Chronic pain in adults: is the relationship between pain processing and number of pain sites or presence of chronic widespread pain moderated by age or sex?

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences

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Abstract

The University of Manchester, Deborah Brown, PhD “Chronic pain in adults: is the relationship between pain processing and number of pain sites or presence of chronic widespread pain moderated by age or sex?” December 2012.

Background Chronic pain is pain which has lasted for more than 3 months and is reported by 40 to 50% of adults in developed countries. The prevalence of chronic pain is consistently higher in women than in men. Chronic pain is more often reported by older adults than younger adults. As well as duration, pain can also be described in terms of its “widespreadness” by counting the number of body areas experiencing pain, or by the source of the pain e.g. musculoskeletal. Many social, psychological, physiological and behavioural factors have been found to be associated with pain. Altered sensitivity to stimuli may indicate aberrant pain processing mechanisms. Quantitative sensory testing (QST) evaluates responses to experimental, painful and non-painful stimuli. Although originally used in neurological conditions, QST data for people with musculoskeletal pain show differences from healthy controls.

Aim The aim of this study was to determine the relationship between sensitivity to stimuli (measured by QST), and both the number of body areas with pain and the prevalence of chronic widespread pain, and how these relationships vary with age and sex.

Methods A postal questionnaire which included questions about pain location and duration of pain, as well as known risk factors for pain, was returned by 2623 participants aged 34 – 101 years. A sub-group of 290 participants aged 34 – 97 years were selected on the basis of their responses to the pain questions and undertook a physical assessment which included QST. Regression models were used to quantify the relationships between QST factors and pain. Pain was classified as a continuum of “widespreadness” (0 – 29) and as “no pain”, “chronic widespread pain (CWP)” and “some pain” (i.e. pain other than CWP). Regression models with interaction terms were used to investigate whether these relationships varied between older (aged over 65 years) and younger (aged 65 years and younger) people, and between men and women.

Results There were very few differences in QST variables (except tender point count) across the two pain classifications, however, differences in several QST variables were found between the age and sex groups (Chapter 6). Three of the QST measures, tender point count, cool detection threshold at the foot and thermal
sensory limen at the foot, were statistically significantly related to number of painful areas, and tender point count and cool detection threshold at the foot were also significantly different among participants with “no pain” and those with CWP (Chapter 7). None of these relationships were significantly moderated by age or sex (Chapter 8). Sleep quality and beliefs about pain duration were found to be statistically significantly related to number of pain areas and to the presence of CWP in all the analyses (Chapter 7).

**Conclusion** The findings from this study indicate that some QST variables are related to pain, but none of the relationships are moderated by age or sex. The importance of sleep quality and pain beliefs as risk factors for pain has been further confirmed. Further research may allow treatments for pain to be tailored to the individual in the light of these facts.
**Declaration**

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification in this or any other university or other institute of learning.

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My first degree was Manufacturing Systems Engineering, after which I worked as a production engineer for 3 years before becoming a factory inspector. Still within the health and safety field, I moved into fire and explosion research, before re-training as a physiotherapist. I worked full-time in the NHS for 11 years, latterly mainly in the rehabilitation of older people. I completed a part-time MSc Ageing, Health and Disease before commencing my PhD programme.

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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ACPRC</td>
<td>Ageing and Cognitive Performance Centre (cohort)</td>
</tr>
<tr>
<td>ALL</td>
<td>Dynamic mechanical allodynia</td>
</tr>
<tr>
<td>CDT</td>
<td>Cool detection threshold</td>
</tr>
<tr>
<td>C.I.</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CPT</td>
<td>Cold pain threshold</td>
</tr>
<tr>
<td>CWP</td>
<td>Chronic widespread pain</td>
</tr>
<tr>
<td>DNIC</td>
<td>Descending noxious inhibitory controls</td>
</tr>
<tr>
<td>Epifund</td>
<td>Epidemiology of functional disorders (cohort)</td>
</tr>
<tr>
<td>FMS</td>
<td>Fibromyalgia syndrome</td>
</tr>
<tr>
<td>HAD</td>
<td>Hospital Anxiety and Depression scale</td>
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<tr>
<td>HPT</td>
<td>Heat pain threshold</td>
</tr>
<tr>
<td>IPQ</td>
<td>Illness Perception Questionnaire</td>
</tr>
<tr>
<td>MDT</td>
<td>Mechanical detection threshold</td>
</tr>
<tr>
<td>MPT</td>
<td>Mechanical pain threshold</td>
</tr>
<tr>
<td>PAALS</td>
<td>Pain Across the Adult Life Span</td>
</tr>
<tr>
<td>PAG</td>
<td>Peri-aqueductal grey (matter)</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal components analysis</td>
</tr>
<tr>
<td>PCS</td>
<td>Pain Catastrophising Scale</td>
</tr>
<tr>
<td>PHS</td>
<td>Paradoxical heat sensations</td>
</tr>
<tr>
<td>PSQI</td>
<td>Pittsburgh Sleep Quality Index</td>
</tr>
<tr>
<td>QST</td>
<td>Quantitative sensory testing</td>
</tr>
<tr>
<td>S.D.</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>TSL</td>
<td>Thermal sensory limen</td>
</tr>
<tr>
<td>VDT</td>
<td>Vibration detection threshold</td>
</tr>
<tr>
<td>WDT</td>
<td>Warm detection threshold</td>
</tr>
<tr>
<td>WUR</td>
<td>Wind-up ratio</td>
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</table>
1 Introduction

1.1 Overview

This section defines chronic musculoskeletal pain and describes its prevalence in adults. Pain’s importance as a cause of disability and its financial implications for the individual and wider society are described. Some of the features which distinguish pain in older adults from pain in younger adults are discussed.

1.2 Definition of chronic musculoskeletal pain

The International Association for the Study of Pain (IASP) defines pain as:

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." (Loeser and Treede 2008)

This definition makes it clear that pain does not need to be associated with a disease or injury, but relies upon the perception of the individual concerned.

Acute pain is an evolutionary development which is often seen as being protective, for example removing the individual from an injurious stimulus or preventing harmful movement (e.g. following a fracture), but the benefit of this pain only exists for a short period (Cousins and Power 1999). Acute pain was viewed in the past as cause-and-effect, due to tissue damage, but now it is acknowledged to be due to an interaction between sensory, emotional and behavioural factors (Cousins and Power 1999). Chronic pain is generally defined as pain that persists past the stage of tissue healing, generally set between 3 months (Wolfe et al. 1990) and 6 months (Donaldson 2009). It should not be thought of simply as persistent acute pain because the link to tissue damage no longer exists (Staud 2005). As well as being defined by its duration, pain can also be described in terms of its location or its likely origin, e.g. shoulder pain, visceral pain, or neuropathic pain. Musculoskeletal pain is pain which originates, or appears to originate, in the musculoskeletal system, namely the joints and associated structures and the muscles, and may be in one body region or several.
1.3 Prevalence of chronic musculoskeletal pain

Pain is a near-universal experience and even chronic pain is very common. In 2009 the UK Chief Medical Officer estimated that 7.8 million people in the UK suffered from chronic pain (Donaldson 2009). A conservative estimate for the number of people suffering chronic pain worldwide is 60 million (Goldberg and McGee 2011). Table 1.1 shows a sample of population-based studies of pain in adults. Values for the prevalence of chronic pain (in any body area) vary between 15.1% (Reitsma et al. 2011) and 63% (Eggermont et al. 2009).

