the prognosis of a musculoskeletal pain disorder and better understand somatosensory phenotypes has potential to guide stratification of the 'right', or high value care, to improve disability and pain outcomes (Georgopoulos, Akin-Akinyosoye et al. 2019). However, understanding pain sensitivity in people with musculoskeletal pain is often limited as studies use a variable battery of QST measures, taken at single time points, and measured at single sites (locally) without the addition of a remote test site or control site away from the main pain site.

Understanding the relationship of pain sensitivity to the pain experience and disability associated with musculoskeletal pain disorders is complicated by inconsistent results and poor strength of association (Hübscher, Moloney et al. 2013). Here, it is important to remember that any pain experience is complex, subjective, and highly personal. Only considering pain intensity or disability limits the potential for understanding pain sensitivity in the context of the multiple contributing and interacting dimensions and constructs of the pain experience. Other contributions to these variable study findings include; systematic reviews and meta-analyses using the available small samples with varying case mixes and conditions; application of varying QST methodologies that do not always adhere to best practice recommendations; most studies are cross-sectional with limited data from longitudinal studies; assessors not being blinded; and a lack of control for confounding by factors that may potentially influence pain sensitivity.

While there is significant literature describing pain sensitivity in musculoskeletal disorders, there are complex mechanisms contributing to the variation in pain sensitivity to noxious stimuli in people without pain and people with pain. While the knowledge of mechanisms that account for the variation in pain sensitivity is nascent, it currently covers genetic, environmental, biological and psychological mechanisms that can influence pain sensitivity in the individual (Nielsen, Stubhaug et al. 2008, Denk, McMahon et al. 2014). Pain sensitivity can change in response to disruption to the homeostasis of the nervous system which is modulated by complex and dynamic interactions across multiple systems including the peripheral and central nervous system, neuroimmune and neuroendocrine system and autonomic nervous system (Denk and McMahon 2017).

The disability associated with persistent musculoskeletal pain is enormous worldwide (James, Abate et al. 2018), placing a significant burden on society with regards to cost to the health system and lost productivity (2019, Karshikoff, Tadros et al. 2019). The substantial money spent medically managing people with musculoskeletal pain has failed to improve outcomes, with reasons including a lack of adherence to contemporary evidence-based guidelines (Allen, Choong et al. 2016, Briggs, Cross et al. 2016, Lin, Wiles et al. 2018) and over emphasis on the biomedical approach to management of musculoskeletal pain disorders (Foster, Anema et al. 2018, O'Sullivan, Caneiro et al. 2018). A large body of evidence suggests complex mechanisms and factors other than musculoskeletal pathology are important in the development and maintenance of persistent musculoskeletal pain (Brinjikji, Luetmer et al. 2015, Arendt-Nielsen 2017, Culvenor, Øiestad et al. 2018). The inadequate current management for persistent musculoskeletal pain highlights the need for a better understanding of the complex neurobiological mechanisms underlying pain and for translation of that knowledge to identify better management options (Karshikoff, Tadros et al. 2019). A better understanding of the contribution of pain sensitivity to musculoskeletal pain is required.

Young adulthood is a particularly relevant life stage as musculoskeletal pain commonly begins to manifest in late childhood and early adolescence (Leboeuf-Yde and Kyvik 1998, Hoftun, Romundstad et al. 2011, O'Sullivan, Beales et al. 2012, Slater, Jordan et al. 2016), with a significant impact by the late adolescence (Eccleston and Clinch 2007, King, Chambers et al. 2011, O'Sullivan, Smith et al. 2017). Late adolescence to young adulthood is a critical life transition stage where trajectories of musculoskeletal pain can become established and can continue into later adulthood, with potentially negative impacts on quality of life and lost productivity (Leboeuf-Yde and Kyvik 1998, Hoftun, Romundstad et al. 2011, O'Sullivan, Beales et al. 2012, Slater, Jordan et al. 2016, Coenen, Smith et al. 2018). While knowledge of the relationship between pain experience and pain sensitivity in the adult population is expanding, there is a lack of large population-based studies to assist our knowledge of pain sensitivity specifically in young adults. Longitudinal studies are required to help understand how pain sensitivity develops and contributes to musculoskeletal pain disorders. An improved understanding of the relationship of pain sensitivity with musculoskeletal pain disorders can provide a better understanding of persistent musculoskeletal pain in young people to inform better preventative and treatment interventions.

The body of work presented in this doctoral thesis significantly contributes to the current knowledge by improving the understanding of pressure and cold pain sensitivity in young adults. Significant contributions include: the measurement of PPT using multiple raters is reliable in large cohort studies; the reference data reported is a valuable resource important for the understanding of 'normal' pain sensitivity in young adults, measurement of cold pain sensitivity may help the understanding of pain mechanisms in young adults with a "medium" or "high" pain experience; and early life stress related to poor family functioning is associated with future pain sensitivity.

8.2.2 Measuring pressure and cold pain thresholds

8.2.2.1 Why is reliability of pain sensitivity measurement important?

Excellent reliability of PPT and CPT measurement is important because if pain sensitivity measurement in going to be used in the clinic and for research, there is a need to know the measurement is reliable. Pain sensitivity measured using psychophysical tests can be influenced by potential systematic bias by raters. For example, knowing the SEM is important, as it can be used to calculate systematic differences between raters and calculate significant differences or changes in measurement. The reliability of measurement, knowledge of systematic bias and SEM is fundamental for clinicians and researchers so pain sensitivity measurement can be used accurately in clinical decision making and research.

In addition, to assist the utility of pain sensitivity measurement in decision making, this thesis contributes to the need for larger studies that investigate the association of pain sensitivity and musculoskeletal pain disorders. PPT and CPT measurement have been used extensively to describe pain sensitivity in musculoskeletal pain disorders and to evaluate effectiveness of interventions in musculoskeletal pain. However, as previously highlighted there are limitations to current knowledge. This thesis used a large, cross-sectional, community-dwelling cohort to improve the understanding of pain sensitivity.