Chronic pain often has a poorly defined onset, and previous episodes may have occurred in the past but be poorly recalled. It is therefore more usual to discuss prevalence (number of cases in the population) than incidence (number of new cases) of pain (McBeth and Jones 2007). Point prevalence refers to the number of people with pain at a particular point in time. Period prevalence refers to the number of people with the condition within a specified period of time. New prevalent episodes are cases (but not necessarily new cases, they could be a recurrence) which begin between two defined points in time.

The studies described in Table 1.1 sampled populations in Northern Europe and North America and may not be representative of non-Western populations. The pain prevalence measures also vary, with point prevalence, 4 week, 3 month, 6 month and 12 month period prevalence being used, so for some of the longer periods an individual may have recovered from their chronic pain by the time of recording.

The highest total prevalence found was 63% (Eggermont et al. 2009). This study exclusively recruited people aged 64 and over. Age has consistently been found to affect pain prevalence, usually with older people having higher prevalence than younger people (Bergman et al. 2001; Brattberg, Thorslund, and Wikman 1989; Reitsma et al. 2011). The lowest prevalence found was 15.1% (Reitsma et al. 2011). These authors reported patterns in pain prevalence over time using a series of seven surveys carried out on adults over the age of 20. The range of total pain prevalence obtained in these seven surveys was 15.1% to 18.9%.

The other 9 out of 11 studies reported prevalence rates ranging from 23.9% (Bergman et al. 2001) to 55.2% (Andersson et al. 1993). The four studies which reported data for males and females separately all found that females had a higher prevalence of pain than males (Brattberg, Thorslund, and Wikman 1989; Kurita et
The four studies which reported pain prevalence by age group found that it differed by age, one finding a mid-life peak at ages 45 – 64 years old (Brattberg, Thorslund, and Wikman 1989), one a rise up to the age of 40 then a plateau (Bergman et al. 2001), one an increase in prevalence with increasing age (Kurita et al. 2012) and one a higher prevalence in the over 65s than in the sample as a whole (Reitsma et al. 2011).

The studies reported in Table 1.1 show that chronic pain is common, it is more common in females than males, and the prevalence of chronic pain is different at different ages.

Several factors can affect figures obtained for the prevalence of musculoskeletal pain. Research which surveys general populations (such as the studies reported in Table 1.1) will obtain different prevalence figures from research which counts health care consultations. A study which compared survey data of 12 month period prevalence of pain in adults with health consultations for pain over the same period found that the ratio of consultation to prevalence (for any body area) was 0.29 (Andersson et al. 1999). A telephone survey (n=498) of adults with chronic musculoskeletal pain found that one in four had never consulted a doctor about their pain (Veale, Woolf, and Carr 2008). A study of adolescents showed that although 45% reported pain in the past 12 months, only 33% had sought health care for pain (Masiero et al. 2010). A large (n = 17,792) health survey of a general adult population found that 4.5% had consulted a health professional for low back pain in the previous 2 months (Plenet et al. 2010), whereas another large (n = 34,902) study showed a 12 month period prevalence of low back pain of 55% (Leboeuf-Yde et al. 2009). These last two studies were both postal surveys carried out in Northern European countries, so it is likely the data are comparable.

It has been shown that the manner in which a pain question is phrased can influence the prevalence obtained. Pope and colleagues used 4 different ways of asking about shoulder pain and obtained 4 different prevalences from 32% to 48%, the lowest figure being in response to the question “During the past month, have you experienced pain in your shoulders lasting more than 24 hours?”, the middle 2 definitions using manikins with increasingly large areas considered as ‘shoulder’ and the highest figure was obtained using a pre-shaded manikin (Pope et al. 1997).

Geographical location can also affect reported pain prevalence rates. Studies determining the prevalence of fibromyalgia (a rheumatological condition whose primary symptom is chronic widespread pain) all using a questionnaire followed by
physical examination found a prevalence of 0.75% in Finland (Makela and Heliovaara 1991), 4.4% in Brazil (Assumpcao et al. 2009), 8.8% in Turkey (Turhanoglu et al. 2008), 0.22% in Cuba (Reyes-Llerena et al. 2009) and 2.4% in Spain (Mas et al. 2008).
Table 1.1 – Studies reporting the population prevalence of musculoskeletal pain

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Age range</th>
<th>Number of subjects</th>
<th>Location</th>
<th>Pain classification and how assessed</th>
<th>Prevalence</th>
<th>Pattern by age and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Brattberg, Thorslund, and Wikman 1989)</td>
<td>Random population sample. Postal questionnaire.</td>
<td>18 – 84 Age groups 1) 18-44</td>
<td>1009</td>
<td>Sweden.</td>
<td>Point prevalence. Chronic &gt; 6 months. Self-report response &quot;do you have pain in any part of your body?&quot;</td>
<td>Point prevalence of chronic regional pain: 40%.</td>
<td>1) 34.2% 2) 50% 3) 36.1% No significant sex differences.</td>
</tr>
<tr>
<td>(Andersson et al. 1993)</td>
<td>Random sample from population register, urban and rural. Postal questionnaire.</td>
<td>25 – 74</td>
<td>1609</td>
<td>Sweden.</td>
<td>Chronic (&gt; 3 months), self report response to “do you feel pain lasting for more than 3 months?”</td>
<td>Point prevalence of regional pain &gt; 3 months: 55.2%.</td>
<td>No significant sex difference in overall prevalence.</td>
</tr>
<tr>
<td>(Bergman et al. 2001)</td>
<td>Subjects sampled from population register. Postal questionnaire.</td>
<td>20 – 74 Age groups 1) 20-39 2) 40-59 3) 60-74</td>
<td>2425</td>
<td>Sweden.</td>
<td>12 month period prevalence. All body areas, pain &gt; 3 months. Self-report with shaded manikin for location.</td>
<td>12 month period prevalence of regional pain &gt; 3 months: 23.9% (N.B. this excludes CWP)</td>
<td>M1) 19.4% 2) 26.8% 3) 26.6% F1) 16.1% 2) 26% 3) 27.5%</td>
</tr>
<tr>
<td>(Picavet and Schouten 2003)</td>
<td>Stratified random sample from population register. Postal questionnaire.</td>
<td>Over 25. Age groups 1) 24-44 2) 45-64 3) 65+</td>
<td>3664</td>
<td>Netherlands.</td>
<td>12 month retrospective and point prevalence, detailed questions about 5 body areas: neck, shoulder, upper back, LBP, hip, knee, ankle, foot.</td>
<td>12 month period prevalence regional pain &gt; 3 months: 44.4%.</td>
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<tr>
<td>(Tripp, VanDenKerkhof, and McAlister 2006)</td>
<td>Sampled from telephone directories. Telephone questionnaire.</td>
<td>18 - 94</td>
<td>1067</td>
<td>Canada.</td>
<td>Self-reported pain &gt; 90 days in past 6 months, all body areas.</td>
<td>6 month period prevalence of pain &gt; 3 months: 49%.</td>
<td>___</td>
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<tr>
<td>Reference</td>
<td>Study design</td>
<td>Age range</td>
<td>Number of subjects</td>
<td>Location</td>
<td>Pain classification and how assessed</td>
<td>Prevalence</td>
<td>Pattern by age and sex</td>
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<tr>
<td>(Svebak, Hagen, and Zwart 2006)</td>
<td>Population of one county invited to participate, 1 year retrospective. Postal questionnaire.</td>
<td>Over 20</td>
<td>64690</td>
<td>Norway.</td>
<td>All body areas &gt; 3 months. Self report of pain or stiffness in muscles or joints.</td>
<td>Point prevalence of chronic regional pain: 44.6%</td>
<td>M – 40.4% F – 48.8%</td>
</tr>
<tr>
<td>(Parsons et al. 2007)</td>
<td>Sample from GP registers. Postal questionnaire.</td>
<td>Over 18</td>
<td>2504</td>
<td>South East England.</td>
<td>All body areas. Self reported using manikin, &quot;troublesome&quot; by questionnaire scale.</td>
<td>4 week period prevalence of chronic pain &gt; 3 months: 38%.</td>
<td></td>
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<tr>
<td>(Eggermont et al. 2009)</td>
<td>Existing cohort selected randomly from town lists. Home interview and clinical examination.</td>
<td>64 – 97</td>
<td>600</td>
<td>Boston, USA.</td>
<td>All body areas by interview and clinical examination. Pain &gt; 3 months.</td>
<td>Point prevalence of chronic regional pain: 63%.</td>
<td></td>
</tr>
<tr>
<td>(McCarthy et al. 2009)</td>
<td>Subjects from electoral register, computer assisted telephone interview.</td>
<td>70 - 101</td>
<td>840</td>
<td>New York, USA.</td>
<td>Self reported to prompt by interviewer. All body areas. Chronic = all or most of past 3 months.</td>
<td>3 month period prevalence chronic regional pain: 52%.</td>
<td>Author states age not a risk factor.</td>
</tr>
<tr>
<td>(Reitsma et al. 2011)</td>
<td>Used two pre-existing national surveys. Postal questionnaire.</td>
<td>Over 20</td>
<td>Between 17,244 and 134,072</td>
<td>Canada.</td>
<td>Answer no to question &quot;Are you usually free of pain or discomfort?&quot;</td>
<td>Point prevalence of habitual pain: 15.1% - 18.9%.</td>
<td>M – 13.6 to 16.2% F – 16.5 to 21.5% Age over 65 – 23.9% to 31.3%</td>
</tr>
<tr>
<td>(Kurita et al. 2012)</td>
<td>Pre-existing national cohort plus data from national registers. Postal or online questionnaire.</td>
<td>Over 16 Age groups 1)16-24 2)25-44 3)45-64 4)65-79 5)80+</td>
<td>14925</td>
<td>Denmark.</td>
<td>Self report using manikin, pain &gt; 6 months. All body areas.</td>
<td>Point prevalence of chronic pain: 26.8%.</td>
<td></td>
</tr>
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</table>

KEY: Bracketed numbers 1), 2) etc refer to specified age groups. M = male, F = female.
1.4 The impact of chronic pain

Impact on health and physical function

Chronic pain is associated with higher levels of psychological distress; when respondents to a large (n=46,394) telephone survey of people with chronic pain were asked if they had ever been diagnosed with depression due to their pain, 21% said “yes” (Breivik et al. 2006). By comparison, a study of non-psychiatric, hospital outpatients found a prevalence of depression of 12% (Zigmond and Snaith 1983). A review reported strong evidence that pain due to arthritis compromised the sufferers' psychological well-being (Backman 2006). Two aspects of psychological distress which have been addressed in pain research are anxiety and depression. A twin study found both depression and anxiety to be significantly co-morbid with chronic widespread pain (Kato et al. 2006). A review by Gambassi (Gambassi 2009) reported that pain was more prevalent in patients with depression than in the general population, depression was more prevalent in chronic pain patients than in the general population, and the likelihood of depression increased with the number of painful body areas, with the duration of pain and with the frequency of pain episodes.

Chronic pain limits the ability of the individual to carry out activities related to work and leisure pursuits as well as essential activities of daily living (Breivik et al. 2006; Jinks, Jordan, and Croft 2007; Reitsma et al. 2011). Older people are already likely to have more restrictions in carrying out activities of daily living than younger people and pain may act to increase age-related functional decline (Gagliese and Melzack 2005). Older people are more likely to have pain in multiple than in single joints, and this increases the likelihood of problems with physical function (Eggermont et al. 2009; Keenan et al. 2006). In people with chronic pain, 65% report difficulty sleeping and nearly half report problems with social activities, walking, driving or sexual activity (Donaldson 2009). Chronic pain in two or more sites has been found to be a risk factor for falls in older people, even after adjustment for multiple confounding factors (Leveille et al. 2009).

Quality of life is a multi-factorial concept which is influenced by physiological, psychological and social wellbeing. One survey found that the impairment to health-related quality of life caused by musculoskeletal pain is comparable to that of complicated diabetes mellitus or terminal cancer (Taylor 2005). A telephone survey (n=498) of adults with chronic musculoskeletal pain found that 67% reported reduced quality of life, as measured by the SF-12 (Veale, Woolf, and Carr 2008).
Onset of chronic widespread pain has been found to be associated with reduced physical health-related quality of life, even after adjusting for psychological and social factors at baseline (Nicholl et al. 2009). In a population-based study, the prevalence of knee pain was found to increase and knee-related quality of life was found to decrease with increasing age (Paradowski et al. 2006).

Excess mortality has been observed in subjects with chronic regional and widespread musculoskeletal pain, even after major confounding factors were taken into account (Macfarlane, McBeth, and Silman 2001). One study found the excess mortality to be due to cardiovascular disease (Andersson 2009), another that the excess was due to cancer and cardiovascular disease (Nicholl et al. 2009).