The pain sensitivity data collection for this thesis required the use of multiple raters. This thesis contributed to current knowledge by establishing PPT measurement is reliable using multiple research assistants. Previously the most comprehensive PPT reliability study reported excellent interrater reliability (Walton, MacDermid et al. 2011). However,

the applicability of the results to a large cohort study were limited by only evaluating two raters as opposed to the multiple rates required for a cohort study. In addition, the two raters were physiotherapists limiting comparison to raters with less training in the use of manual skills, such as research assistants used to collect data in cohort studies. The excellent intrarater and interrater reliability of PPT measurement reported in Study 1 reflects thorough training of raters and the use of best practice protocols. The raters used for Study 1 were five of the twelve research assistants that collected data for the Raine Study 22-year follow-up. The same thorough training used in Study 1 was also used for all research assistants that measured PPT at the 22-year follow-up. In addition, during the 2.5-year data collection period for the 22-year follow-up, research assistants were regularly assessed to ensure correct algometer technique and that protocols were being applied appropriately. Another important consideration is the purpose of this study was to establish reliability of measurement of PPT for subsequent investigations of PPT within the Raine Study in this thesis, rather than for interpretation of magnitudes of change in clinical situations. Although intrarater SEMs are used for distribution-based methods for obtaining estimates of the minimally important and minimal detectable clinical change, Study 1 (Chapter 3) only calculated interrater SEMs and did not aim to calculate measures of reliability to related to individual change. The results of this study provide confidence that PPT data collected for this thesis are reliable.

In contrast to the manual skills required to apply handheld algometry for measurement of PPT, the measurement of CPT does not involve manual skills and is technically easier to measure. There is excellent intrarater and interrater reliability reported for CPT measurement (Wasner and Brock 2008, Geber, Klein et al. 2011). Subsequently for this thesis there was no reliability testing done for CPT measurement. However, research assistants who measured CPT at the 22-year follow-up received thorough training in the procedure and protocols. In addition, the PPT and CPT data collection protocols used for this thesis were consistent with current best practice recommendations and is an important consideration that adds support to the reliability of data collected (Rolke, Mageri et al. 2006, Backonja, Attal et al. 2013).

8.2.2.2 How can findings from this thesis inform the measurement of pain sensitivity in the clinical setting?

The results of this thesis, in combination with other research, suggest in musculoskeletal pain disorders there are differentiated pain groups with different somatosensory profiles suggesting mechanisms that need to be considered in the clinical setting. The thesis informs the need for clinical assessment of pain sensitivity and there are calls for better bedside QST protocols (Backonja, Attal et al. 2013). Currently further research is required to improve the clinical utility and cost of quantitatively measuring pain sensitivity in musculoskeletal pain disorders (Zhu, Böttger et al. 2019). One barrier of integrating QST into the clinical setting is equipment cost. For this thesis and for many research studies, PPT is measured using a handheld Somedic Algometer (approximate cost AUD$8000) and cold pain sensitivity is measured using a Somedic MSA Thermal Stimulator (approximate cost AUD$50,000). While clinically PPT can be measured using a cheaper handheld algometer (approximate cost AUD$400), the use of handheld algometers in clinical practice is currently not widespread. The cost of purchasing the equipment may not be feasible for most clinicians, subsequently clinical sensory tests using manual pressure and cold via the application of ice are being developed and have potential to be low-cost and time-efficient alternatives to QST.

There is potential to measure pressure pain sensitivity based on information gained from a clinical physical examination applying graded manual pressure with some emerging evidence for the utility of manual palpation for pressure pain testing. Using multiple body sites (painful neck site, upper trapezius, wrist and tibialis anterior), one study (n=80) has reported fair correlation (-0.26 to -0.45) between graded manual pressure and PPT measured using a handheld Somedic algometer (Rebbeck, Moloney et al. 2015). Physiotherapists applied the graded pressure with forced based on "Maitland mobilization" with mild force equivalent to a grade I, moderate force as a grade II, and firm force as a grade III to IV pressure (Maitland, Hengeveld et al. 2005) with participants rating pain intensity at each pressure using an 11-point numeric rating scale (NRS). Another study reported the strength of correlation between clinical sensory tests and QST (Zhu, Böttger et al. 2019). Manual pressure was applied using the thumb or eraser of a pencil at several sites with the intensity of pain rated on an 11-point NRS. There was a fair correlation to algometer testing of PPT ranging from 0.365 to 0.438.

There is emerging evidence for the utility of using a clinical ice pain test to measure cold pain sensitivity. Due to the presence of cold pain sensitivity being a predictor of poor prognosis following injury (Goldsmith, Wright et al. 2012), a clinical test to identify cold pain sensitivity may assist clinical decision making. The presence of initial cold hyperalgesia is one domain recommended by current WAD guidelines to assist the early identification of people at risk of poor recovery (State Insurance Regulatory Authority 2014). Three studies have compared the association of ice applied to the skin for between 5 and 10 seconds (ice pain test) with CPT measured using a Somedic MSA Thermal Stimulator (Zhu, Böttger et al. 2019 , Maxwell and Sterling 2013, Rebbeck, Moloney et al. 2015). For the ice pain test, all three studies used a protocol where participants were asked to rate their pain intensity on the 11-point NRS. Multiple sites were tested across the studies including the neck, upper trapezius, lumbar spine, wrist and tibialis anterior. The studies reported either moderate to good correlations between the ice pain test and CPT, or the ability for the ice pain test to determine heightened cold pain sensitivity. These results support the use of a clinical ice pain test to assess cold hyperalgesia and as a clinical screening tool. However, the strength of correlations varied between patient cohorts (neck pain, low back pain and carpal tunnel diagnoses) and test sites. Consequently, further research is required to improve the utility of the clinical ice pain test.

This thesis supports the need for pain sensitivity measurement in the clinical setting and clinical sensory tests have been advocated as part of a comprehensive examination of people presenting with musculoskeletal pain. Understanding the presence and relative contribution of pain sensitivity to the pain experience in clinical musculoskeletal pain disorders is important and can help guide clinical decision making. Using clinical sensory tests as part of the clinical assessment to assist understanding of pain mechanisms would be most relevant in the presence of increased risk for pain persistence as assessed by using a screening tool such as the Örebro Musculoskeletal Pain Questionnaire (Linton and Boersma 2003). While current clinical guidelines support the use of pain sensitivity assessment in clinical decision making to stratify appropriate care (State Insurance Regulatory Authority 2014, Mitchell, Beales et al. 2017), clinically there are difficulties with regard to the feasibility of using QST in the clinical setting. There is emerging evidence for the clinical utility of clinical sensory tests using pressure and cold stimuli to measure pain sensitivity, however currently there is limited ability to accurately compare these measures with QST (Zhu, Böttger et al. 2019).

8.2.3   How do you interpret pressure and cold pain sensitivity values?

In addition to establishing reliability of pressure and cold pain sensitivity measurement, interpretation of values from these tests for both clinical and research contexts is important. A better understanding of the association between a person's pain sensitivity and their pain experience can help inform underlying mechanisms of the pain experience. This is important as young adults are at an important developmental window where prevalence for musculoskeletal pain is reaching peak adult rates and trajectories of musculoskeletal pain become established (Hoftun, Romundstad et al. 2011, O'Sullivan, Beales et al. 2012, Slater, Jordan et al. 2016). The results of Study 3 support the problem of musculoskeletal pain in young adults with 29.5% (n=271) of participants classified as having a "Medium" or "High" pain experience where frequent, intense, long-lasting pain in multiple body areas was reported. A substantial body of literature describes changes in nociceptive processing suggesting heightened pain sensitivity as an important mechanism in persistent musculoskeletal pain disorders including knee osteoarthritis (Suokas, Walsh et al. 2012), low back pain (Rabey, Slater et al. 2015), whiplash associated disorders (WAD) (Van Oosterwijck, Nijs et al. 2013) and elbow pain (Slater, Arendt-Nielsen et al. 2005). The poor correlation between pathology measured by imaging techniques and severity of pain in musculoskeletal pain disorders (Arendt-Nielsen, Nie et al. 2010, Brinjikji, Luetmer et al. 2015) suggests aspects other than structure are important in understanding the underlying mechanisms of the pain experience. One of these aspects is pain sensitivity.

Meaningful interpretation of pressure and cold pain sensitivity values requires appropriate reference values to help understand what is 'normal'. This thesis provided age-sex site specific reference values for PPT using four test sites and CPT at the wrist. The percentiles provided for hypersensitivity and hyposensitivity can assist more accurate and considered interpretation of the contribution of pain sensitivity to a musculoskeletal pain disorder. For example, the pain sensitivity for someone presenting with back pain could be tested locally to the pain site and remotely. The measurements for the individual could be compared to the reference values for each site to interpret how they compare to the range for those of the same age and sex. The remote measurements could assist in understanding the individual's overall pain sensitivity. Increased pain sensitivity remote or discrete from pain sites, suggests augmented central nociceptive processing, with

comparison to sex-specific reference values fundamental to the interpretation of pain sensitivity measurements. Of importance, the reference values (measured in people without current pain) vary significantly via site, with the neck and wrist sites being significantly more pressure sensitive than the lumbar and leg sites, hence having reference values by site is fundamental to interpretation of measurement at different sites. The variation seen in PPT between sites will partially reflect peripheral nervous system sensitivity that is influenced by local anatomical variations in density of receptive fields and nociceptors (Graven-Nielsen, Vaegter et al. 2015). While QST test values can be quantitatively compared for research purposes, it is not commonly used as part of standard clinical practice. However, as discussed above, there is scope to extend practice by using clinical sensory testing or cheaper algometers. While clinical sensory testing using manual pressure or ice can measure a pain rating using the NRS, the ability to interpret pain sensitivity will be more limited than when using QST. However, it may be that the measurement error of this type of testing limits ability to detect and evaluate change in clinical practice settings. QST has been used as an outcome measure in randomised controlled trials (Fuentes C, Armijo-Olivo et al. 2011, Kardouni, Shaffer et al. 2015). Interpretation of treatment effectiveness can use reference values and standard deviations to assist in determining what might be clinically meaningful change. Additionally, pain sensitivity measures can be used clinically as an outcome measure to evaluate effectiveness of interventions. Using QST as an outcome measure has limitations, as currently it is not known how a change in pain sensitivity correlates with clinically meaningful changes in pain experience and disability. The age, sex and site-specific values reported by this study provide an important resource that may be used in this context.

While age, sex and site specific PPT and CPT reference values are important, interpretation of these values also requires an understanding of their correlates. A major strength of this thesis was the consideration of several known and potential correlates of pressure and cold pain sensitivity. Only one other existing study reporting reference values has investigated a broad range of potential correlates (demographic, physical, psychological and health-related factors), but this study was limited by investigating a wide age range (20-49 years) containing relatively small numbers within this age range (n=150) (Neziri, Scaramozzino et al. 2011). Study 2 reported significant correlates of PPT and CPT. Consistent with a significant volume of literature to date (Racine, Tousignant-Laflamme et al. 2012), sex was the strongest correlate of pain sensitivity in this data set

with females more pain sensitive than males, supporting the need for sex specific reference values. The significant correlates of PPT (sex, waist-hip ratio, poorer mental health) and CPT (sex, poorer mental health, smoking) reported in Study 2 allow for improved clinical interpretation of pain sensitivity and can guide future research planning by adding to knowledge of existing and potential correlates of pain sensitivity.

A better understanding of pain sensitivity can assist in the interpretation of the pain experience. This body of work further informs the interpretation of pain sensitivity by providing evidence of the link with pain experience. Study 3 of this thesis contributes to the literature by being the most extensive investigation to date of the relationship between pressure and cold pain sensitivity, and pain experience in young adults. Study 3 reported young adults with higher pain experience had increased cold pain sensitivity, but not pressure pain sensitivity. The findings contribute to clinical practice by improving the understanding of the association between pain experience and pain sensitivity for young adults. The results emphasize that for young adults presenting to clinicians describing a higher pain experience, augmented nociception should be considered as a potential mechanism contributing to the pain experience and suggests a targeted clinical assessment of pain mechanisms using clinical sensory testing is appropriate (Smart, Blake et al. 2011, O'Sullivan, Waller et al. 2014).