**Financial impact on the individual**

Pain-related physical disability can have financial implications for the individual concerned. Inability to carry out activities of daily living as a consequence of pain may lead to the need for additional assistance to carry out those activities, but there are no published studies regarding the cost of home care for pain-related disability. A meta-analysis of studies in the USA found that people needing help with 3 or more activities of daily living had an odds ratio of 3.25 for nursing home admission compared to people independent in activities of daily living (Gaugler et al. 2007), although the reasons for the loss of independence were not discussed so it is not possible to assess how much of this excess risk was due to pain-related disability. In people of working age, one source reported that 25% of chronic pain sufferers lost their jobs (Donaldson 2009), whilst a large telephone survey found that 19% lost their jobs but 29% had to modify or move jobs due to pain (Breivik et al. 2006). Chronic pain was found to be strongly associated with disability-related retirement, even in the absence of a physician-diagnosed condition or disease (Saastamoinen et al. 2012). Although there are no data on how much disability is actually caused by pain, disability itself is associated with low income, for example a campaigning group found that disabled adults were twice as likely to live in low-income households as non-disabled adults, where low income is defined as 60% or less of the national median income (The Poverty Site 2011).
Financial impact on wider society

A survey found that between 42% and 53% (depending on the body area affected) of people who reported pain within the past 12 months had consulted a medical professional about it (Picavet and Schouten 2003). There is a substantial loss to the national economy due to time taken off paid employment due to pain. A study based on the island of Jersey found that 10.5% of all work absences were due to low back pain (Maetzel and Li 2002). Many people not in paid employment also provide productive work to society. One study found that 13% of people aged over 65 years were providing some form of informal care for another person (McGarry and Arthur 2001). Government financed benefits are paid to people with pain-related disabilities; chronic pain is the second most common reason for claiming incapacity benefit in the UK (Donaldson 2009).

The costs to health care providers and employers, and in benefits paid as a result of pain, are part of the impact on wider society. Several studies and reviews have attempted to determine the total cost of specific types of pain. There is high variability between these estimates depending upon the parameters used. For example, the cost of training replacements for airmen in the US Air Force to replace those discharged with low back pain was $446,320 per year (1993 figures) (Dionne 1999). The Chief Medical Officer estimated that back pain alone cost the UK economy £12.3 billion (2009 figures) (Donaldson 2009). A review found the cost of low back pain was comparable to that of heart disease, depression or diabetes (Maetzel and Li 2002). The same review cited a UK study (Maniadakis and Gray 2000) which estimated that the direct costs of low back pain were £1.6 billion and the total costs between £6.6 and £12.3 billion (1998 figures).

There is a cost to employers in lost productivity due to sickness absence. Low back pain is a common cause of employees taking time off work; studies found 12.5% of sick days in the UK and 13.5% in Sweden were due to this cause (Andersson 1999). A study in the Netherlands following patients for 6 months following consultation with a GP for a shoulder problem found that almost 50% of the mean €689 (direct and indirect) cost per patient was due to time off work (2001 – 2003 figures). This was as a cost to the employer in lost production, not lost earnings for the individual. Patients with the most persistent pain incurred much higher costs (Kuijpers et al. 2006).

Health care may be paid for by the state or by private insurance. A study in the Netherlands reported that musculoskeletal pain accounted for 6% of the total cost of
healthcare (Kuijpers et al. 2006). Pain is the third most common reason why people in the UK visit a general practitioner (The British Pain Society and The Royal College of General Practitioners 2004). Low back pain is one of the five leading reasons for primary care consultations (Dionne 1999). In the UK each year, 7% of the adult population present to their GPs with back pain (Johnson et al. 2007). In the UK £584 million (2009 figures) was spent on prescriptions for pain medications in one year (Donaldson 2009).

People unable to work due to pain may claim disability benefits. A study in Brazil found that there were 29.96 claimants of disability pensions due to back pain per 100,000 tax payers (Meziat and Silva 2011). A study in the USA followed 1372 claimants of worker’s compensation for back pain acquired at work, and found that 19.6% of them went on to apply for social security disability insurance, which is a government-funded payment made to people limited in their ability to work due to a disability (Chibnall et al. 2006).

1.5 Why is studying pain with respect to ageing important?

The proportion of older people in the population in developed countries is increasing. The percentage of the UK population over the age of 65 has increased from 15% in 1983 to 16% in 2008, and is projected to be 23% in 2033, as shown in Figure 1.1 (Office for National Statistics 2009). Understanding health problems as they relate to older people will become increasingly important for the provision of health care as the population ages.
A critical review of pain and ageing assessed the evidence for the existence of a geriatric pain syndrome, i.e. a condition sufficiently different from pain in younger people to warrant separate study (Gagliese 2009). The author reported several major differences. In clinical disease, older people are more likely than younger people to develop neuropathic pain following acute herpes zoster (shingles), but are less likely to have pain during myocardial infarction. In experimental pain studies older people were found to have more temporal summation (increased pain perception with repeated applications of the same painful stimulus) than younger people (Lautenbacher et al. 2005). This may be due to changes in the endogenous pain inhibitory systems which could leave them vulnerable to prolonged sensitisation following injury. Gagliese also reported that the importance of cognitive and affective risk factors differs between older and younger chronic pain patients. Depression and pain were associated in both younger and older patients, but the mediating factors differed, with pain interference and life control important for the younger group but pain severity more important for the older group. Fear of reinjury mediated the relationship between catastrophising (a maladaptive coping strategy) and depression in older pain patients, whereas the same relationship was a direct one in younger pain patients (Gagliese 2009).

Despite these findings, relatively little pain research has focussed on older people, although this has increased in the past 25 years (Gagliese 2009). Some studies of pain prevalence in the population focus on people of working age and have an
upper age limit of 64 or 65 years old (Feleus et al. 2008; Ghaffari et al. 2006; Leijon, Wahlstrom, and Mulder 2009). Samples drawn from primary care registers generally include older people but may not specify how many subjects are in the very oldest age groups (80+) and may simply refer to over 65s (Huisstede et al. 2008). Only large studies have sufficient numbers of participants to be able to carry out analyses on the oldest age sub-groups (Andersen et al. 2003; Bot et al. 2005a; Svebak, Hagen, and Zwart 2006).

Studies of sensitivity to painful laboratory stimuli in healthy people often use volunteers under 60 and have health based exclusion criteria (Garcia et al. 2007; Rolke et al. 2006b). As older people have greater numbers of illnesses than younger people (Gagliese 2009) these exclusion criteria will tend to exclude older people even if the age limits do not. Even those studies particularly looking at the responses of older people (Farrell and Gibson 2007; Nebuchennykh et al. 2008) rarely contain subjects over 80 (Lautenbacher et al. 2005).