In summary, one of the significant contributions of this thesis to the literature is the findings of Study 2 and 3, which assist better interpretation of pressure and cold pain sensitivity measurements in research and clinical settings. Study 2 provided the most comprehensive sex specific reference value data for PPT at four body sites and CPT at the dorsal wrist for young adults aged 21–24 years. The reference data can assist interpretation of future clinical pain studies. The additional knowledge of potential and known correlates of pain sensitivity can be used in future research and clinical practice. Study 3 was a comprehensive investigation of community based young adults reporting increased cold pain sensitivity to be associated with a heightened pain experience. The findings support the clinical use of pain sensitivity measurement, along with considering the pain experience, to assist in understanding mechanisms in musculoskeletal pain disorders. The large, population-based, non-clinical Raine Study cohort is widely representative of similarly aged young Western Australian adults on a range of variables (Straker, Mountain et al. 2017), providing generalisability of the findings of the thesis to the Australian population.

8.2.4 Can a better understanding of pain sensitivity inform the prevention and/or management of musculoskeletal pain?

Current approaches for pain management only work for some people, some of the time. A better understanding of pain mechanisms informed in part by pain sensitivity profiles or somatosensory phenotypes may assist the clinical interpretation of the musculoskeletal pain experience and better guide the provision of individualised, mechanism-based, pain management approaches for young adults that can help address the global burden of persistent musculoskeletal pain. Study 3 reported an association between a heightened pain experience and increased cold pain sensitivity. Study 5 reported that for those with a moderate/high pain experience at 22 years, poor family functioning in early life increased the odds ratio for high cold pain sensitivity. Heightened cold pain sensitivity suggests the potential contribution of augmented central nociceptive processing to the pain experience. Current evidence suggests when augmented central nociceptive processing is present, management should consider interventions targeting reduction of pain sensitivity and this could mediate an improvement in function, however currently this is only speculative. For example, interventions shown to potentially improve function for those with musculoskeletal pain include prescription of appropriate pharmaceuticals (Grosen, Fischer et al. 2013), physical activity (Daenen, Varkey et al. 2015), advice on sleep hygiene (Sivertsen, Lallukka et al. 2015) and targeting of psychosocial factors that are related to the pain experience (Dunne, Kenardy et al. 2012, Nahman-Averbuch, Nir et al. 2016, Rabey, Smith et al. 2016, Bunzli, Smith et al. 2017). These interventions may improve function via reduction in pain sensitivity. However, the findings of Study 4 did not support that higher levels of physical activity at a population level are associated with less pain sensitivity and this is discussed in more detail below.

There is a need to investigate if the use of pain sensitivity measurement, as one component of profiling pain phenotypes, to guide the provision of individualised, mechanism-based, pain management can improve outcomes for people with musculoskeletal pain. However, while there has been substantial progress in understanding nociceptive mechanisms in musculoskeletal pain disorders, translation to improved patient outcomes is still lacking. There is a need to better understand the role of pain sensitivity in musculoskeletal pain disorders over the life course, including the

emergence of musculoskeletal pain disorders, patterns of persistence and recurrence, the resolution of conditions and factors controlling this. This will require answers to questions such as:

- What are normal QST values in various age ranges? How does pain sensitivity vary with factors such as age, sex, genetics, environment and comorbidities?
- How does pain sensitivity change over time, particularly in relation to the presence of musculoskeletal pain disorders?
- What factors, such as physical activity, sleep, adiposity and mental health, are pathways to and from heightened pain sensitivity and potentially musculoskeletal pain disorders?

Improved understanding of such questions may enable clinicians to better interpret QST measures to assist planning management with patients. While this thesis contributes to current knowledge, further longitudinal studies are required to better understand the above questions.

There has been little investigation between the association of pain sensitivity with objectively measured, habitual PA and SB in community-based cohorts. Understanding the association of habitual PA with pain sensitivity may provide more insight into the longer-term associations of PA with pain sensitivity in both clinical and community-based settings. Study 4 is the largest community-based, comprehensive investigation into the association of pressure and cold pain sensitivity with objectively measured, habitual PA and SB. Overall, while little association was reported between pain sensitivity and PA or SB, the results of this thesis do provide some potential implications for clinical practice.

Of relevance for clinical practice, the results of Study 4 allude to potentially important dose-relationships between pain sensitivity and PA or SB. For those with "Single-site pain", higher levels of moderate-vigorous PA in ≥10 min bouts were associated with more pressure pain sensitivity. Those with "Multisite pain" displayed increased cold pain sensitivity with greater amounts of vigorous PA. In addition, Study 4 reported an association of lower cold pain sensitivity with an increase in the number of breaks from sedentary time for participants in the "No pain areas" group, suggests the way sedentary time is accumulated may be related to pain sensitivity. For clinical management of persistent musculoskeletal pain, prescribed exercises and PA advice is

commonly recommended best practice care (Lin, Wiles et al. 2019) and is effective in reducing disability, providing high value care (Hauser, Klose et al. 2010, Lin, McAuley et al. 2011, Uthman, van der Windt et al. 2013). This thesis suggests that for some musculoskeletal pain conditions, particularly for those with two or more pain areas, there may be an upper limit to how much vigorous PA is ideal, as too much may result in higher pain sensitivity. Additionally, how moderate-vigorous PA is accumulated (i.e. time accumulated in longer bouts) may be important. Therefore, considering and questioning patients more closely regarding their PA and SB levels maybe important, particularly if they present with more widespread pain. Clinical measurement of the pain experience and pain sensitivity before and after PA, and over the period of a clinical intervention has potential to assist clinical decision making to prescribe optimal levels of therapeutic PA.

A better understanding of how pain sensitivity develops over time can potentially provide targets for interventions to reduce pain sensitivity. This thesis reported some evidence that early life stress in the form of social relationships may be a potential target with Study 5 reporting an association of poor family functioning with increased odds for more cold pain sensitivity for those reporting a moderate/high pain experience at 22-years. Significant exposure to early life environmental stressors is associated with alterations in adult biological processes that are mediated via complex interactions between epigenetic, endocrine and immune systems (Zhang 2013). The association between heightened cold pain sensitivity and ELS reported in Study 5 may partially represent long-term alterations in the stress regulation system. There is emerging evidence suggesting the involvement of the sympathetic nervous system in heightened cold pain sensitivity (Sterling, Jull et al. 2003). Importantly the sympathetic nervous system is involved in central nociceptive processing and can be sensitized by the stress regulation system, particularly by the hypothalamic-pituitary-adrenal (HPA) axis and subsequent alteration of circulating cortisol levels (McEwen 1997, Paananen, O'Sullivan et al. 2015, Nees, Löffler et al. 2019). ELS, particularly when cumulative, places significant allostatic load on the body's sympathetic and parasympathetic nervous system, creating HPA axis dysfunction (Vachon-Presseau, Roy et al. 2013, Nelson, Cunningham et al. 2017). HPA axis dysfunction has been directly implicated in greater risk of developing and maintaining persistent pain in both adolescent and adult populations (Evans, Kim et al. 2007, McEwen and Kalia 2010, Nelson, Cunningham et al. 2017).

Interventions for people with persistent musculoskeletal pain disorders and heightened pain sensitivity could consider targeting the stress response system. There is evidence stress inoculation training for those with a heightened stress response post whiplash resulted in clinically significant improvements in pain related disability when compared with guideline based exercise alone, with the benefit maintained at 12-month follow-up (Sterling, Smeets et al. 2019). While the mechanisms for how this is mediated are speculative, improvements in pain related disability were potentially mediated via reduction in stress and pain sensitivity.

8.2.5   Understanding how pain sensitivity develops over the lifespan

Current evidence suggests heightened pain sensitivity is a factor associated with the development of a new musculoskeletal pain disorder (Greenspan, Slade et al. 2013) and the maintenance of an existing musculoskeletal pain disorder (Georgopoulos, Akin-Akinyosoye et al. 2019). It is important to highlight that heightened pain sensitivity is not always associated with musculoskeletal pain disorders, nor is it a pre-requisite for persistent pain. Multiple dimensions interact over time to contribute to the musculoskeletal pain experience and for some people augmented central nociceptive processing reflected by pressure and/or cold pain sensitivity maybe important. While Study 3 reported an association between a heightened pain experience and increased cold pain sensitivity, the study was cross-sectional, and therefore it cannot be determined from the results if cold pain sensitivity is causal to the pain experience, or if the pain experience drives pain sensitivity. Knowing how pain sensitivity changes over time and understanding the mechanisms associated with vulnerability to pain sensitivity may offer opportunities to inform the prevention of musculoskeletal pain.

Improved understanding of the link between pain sensitivity with habitual PA or SB may provide insight into pathways in and out of heightened pain sensitivity which might be important to understand for some individuals. Future research investigating how pain sensitivity shifts over time will be important here. How pain sensitivity shifts over time with change in PA, SB or training load is unknown. There is some evidence that the relationship between injury risk and PA resembles a "U" shaped curve, with an increase in injury risk with low or high PA load (Heneweer, Vanhees et al. 2009, Gabbett 2016). Whether this "U" shaped relationship is partially mediated by change in pain sensitivity

is unknown, however the little association reported between pain sensitivity and PA or SB in Study 4 challenge this possibility. Further research is in this area is required and discussed below in the future research directions.

While pain sensitivity is partially determined by genetics (Nielsen, Stubhaug et al. 2008, Denk, McMahon et al. 2014), socioenvironmental pathways to heightened pain sensitivity are important to understand with respect to what might prime the individual for a future persistent pain event. Considering how early life socioenvironmental factors may have influenced the development of an individual's current pain sensitivity is important when considering emerging literature that describes a relationship between early life stress and increased propensity for pain disorders in childhood, adolescence and adulthood (Nelson, Cunningham et al. 2017). Data from human studies demonstrate higher pain sensitivity in adolescence and early adulthood following exposure to a significant neonatal pain experience, findings consistent with augmented nociceptive processing (Peters, Schouw et al. 2005, Van Ganzewinkel, Been et al. 2017). One critical gap in existing literature is an understanding of the relationship between young adult pain sensitivity and early life stressors.

Study 5 of this thesis is a unique investigation utilizing a large longitudinal dataset and contributes to foundational knowledge in the area. The investigation provides some support for early life being a critical period of development, with results showing an association between early life stress and future pain sensitivity. More problematic behaviour at age two was associated with less sensitivity to pressure pain at 22 years, after adjusting for sex and 22-year correlates with no difference in associations according to levels of current pain experience. For those reporting a moderate/high pain experience at 22-years, poor family functioning increased the odds for more cold pain sensitivity. A strength of the study is the testing of specific early life factors separately as opposed to creating an early life stress profile, allowing a better understanding of which factors are relevant for pain sensitivity in young adulthood.

While interventions for pain disorders might consider targeting a heightened stress response, better evidence for how pain sensitivity develops can help predict those at risk for persistent pain and can potentially guide interventions targeting prevention during development. Current evidence suggests early life is an obvious target due to the human brain rapidly developing after birth (Thompson 2001). ELS may be a potential marker for

future pain sensitivity and risk of pain, providing a potential target for early identification for risk of pain and timely management (Cole 2014, Incledon, O'Connor et al. 2016). However, it is likely there are cumulative and interactive effects of temporally variable, multidimensional biopsychosocial and epigenetic factors relevant to pain sensitivity. Currently these factors are largely unexplored over early life and young adulthood.

The mechanisms underlying the association of less pressure pain sensitivity with more problematic behaviour are unclear. Although previous links between early childhood problematic behaviour and antenatal or postnatal events in the Raine Study have been identified, the antenatal and postnatal events investigated in Study 5 were not associated with pain sensitivity in young adulthood. In the Raine Study cohort there was increased risk for more problematic behaviour at age two if there was exposure to maternal stress and smoking during pregnancy (Robinson, Oddy et al. 2008). At age five, there was increased risk due to exposure of multiple life stress events, exposure to smoking and short length of breastfeeding (Robinson, Oddy et al. 2008). In Study 5, the above early life stressors were not associated with pain sensitivity, however the other socioenvironmental factors that were not captured, such as neonatal pain events or physical abuse, may be reflected by behaviour problems. While speculative, the association of less pressure pain sensitivity with more problematic behaviour may be related to less perceived threat to pressure stimuli (Vassend, Røysamb et al. 2013) and different pain coping strategies such as behavioural distraction, affect and attentional focus (Lee, Watson et al. 2010, Bartley and Fillingim 2013, Vassend, Røysamb et al. 2013, Strachan, Poeschla et al. 2015).