The consequences of pain are different for older people and younger people. The same intensity of pain is more disabling in older than in younger people (Ayis and Dieppe 2009; Paradowski et al. 2006). Pain in a single body area is unusual in an older population (Thomas et al. 2004). In one population-based study of over 55 year olds, median joint involvement was 4 (Keenan et al. 2006). This may also contribute to reduced function in older people with pain, as a study of knee pain related disability in people over 50 found that pain in other areas of the body was associated with more severe disability (Croft, Jordan, and Jinks 2005).

The treatment of pain is different in younger and older adults. A population survey (n=15,272) found that people with low back pain aged over 70 were more likely to consult a medical professional than people with low back pain aged under 40, but the older group were more likely to be prescribed analgesics and less likely to be referred for physiotherapy or exercise therapy than the younger group (Macfarlane et al. 2012). However, a review cited studies showing that pain in older people is under-treated, possibly due to the increased risk of adverse drug effects in older compared to younger people (Gagliese and Melzack 2005).
1.6 Summary

Chronic pain is highly prevalent in the population, with typical values for the prevalence of chronic pain (in any body area) in adult population studies between 15% and 63%. Pain limits the ability of an individual to carry out normal activities of daily living, and is also linked with poor psychological wellbeing. Pain is costly, both to the individual suffering from it and to society at large. The proportion of people aged over 65 in the population in developed countries is increasing. Older people generally suffer from a higher prevalence of chronic pain than younger people, and their pain is more widespread and more disabling. There has been less pain research on older than on younger people. There is evidence that pain in older people may be qualitatively different from pain in younger people. More research is needed to elucidate these differences.
2 Background

2.1 Overview

The different pain phenotypes used in research are discussed. Risk factors for chronic pain, including pain beliefs, psychological distress, physical activity, sleep quality, social deprivation and co-morbidities are discussed.

Sex and age are each covered in more detail as risk factors for chronic pain. The differing prevalence of pain and differential risk factors between men and women are discussed, as are the variation of pain prevalence and risk factors which alter with age.

Central sensitisation as a possible mechanism for the initiation and maintenance of chronic pain is discussed. Quantitative sensory testing (QST) is a possible means of investigating central mechanisms. It is described and some of the literature regarding QST in musculoskeletal pain conditions is reviewed. Differences in QST results with age and sex are discussed.

2.2 Pain phenotypes

A phenotype is a collection of characteristics which can be observed, for example seen by the naked eye or imaging, or found by tests such as blood tests (Felson 2010). Even among apparently well understood diseases such as osteoarthritis, hundreds of phenotypes could be defined (Felson 2010). Pain phenotypes are notoriously difficult to define, partly because of a lack of objective markers such as X-rays or blood tests, but they are essential in both research and clinical practice.

2.2.1 Definition of phenotype

Phenotype can be defined as:

“The expression of a specific trait, such as stature or blood type, based on genetic and environmental influences.” (Farlex 2010)

Disease phenotypes are used in health care and in research to classify an individual according to whether or not they have the disease or condition of interest, or the
degree to which they have it. They have differing purposes, as they indicate “caseness” in research, but are an indication for treatment in clinical practice, and these do not necessarily coincide.

2.2.2 Pain phenotypes used in research

Pain is generally defined by its duration, severity and location. Some researchers are also interested in how disabling or troublesome pain is to the individual.

One measure of duration is the distinction between acute and chronic pain. As was mentioned in the Introduction, chronic pain persists past the stage of tissue healing, so the connection to any tissue damage no longer exists (Staud 2005). A definition of chronic pain generally refers to a duration of 3 months or longer (Bergman et al. 2001; McCarthy et al. 2009), but some studies specify a different duration e.g. over 6 months (Brattberg, Thorslund, and Wikman 1989; Breivik et al. 2006).

Pain severity can also be measured in different ways. A telephone survey asked participants how severe their pain was between 1 and 10 where 1 was “no pain” and 10 “the worst pain imaginable” (Breivik et al. 2006). A postal survey which divided the body into 5 areas asked whether participants had experienced pain in that area in the past 12 months, and whether it was mild or severe (Picavet and Schouten 2003). A postal survey of older people (aged over 70) used the pain severity subscale of the Brief Pain Inventory. This asks participants to rate their worst pain, least pain, average pain and pain now each on a 0 – 10 numeric scale, where 0 is “no pain” and 10 “severe or excruciating pain as bad as you can imagine” (Eggermont et al. 2009). A study which collected data from older people (aged 77 – 98) by face-to-face interview asked about a list of complaints such as chest pain and abdominal pain, and in each case when the problem was present asked if it was mild or severe (Brattberg, Parker, and Thorslund 1996).

Pain-related disability can be ascertained by asking about pain-related interference with activities. A telephone survey gave participants a list of activities, e.g. driving, walking and sleeping, and asked them to rate the effect of their pain on their ability to do the activity as “just as able”, “less able” or “no longer able” (Breivik et al. 2006). A postal survey asked how many activities pain prevented the participant from undertaking, “none”, “a few”, “some” or “most” (Reitsma et al. 2011). A postal survey of adults aged over 50 asked “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and
housework)?” (Thomas et al. 2004). A telephone survey asked how much pain had interfered with usual activities between 0 “no interference” and 10 “unable to carry on any activities” (Tripp, VanDenKerkhof, and McAlister 2006).

The degree to which pain bothers the individual (“troublesomeness”) is a means of assessing relative health impact and the need for provision of health care (Parsons et al. 2007). A postal survey asked how troublesome pain in a list of body regions (e.g. head, neck) had been in the past 4 weeks: “not at all”, “slightly”, moderately” or “very” (Parsons et al. 2007).

Many studies have focussed on regional pains because of their links with function, e.g. low back pain or shoulder pain related to manual handling (Waters et al. 2007), or mobility restriction due to knee pain (Rejeski et al. 2001; Wilkie et al. 2007). However, studies did not always ask whether the participants had pain elsewhere, in spite of the fact that pain at other sites worsens disability (Croft, Jordan, and Jinks 2005).

The method of ascertaining pain location can lead to differing reports of prevalence. Commonly used methods include coding of shaded manikins (Taylor 2005; Veerapen, Wigley, and Valkenburg 2007), physician examination (Andersson et al. 1999), verbal questioning by face-to-face interview (Brattberg, Parker, and Thorslund 1996; Minaur et al. 2004) or on the telephone (Breivik et al. 2006; Tripp, VanDenKerkhof, and McAlister 2006), and written questions in a questionnaire (Ihlebaek, Eriksen, and Ursin 2002; Wolfe et al. 2011). The work of Pope and colleagues (Pope et al. 1997) showed the importance of definitions and how they could alter the apparent prevalence of shoulder pain. Four definitions gave prevalence rates of between 32% and 48%, the lowest figure being in response to the question “During the past month, have you experienced pain in your shoulders lasting more than 24 hours?”, the middle 2 definitions using manikins with increasingly large areas considered as ‘shoulder’, and the highest figure obtained using a pre-shaded manikin. Some studies, e.g. (Cassou et al. 2002) required the pain location to be confirmed by an occupational physician. Studies which collect data by telephone e.g. (Breivik et al. 2006) simply name the part of the body, and participants may have differing ideas as to what that means, which can lead to misclassification of the pain location.