There are many changes during development that might drive or moderate pain sensitivity and the association between pain sensitivity and future pain vulnerability. Study 5 provides a base for further research using the Raine Study cohort to better understand how during development cumulative socioenvironmental stressors influence pain sensitivity in young adulthood. A better understanding may offer opportunities to address and reduce the impact of pain from a broader public health and epidemiological perspective.

8.3   Strengths and limitations of thesis

8.3.1   Strengths

This doctoral thesis has some significant strengths. The large data-set from the Raine Study cohort has allowed a unique investigation in a community-based nonclinical cohort. The cohort has been shown to be representative of the Western Australian population (Straker, Mountain et al. 2017), providing generalizability to the general young population of Australia. The Raine Study was established 1989-1991 and has been regularly followed up since birth. Over time there has been attrition with a gradual reduction in participants and many remaining participants will have missing data at various time points. The representativeness of the cohort has been examined at birth, childhood (year 8), adolescence (years 14 and 17) and young adulthood (years 20 and 22) (Straker, Mountain et al. 2017). An assessment of attritional bias reported that in general the proportions of participants and non-participants based on several infant characteristics such as birthweight, ethnicity and gestational age has remained constant across follow-ups (Straker, Mountain et al. 2017).

The longitudinal collection of data in the Raine Study, including antenatally and in early life, has allowed a unique exploration of the association between early life stressors and pain sensitivity in young adults. A strength of the Raine Study here is the data has been collected at multiple and regular time points overcoming a limitation of many existing studies of ELS and future health outcomes that rely on retrospective report of early life stressors (Nelson, Cunningham et al. 2017). This thesis provides foundational knowledge and the base for further exploration of factors associated with the development of pain sensitivity using the Raine Study.

The pain sensitivity data has been collected using current best recommended practice and protocols (Backonja, Attal et al. 2013) and Study 1 supports that the PPT data collected for this thesis has excellent reliability. The study has answered a call for large sets of age-specific pain sensitivity data (Gierthmuhlen, Enax-Krumova et al. 2015). The young adult data is important to help improve the understanding of potential pain mechanisms in younger populations. Consistent with current recommended best practice, the broad range of data collected in the Raine Study has allowed consideration of the independent associations of a comprehensive number of potential known correlates of pain sensitivity.

This doctoral thesis has used robust statistical analysis throughout. Importantly the major findings of investigations in this thesis are reported from final models using multivariable regression analysis that adjusted for these significant correlates. Therefore, the findings are due to differences in pain sensitivity not confounded by differences in other factors such as sex, age, mental health, physical activity, adiposity and sleep. Chapter 4 (Study 3) reported the association of these factors with PPT and CPT, informing what factors needed to be adjusted for, in this thesis and in future research, when examining links between PPT and CPT and outcomes of interest such as musculoskeletal pain. Multivariable models for PPT used generalised estimating equations to account for the non-independence of the data due to repeated measures of PPT by site. Two recent comparable population-based studies (Tham, Palermo et al. 2016, Skovbjerg, Jørgensen et al. 2017) have analysed data in multivariable models by test site, not accounting for the non-independence of that data which increases the risk of reporting spurious results.

The reliability of pressure pain sensitivity data collected for this thesis was important to establish as previous interrater reliability studies had only used two raters. The overriding aim of Study 1 was to ensure reliability between raters (who were research assistants employed to take a range of measures including PPT in the Raine Study) to assess if any potential confounding by rater should be considered in subsequent investigations for this thesis. Analyses in this thesis are subsequently adjusted where necessary, to ensure group results were not a result of any confounding by rater, i.e. systematic differences between raters assessing each pain group. Any random error of measurement by rater is adequately dealt with by the large sample sizes utilized in in Chapters 4-7. There was adequate power to detect even small group differences that could be attributed the factors under investigation other than random error. The last two columns of Table 3.2 report sample size numbers required to detect differnces of varying magnitude between groups given the SEMs observed in the reliability study. This table shows that there is adequate power to detect even small group differences in the presence of the levels of random error observed in Study 1. The numbers included in all other studies of this thesis exceed these calculated sample size requirements. Study 1 established that using more than two raters to measure PPT, as practically required in large cohorts, has excellent reliability.

A strength of this thesis is the consideration of broader pain experience rather than only unidimensional aspects of the pain experience. The determination of pain experience groups in Study 3 by latent class analysis allowed consideration of a broader pain experience in a single measure rather than using only pain intensity or unidimensional aspects of the pain experience. A strength of Study 5 was that it also considered the broader pain experience, using these pain experience groups of Study 3, rather than just unidimensional aspects of the pain experience.

The statistical analysis used for this thesis was advanced and unique in the field of pain sensitivity research. Study 5 used Raine Study data from multiple follow-ups spanning 23 years resulting in variation in patterns of missing data. The use of multiple imputation data sets minimised bias due to missing data, and the bootstrapped step-wise selection procedure provided internal validation of results guarding against spurious associations and ensured stability of the final regression models (Vergouw, Heymans et al. 2010). In addition, the bimodal distribution of CPT was suggestive of two separate underlying populations of cold pain sensitivity (Ruscio and Kaczetow 2009). Subsequently, Study 5 participants were classified into two groups, with the relative uncertainty of group membership for those close to the cut-off accounted for in logistic regression models by weighting analyses by the estimated probability of membership for the allocated group of each individual.

8.3.2   Limitations

Some limitations of this thesis include: the capture of only two static not dynamic QST measures; the measurement of pain sensitivity at one age and time point; the lack of capture of current and past pain sites; and the use of a predominantly Caucasian sample from a single geographic setting. However, while acknowledging these limitations they are unlikely to invalidate the associations identified in this thesis.