Pain is also sometimes classified by its cause, although this may not be known, particularly if the sufferer has not consulted a health care professional (see section 1.3). A large (n = 46,394) telephone survey across 15 European countries and
Israel asked respondents with pain what they thought was the cause (Breivik et al. 2006). The majority of the attributed causes were musculoskeletal: arthritis/osteoarthritis (34%), spinal disk problems (15%), rheumatoid arthritis (8%), fracture or deterioration of the spine (6%), and cartilage damage (4%). Some pain was also attributed to traumatic injury (12%) or whiplash (4%), which might be musculoskeletal in nature (Breivik et al. 2006).

### 2.2.3 The phenotype of fibromyalgia

Fibromyalgia is a disorder characterised by multiple symptoms, primarily chronic, widespread musculoskeletal pain, but also tenderness to pressure (tender points), fatigue and sleep disturbance (Katz, Wolfe, and Michaud 2006). These symptoms are certainly not new, but the attempt to define a condition in which they co-occur is more recent.

Pain is the primary symptom of fibromyalgia, generally defined by its location and distribution. The American College of Rheumatology (ACR) requires pain of over 3 months’ duration on the left and right side of the body, above and below the waist, and in the axial skeleton in their definition of fibromyalgia (Wolfe et al. 1990).

Various definitions of “trigger points” and “tender points” have been put forward in chronic pain conditions (Smythe 1989). In the original study that was endorsed by the ACR (Wolfe et al. 1990), 24 points thought likely to be painful in fibromyalgia (active) and 6 points not thought likely to be painful in fibromyalgia (control) were identified; 18 of the active tender points gave an acceptable specificity and sensitivity (when combined with the ACR pain criteria) to identify rheumatologist-diagnosed fibromyalgia, so were included in the ACR definition. These are shown in Figure 2.1. Tender points are tested by applying manual, digital force of approximately 4kg to the area indicated (Wolfe et al. 1990). However, it has been found that tender point examinations are rarely used in clinical practice (Wolfe et al. 2010), and they are not possible in survey research where the participant is not physically examined. It has been shown that the number of tender points tends to increase with the number of body regions with pain, indicating that this is a feature of musculoskeletal pain which is not exclusive to fibromyalgia (Croft, Schollum, and Silman 1994).
The Wolfe (1990) criteria remain the most widely accepted definition of fibromyalgia, although these have been criticised because of the exclusion of other symptoms such as fatigue from the definition (Wolfe et al. 2010) and also because the body segments described are very general so the pain need not be truly widespread (Hunt et al. 1999). A more recent proposal from the ACR uses a tool called the Widespread Pain Index (WPI), which asks whether a participant has had pain during the past 7 days in the chest, upper back, lower back, neck, and the left or the right jaw, forearm, upper arm, lower leg, upper leg, hip or shoulder (19 areas in all) (Wolfe 2003). This new definition requires at least 7 of the 19 body areas to be painful, in addition to the presence of somatic symptoms, which is described in more detail below (Wolfe et al. 2010). Another version of the same criteria, which has been modified for survey questionnaire administration, also uses the WPI but varies the number of painful areas required in the definition of fibromyalgia depending upon the number and severity of somatic symptoms present (Wolfe et al. 2011), see Table 2.1.
Other symptoms are also associated with fibromyalgia. Patients with “tension rheumatism” (a poorly defined condition referred to in the 1940s and 1950s which included muscular tension and pain) were found to have disturbance in deep, non-dreaming sleep and an associated increase in symptoms in the morning (Smythe 1989). The ACR considered inclusion of somatic symptoms in their 1990 definition of fibromyalgia (including sleep disturbance, fatigue, morning stiffness, anxiety, irritable bowel syndrome, and frequent headaches) but concluded that the “best fit” definition only included widespread pain and tender points (Wolfe et al. 1990). This definition was criticised because it did not include somatic symptoms, which clinicians agreed were part of fibromyalgia, but did include a tender point examination, which was rarely used in clinical practice (Wolfe et al. 2010). A more recent study by Wolfe and colleagues endorsed by the ACR (Wolfe et al. 2010) proposed a somatic symptom scale (which included fatigue, waking unrefreshed and cognitive symptoms) to be used in combination with widespread pain in the definition of fibromyalgia, for physician use. A further study was carried out to test modified criteria (based upon the ACR 2010 criteria) which could be self-administered in questionnaire surveys (Wolfe et al. 2011). A simplified somatic symptom scale was used, in which participants were asked to rate the severity of fatigue, trouble remembering or thinking and waking unrefreshed between 0 “no problem” and 3 “severe and continuous”, giving a total between 0 and 12.

The 3 alternative definitions of fibromyalgia approved by the ACR are summarised in Table 2.1. The 2010 and 2010 (modified) definitions only apply if a) the symptoms have been present at around the current intensity for at least 3 months, and b) there is no other co-morbid disease or conditions which better explains the symptoms (Wolfe et al. 2010; Wolfe et al. 2011). Under the 2010 criteria, a) and b) are alternative combinations of the pain and somatic symptoms scores (Wolfe et al. 2010).
Table 2.1 – American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia

<table>
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<tr>
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<th>PAIN CRITERIA</th>
<th>OTHER CRITERIA</th>
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<tr>
<td>ACR 1990</td>
<td>Pain on left and right, above and below waist and in axial skeleton.</td>
<td>Tender points in 11 or more locations out of 18.</td>
</tr>
<tr>
<td>ACR 2010</td>
<td>Widespread Pain Index (max. 19)</td>
<td>Somatic Symptoms Scale</td>
</tr>
<tr>
<td></td>
<td>a) ≥7 painful areas or</td>
<td>a) ≥5 symptoms or</td>
</tr>
<tr>
<td></td>
<td>b) 3-6 painful areas</td>
<td>b) ≥9 symptoms</td>
</tr>
<tr>
<td>ACR 2010 (modified)</td>
<td>Total score of Widespread Pain Index + Symptom Scale ≥ 13</td>
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The Widespread Pain Index is scored from 0 – 19, scoring one for each positive response to the question “Have you had any pain or tenderness over the past week in the shoulder girdle, hip, jaw, upper back, lower back, upper arm, upper leg, chest, neck, abdomen, lower arm, and lower leg.”

The Somatic Symptoms Scale is a list of 56 symptoms including fatigue, blurred vision, abdominal cramps and waking unrefreshed. It is scored 0 – 56 for any symptoms experienced in the past 3 months.

The Symptom Scale rates the severity of fatigue, trouble remembering or thinking and waking unrefreshed between 0 (no problem) and 3 (severe and continuous), giving a total between 0 and 12.

Phenotypes of diseases may also be defined by their causative mechanisms. The aetiology of fibromyalgia is still poorly defined, but alterations in pain processing mechanisms have been considered as part of the cause (McBeth and Mulvey 2012). The idea of central rather than localised excitation leading to hypersensitivity was first put forward in the 1920s (Smythe 1989). The magnitude of the nociceptive flexion reflex (NFR) can be quantified by directly stimulating the sural nerve and measuring the corresponding contraction of biceps femoris. It provides an objective measure of central sensitisation, as it does not require a response from the subject (Yunus 2007). Yunus cited evidence of hypersensitivity to experimental stimuli, as well as functional magnetic resonance imaging (fMRI) and accentuated NFR evidence, to support his hypothesis that central nervous system sensitisation exists in fibromyalgia sufferers (Yunus 2007). If central nervous system sensitisation is
accepted as a diagnostic criterion for fibromyalgia, its inclusion may depend upon
development of a suitable measure.

The main difficulty in developing a phenotype for fibromyalgia is that there is no
definitive test, so the argument can become circular, i.e. this is the definition of the
condition, and it defines which patients have it and which do not. Rheumatologists
use their own clinical judgement in diagnosis, so it is unlikely to be completely
consistent between clinicians. Rheumatologist diagnosis has been used as the
“gold standard” in the development of both the 1990 and 2010 ACR criteria (Wolfe
et al. 1990; Wolfe et al. 2010).

In addition to being part of the ACR 1990 definition of fibromyalgia, chronic
widespread pain by that same definition had become a phenotype in its own right. If
the location of pain is recorded on a manikin, a coding schedule can be used which
divides the body into 10 regions for recording purposes, making it more convenient
and clear-cut to determine whether CWP is present (Wolfe et al. 1990). Other
definitions exist, for example the “Manchester” manikin uses 29 regions, and defines
chronic widespread pain as pain reported in at least 2 sections of 2 contralateral
limbs and in the axial skeleton, for at least 3 months (Hunt et al. 1999). This was
developed in order to apply a more stringent definition of widespread pain than the
ACR definition, for use in research studies. However, it does not appear to have
been adopted in the analysis of study data.

As a phenotype, CWP has no particular clinical significance in terms of being a cut-
off point for risk factors. A study of the relationship between pain and mortality
found that risk of dying increased with the number of reported pain sites rather than
a “step change” when CWP was present (McBeth et al. 2009). A study employing a
postal survey and physical examination found that an increasing number of painful
body regions was related to decreasing quality of social function (as measured by
SF-36), with no sharp deterioration when widespread pain was present (Schmidt
and Baumeister 2007). Another postal survey which divided the body into 10
regions found a strong relationship between number of pain areas and receipt of
disability pension at follow-up 14 years later (Kamaleri et al. 2009b).

A large amount of research data has been collected using the CWP phenotype as
defined by the 1990 ACR criteria (Buskila et al. 2000; Croft et al. 1993; Kato et al.
2006). Its widespread use allows comparisons to be made between different
populations e.g. native Americans (Jacobsson et al. 1996), Finns (Makela and
Heliovaara 1991), Brazilians (Assumpcao et al. 2009) and Spaniards (Mas et al.
2.2.4 Continuum of pain

Medical conditions which have traditionally been considered as a present/absent dichotomy may be considered as a continuum, with the risk of adverse outcomes increasing with reference to some clinical measure. Geoffrey Rose was a pioneer in this field, he argued that many diseases presented as a continuum (Rose and Barker 1978). Rose argued that dichotomisation wasted information, as it did not convey as much meaning as the full data distribution. Although he did concede that sometimes an acceptable/unacceptable cut-off needed to be applied, he stated that this depended upon the purpose, e.g. the point at which risk of treatment outweighed risk of adverse outcomes (Rose and Barker 1978).

Not all authors agree with Rose’s view that the majority of medical conditions form a continuum. The opposing view is that most diseases of clinical relevance are discrete, and even those conditions which form a continuum may need to be dichotomised, or perhaps only the cases at the extreme ends of the continuum used, for research studies. However, this is not necessarily the case; one study found that number of pain sites was associated with the presence of certain single nucleotide polymorphism (SNP) alleles, avoiding the need for dichotomisation e.g. into “no pain” and “pain” or “CWP” (Holliday et al. 2010). A genetics study found that dichotomisation of a continuous trait actually reduced the power to detect genetic linkage (Duggirala et al. 1997).

The question of whether pain can be considered to be a continuous phenomenon in the population has been considered (Croft 2009). One method of classification is number of areas of the body having pain, which can be determined using a manikin and coding schedule. There is a continuum between localised pain, which tends to be more acute, and widespread pain, which is more chronic, but there are no sharp distinctions in prevalence or aetiology (Macfarlane 1999). Figure 2.2 shows that, although a substantial minority of people have no pain at all, there is no sharp distinction in prevalence between pain at single and multiple sites. It also shows that single site pain is less common than pain at 2 – 5 sites. The relative rarity of single site pain has been replicated in other studies (Carnes et al. 2007) and reinforces the idea that single site pain due to localised pathology is unusual rather
than the norm. Svebak et al divided the body into 10 areas, and found that sick leave from work increased as the number of pain areas increased (Svebak, Hagen, and Zwart 2006). Kamaleri et al found that localised pain (i.e. pain at a single site) had little impact on physical fitness or daily activities, but as the number of pain sites increased, functional ability decreased (Kamaleri et al. 2008). Eggermont et al (Eggermont et al. 2009) found that multisite pain had more effect than pain severity on lower limb function. Kurita and colleagues found that pain intensity was strongly associated with the number of body areas having chronic pain (Kurita et al. 2012), showing that pain “widespreadness” is related to pain severity.

**Figure 2.2 – Number of regional pain sites (by Manchester definition) in a population sample**

![Distribution of pain sites](https://example.com/painSitesGraph.png)

(Number of pain sites using the Manchester definition (Hunt et al. 1999).)

(Macfarlane 1999)
2.3 Risk factors for chronic musculoskeletal pain

There is a very large body of evidence for risk factors for chronic musculoskeletal pain. This section will address the major risk factors, although it is acknowledged that the coverage of the literature is not comprehensive.

2.3.1 Some useful definitions

Precise use of language is important when describing the relationships between factors. The following definitions given by Kraemer and colleagues (Kraemer et al. 2001) will apply in this report.

Risk factor – a measure shown to precede an outcome.

Causal risk factor – a risk factor which, when changed, changes the outcome.

Mediator – a variable in a causal pathway from an independent to a dependent variable. It is caused to vary by the independent variable, and causes variation in the dependent variable.

Confounder – a variable which is not a mediator, can cause or prevent the outcome of interest and is associated with the factor under investigation.

Moderator – an effect modifier, which alters the relationship between the independent and dependent variable, dependent upon its value.