The PPT reliability study (Chapter 3, study 1) while showing excellent intrarater and interrater reliability had some limitations. The primary aim of Study 1 was to assess the intrarater and interrater reliability, including systematic bias, of PPT testing by the same method (handheld algometer) and at the same body sites (wrist, leg, cervical and lumbar spine) as in the larger cohort study. The study included 20 non-Raine Study pain-free participants of comparable age to the Raine cohort at the time of testing. As people with

pain could potentially demonstrate larger between and within person-variability, it is possible that the reliability measures reported in Chapter 3 are only directly valid for pain-free participants. However, Study 5 compared the mean and standard deviation of PPT by site (Table 5.3), reporting comparable standard deviations across participant groups with and without musculoskeletal pain. In addition, a previous high-quality reliability study that tested 60 healthy volunteers and 40 people with neck pain reported similar results to study 1 for intrarater and interrater reliability (Walton , Macdermid et al. 2011). The Walton et al study compared intrarater and interrater reliability between those with neck pain and without pain, reporting very comparable ICCs, SEMs and minimal detectable changes between the groups of participants. There could be concerns around the protocol where raters were not blinded to repeated measures within subject and whether a 10 second rest between repeated tests at the same site was sufficient to avoid pain adaptation. The 10 second rest between repeated tests was chosen to ensure the PPT protocol limited participant burden and was time efficient as all data collection at the Gen2-22 year follow-up took several hours. The ICC values reported in Study 1 may have been affected by these factors.

There were some limitations to the pain sensitivity data collected for this thesis. Due to time constraints on data collection and the need to limit the already significant participant burden, PPT and CPT were the only pain sensitivity measures collected, as they were have previously been used extensively to investigate pain mechanisms in musculoskeletal pain disorders (Goldsmith, Wright et al. 2012, Suokas, Walsh et al. 2012, Hübscher, Moloney et al. 2013). While other pain sensitivity measures such as conditioned pain modulation and temporal summation can provide valuable insight into efficiency of central nociceptive mechanisms, the testing process is more complex and time consuming than measuring PPT and CPT. These additional tests would be been impractical to collect during the 22-year follow-up.

The PPT was measured at four sites to obtain a broad capture of pressure pain sensitivity. However, while these are commonly used sites there is no best practice recommendation as to the best sites to use. Pain sensitivity measures are considered site specific which limits direct comparison of the data to studies measuring pain sensitivity at different body sites. In comparison CPT was tested at the wrist only as the

measurement is more time consuming. While only one site is potentially limiting, the wrist is likely to be remote from common pain sites in most participants.

The pain sensitivity data used for this thesis was cross-sectional, and as the PPT and CPT data was obtained only at the age of 22-years, results may not be generalizable across age groups. There is a need to have comprehensive cross-sectional data across a range of age groups.

While this thesis considered the broader pain experience, this was captured using questionnaire measures which cannot fully characterize and differentiate nociceptive mechanisms. The pain experience is complex and unique to each individual, reflecting multidimensional factors that influence a pain experience (Fillingim 2017). The studies in this thesis grouped participants according to current pain status using the question "do you have any current body pain?" However, current pain sites were not captured which is a limitation as pain sensitivity is likely to be elevated when measured over a current pain site compared to a site without current pain and could confound results. Similarly, previous pain sites were not captured and pain sensitivity over a previously painful site is likely to be elevated compared to a pain naive site and may have influenced results. While these limitations would be minimised if there was a clinical examination to allow a more individualized characterization of each pain experience, this is impractical in larger cohort studies.

The findings of this thesis did not support the existence of an association between PPT and pain experience. However clinical studies report increased pressure pain sensitivity in site specific conditions such as WAD (Walton, MacDermid et al. 2011, Rebbeck, Moloney et al. 2015), and lateral epicondylalgia (Slater, Thériault et al. 2010) when compared to people without pain. Other studies have reported increased pressure pain sensitivity at local and remote sites in persistent widespread pain disorders when compared to persistent localised pain disorders (Carli, Suman et al. 2002, Blumenstiel, Gerhardt et al. 2011). The lack of any identified associations between PPT and pain experience may be due to a lack of consideration of the location of current and past pain areas, as this data was not collected concomitantly with PPT at the 22-year follow-up Knowing the location of pain would allow contrast of pain sensitivity measurements between painful and non-painful test sites. The Raine Study 22-year follow-up tested pain sensitivity at standardised sites, in contrast to studies investigating site specific conditions

that compared pain sites to control sites. The findings of this thesis suggest that PPT measured at predetermined multiple sites in a population cohort without knowing pain locations and pain history may not be so useful. Previous studies suggest for clinical utility, PPT measurements require comparison between pain sites and remote non-pain sites.

A limitation of this thesis is there was only cross-sectional measurement of pain sensitivity. Ideally repeated QST measurement on individuals is required to better understand the contribution of pain sensitivity to the pain experience. It is largely unknown how pain sensitivity changes over time in the same individual, including how pain sensitivity contributes to the onset of a pain disorder, and if or how pain sensitivity changes following the onset of a pain disorder. Longitudinal data can help in the understanding of how pain sensitivity changes in the individual, including due to life events such as major stress or traumatic experiences and pain events.

This thesis only considered the association of early life stressors with pain sensitivity in young adulthood which is a limitation as pain sensitivity has socioenvironmental influences that will vary over time. While Study 5 reported the association of pressure and cold pain sensitivity and pain experience in young adults with early life stressors, it was beyond the scope of this thesis to consider accumulative or moderating effects of life events between 3 and 22 years.

The Raine Study participants studied for this thesis are a largely Caucasian population living in a warm Mediterranean type climate, limiting generalizability of results to other regions of the world. The cohort may differ in pain sensitivity from other cohorts due to ethnicity, lack of exposure to cold temperatures, sunlight exposure and inflammatory status [60].

There may be plenty of reasons why little was detected in the way of association between pain sensitivity and PA or SB. Firstly, while the Raine Study considered habitual activity at one time point, there is also a need to consider the relationship between pain sensitivity and PA or SB over time. A longitudinal investigation would allow evaluation of the association between a change in PA or SB and pain sensitivity not only between individuals but also within individuals. Secondly, for analysis participants were grouped by the number of pain areas, as current literature suggests pain sensitivity decreases following PA for those with single site pain but increases for those with multisite pain (Cook, Stegner et al. 2010, Daenen, Varkey et al. 2015). However, grouping participants

with consideration of the broader pain experience as done for Study 3, as opposed to number of pain sites maybe important.

A third reason for detecting little in the way of association between pain sensitivity and PA or SB may be related to the limitations of accelerometry to measure habitual activity. For this thesis PA and SB were measured objectively using accelerometry, as self-report questionnaires show limited reliability and validity compared with objective measurement (Shephard 2003). In addition, the strength of association between subjective and objective measurement of PA or SB is generally low to moderate making accelerometry a more valid choice compared with self-report questionnaires (Prince, Adamo et al. 2008). While currently accelerometers provide the most widely used and cost-effective method for objective PA and SB measurement, there are limitations to their accuracy (Ainsworth, Cahalin et al. 2015). Accelerometers are typically worn on the hip and do not pick up arm movement and are not worn while swimming (Prince, Adamo et al. 2008). Another limitation of accelerometers is they are insensitive to cycling, gradients while walking or running, and moderate to vigorous activity that has limited torso activity such as yoga (Armstrong and Welsman 2006, Warner, Wolin et al. 2012).

A fourth reason for detecting little in the way of association between pain sensitivity and PA or SB may be related to the pressure and cold pain threshold measures used to capture pain sensitivity. One underlying mechanism for PA inducing exercise induced hypoalgesia includes the recruitment of descending inhibitory control mechanisms (McLoughlin, Stegner et al. 2011). The use of dynamic QST such as conditioned pain modulation or temporal summation may better capture of underlying mechanisms for pain sensitivity modulation with PA (Vaegter, Handberg et al. 2014).

8.4   Future research directions

There are several directions for future research investigating the association of pain sensitivity with musculoskeletal pain. Expanding current knowledge can improve interpretation of QST findings, help understand pain mechanisms in musculoskeletal pain disorders and help develop management approaches that address the worldwide burden of musculoskeletal pain.

There is a need for longitudinal pain sensitivity data to better understand how pain sensitivity might change over time, temporal influences on pain sensitivity and whether pain sensitivity predicts future pain. Cohort study planning should consider capturing pain sensitivity and pain experience measures at more than one time point. Collection of pain sensitivity data ideally should use large samples at multiple time points to address the call for more age-sex specific data (Gierthmuhlen, Enax-Krumova et al. 2015). There is potential to obtain longitudinal pain sensitivity data in the Raine Study at future follow-ups. Repeated measurement of pain sensitivity and the pain experience at future follow ups of the Raine Study will allow investigation of the predictive ability of pain sensitivity for persistent musculoskeletal pain and for the onset of a new musculoskeletal pain disorder. To date there has been very limited investigation of the predictive ability of pain sensitivity for the onset of a new pain disorder with the largest study (n=2,737) investigating the onset of a new TMJ disorder over 5.2 years (Greenspan, Slade et al. 2013).

There is a need to explore how accumulative or moderating effects from life stress events during critical periods of development, such as later childhood and adolescence and early adulthood, influence future pain sensitivity. Study 5 considered socioenvironmental influences on the development of pain sensitivity, but only considered early life stressors. How the effect of life stressors is accumulated or moderated may be via HPA axis plasticity potentially leading to either hyper-responsiveness or hypo-responsiveness (Agorastos, Pervanidou et al. 2019). The Raine Study captured HPA axis function of participants using the Trier Stress Test at 17 years of age, and this data could be used to explore the association between life stressors, stress responsiveness and pain sensitivity in young adulthood. It was beyond the scope of this thesis to explore the questions above. In addition, there is pain sensitivity data collected on Gen 1 Raine participants (parents of the Gen 2 cohort used for this thesis) that can be analysed to help understand genetic and environmental influences on pain sensitivity.

There is good potential for international collaboration to pool data from other longitudinal cohort studies that have captured pain sensitivity data such as the Northern Finland Birth Cohort (www.oulu.fi/nfbc) and The Tromsø Study (www.en.uit.no). This can build on existing reference values and help quantify if there are geographical differences in pain sensitivity resulting from genetic and/or environmental factors. Understanding

these differences could help the generalizability of current and future research findings. In addition, pooled data can provide more sex specific reference values across different age spans. For example, the Raine Study has pressure and cold pain sensitivity data collected on the parents of the children used for this study.

Based on the experience of this thesis, there are some recommendations to consider for future research planning. There is a need for to establish thresholds for real or meaningful change of repeated PPT and CPT measures in people with pain over time, and the use of anchor-based methods to relate changes in QST to perceptions of improvement in a clinical disorder. The PPT and CPT findings reported in this thesis allude to different mechanisms for pressure and cold pain sensitivity. With this in mind, more than one site to measure cold pain sensitivity is advisable and another peripheral site such as the tibialis anterior would be appropriate. In addition, if practicable the collection of dynamic pain sensitivity measures such as conditioned pain modulation and temporal summation are recommended as they can provide valuable insight into efficiency of central nociceptive mechanisms. This thesis highlights that for PPT measurements at a population level to provide more insight into pain mechanisms, there is a need to capture broader information on the pain experience. Aspects of the pain experience not considered for this thesis include current pain sites, pain history and current use of pain medication. In addition, current pain sites and pain history would allow PPT to be measured at these previous or current pain sites. Pain sensitivity data collection should use best practice recommendations and measurement of a broad range of potential correlates is essential. The correlates of pain sensitivity reported throughout this thesis can help guide future data collection.

8.5   Conclusion of thesis

The body of work presented in this doctoral thesis significantly contributes to the understanding of pressure and cold pain sensitivity in young adults. The work confirmed that the measurement of PPT is reliable in large cohort studies; the reference data reported is a valuable resource important for the understanding of 'normal' pain sensitivity in young adults, measurement of cold pain sensitivity may help the understanding of pain mechanisms in young adults with a "medium" or "high" pain experience; and early life stress related to poor family functioning and problematic

behaviour is associated with future pain sensitivity. Together these findings support the value of pain sensitivity measurement in musculoskeletal pain disorders to assist the understanding of pain mechanisms behind the pain experience. Improving the understanding of the association of pain sensitivity with musculoskeletal pain disorders and how pain sensitivity develops offers opportunities to address and reduce the global impact of musculoskeletal pain.

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