The difference between a mediator and a moderator is ambiguous, as both produce variations in the relationship between the independent and dependent variable (Kraemer et al. 2001). The theoretical basis used to underpin the model being tested must be used to justify the role of each variable.

2.3.2 Psychological factors

For the purpose of clarifying the descriptions, psychological factors will be divided into cognitions (e.g. beliefs, attitudes and perceptions), and emotional factors (e.g. anxiety, distress, depression).
Pain cognitions

A review of study evidence found that catastrophising, fear-avoidance beliefs and pain self-efficacy have a strong influence on recovery from back pain (Main, Foster, and Buchbinder 2010). Pain catastrophising is a coping style which involves the application of negative or pessimistic perceptions to the pain, leading to an exaggeration of the perceived threat of the pain (Velly et al. 2011). Fear-avoidance describes the anxiety and catastrophic thoughts generated by pain, leading to fear about the harmfulness of pain and avoidance of certain activities (Kamper et al. 2012). This can lead to pain-related disability (Vlaeyen and Linton 2012). Pain self-efficacy describes a person’s belief that they can carry out behaviours which they believe will control the threat presented by the pain; it has generally been linked to pain-related disability rather than pain status (Knittle et al. 2011; Richard, Dionne, and Nouwen 2011). A study on people with chronic widespread pain used factor analysis on 16 different cognitive concepts, and found that the first factor (labelled negative emotional cognitions) included low self-efficacy, catastrophising, fear-avoidance cognitions, illness consequence beliefs, understanding of the illness, and emotional representation of the illness (de Rooij et al. 2011).

A study on temporomandibular joint pain found that catastrophising and depression at baseline were both associated with an increased severity of symptoms at follow-up (Velly et al. 2011). A study of post-surgical patients found that catastrophising was associated with higher reported pain severity (George et al. 2008). The Illness Attitude Scales measure concerns and attitudes about illness and health; one study found that the subscale “Hypochondriacal Beliefs” was significantly associated with coexistence of chronic widespread pain (Hunt et al. 1999). A study of health care workers found that high levels of fear-avoidance beliefs, e.g. “I cannot do my normal work with my present pain”, significantly increased the subsequent risk of sickness absence due to low back pain (Jensen et al. 2010).

Emotional factors

Backman reviewed psychological and social factors in the management of arthritis pain, and pointed out the two-way nature of the relationship: psychological factors (including cognitions and emotional factors) influence the perception of pain, and pain affects psychological wellbeing (Backman 2006). The co-occurrence of pain and depression leads to more disability, and increased severity of either condition.
leads to worse outcomes in the other (Gambassi 2009). Stress, anxiety and depression have been linked to prevalence of low back pain and knee pain (Macfarlane, Jones, and McBeth 1999). A study of middle-aged and older men (aged 40 – 79) found that depression was positively associated with chronic widespread pain (Macfarlane et al. 2009). However, another study found that there was a strong association between depression and pain severity in older (aged 70 and over) but not in younger (under 70) people (Turk, Okifuji, and Scharff 1995). One study found that somatic symptoms (such as difficulty breathing and frequent vomiting, in the absence of a known physiological cause) were associated with a subsequent increased likelihood to develop chronic widespread pain (Gupta et al. 2007b).

Leventhal’s model

There is a theoretical model developed by Leventhal which can help to explain the relationship between beliefs, emotions and behaviour in the face of a health threat (see Figure 2.3) (Leventhal, Brissette, and Leventhal 2003). The implication of Leventhal’s model is that the cognitive and emotional responses to pain interact with one another, whilst mediating the relationship between pain and action to be taken by the individual. The effectiveness of the response is monitored by the individual and the perceived outcome is compared to the desired outcome. Any disparity leads to a modification of the perception of the threat (Leventhal, Brissette, and Leventhal 2003).

New representations of the threat (pain) are formed when new information becomes available, and pain beliefs may change based on an appraisal of the effectiveness of the behavioural response (Hale, Treharne, and Kitas 2007).
**Experimental pain and pain beliefs**

There have also been studies looking at the relationship between psychological factors and the perception of experimental pain. A study on women with fibromyalgia and healthy controls found that catastrophising led to decreased heat pain thresholds in both groups, but depression led to increased heat pain thresholds in both groups (Geisser *et al*. 2003). Another study found that catastrophising predicted lower descending noxious inhibitory controls (DNIC), a mechanism of endogenous analgesia (see section 2.7) in both men and women (Goodin *et al*. 2009).

**Experimental pain and emotional factors**

A study on fibromyalgia (FMS) patients found that the presence of depression did not influence pressure pain threshold or pressure pain sensitivity (Giesecke *et al*. 2005). Another study on women with FMS and healthy controls found that anxiety
and depression were both associated with increased sensitivity to cold pain, but this difference was no longer significant when group (FMS or control group) was controlled for (Smith et al. 2008). A study comparing depressive psychiatric in-patients with controls found no difference in heat, cold, pinprick and pressure pain thresholds (Klauenberg et al. 2008). A study of DNIC response in fibromyalgia patients with and without depressive symptoms, and healthy controls, found that reduced DNIC in the FMS patients was even more pronounced in those with comorbid depression (De Souza et al. 2009).

2.3.3 Levels of physical activity

There are two aspects to physical activity: activity incidental to functional tasks, and leisure activity such as exercise and gardening. This section will cover leisure activity. Occupational activity is a subset of functional task activity which is relevant for people in employment, and is discussed separately.

A longitudinal study recruited 2 groups of participants aged over 50 years old from members of the “Fifty Plus Runners’ Association” and a community sample (controls), and collected data on the presence and severity of pain using a VAS annually over a period of 14 years (Bruce, Fries, and Lubeck 2005). The runners had significantly lower pain scores at all time points than the controls, even after adjusting for gender and baseline body mass index. The authors acknowledged that withdrawal from the study might be associated with increased pain and repeated the analysis for study completers only, obtaining the same results (Bruce, Fries, and Lubeck 2005). A population survey collected data on pain prevalence and exercise frequency, duration and intensity (Landmark et al. 2011). It found that adults aged over 20 exercising 2-3 times per week had significantly lower chronic pain prevalence than sedentary people of the same age, but whilst those aged under 64 who exercised 4 or more times per week had a similar chronic pain prevalence to sedentary people, for those aged 65 or over the pain prevalence was even lower when exercising 4+ times per week than 2-3 times per week (Landmark et al. 2011).

Exercise may mitigate other risk factors for pain. A survey of headaches in full-time workers aged 20-65 years old found that the prevalence of severe headaches was positively associated with long working hours only in participants who undertook a
low level of physical exercise, but there was no association between headaches and working hours in those who undertook a high level of exercise (Sato et al. 2012).

The effect of exercise interventions on pain can also provide evidence for physical activity levels as a modifiable risk factor for pain. A 24 week resistance training programme performed by sedentary men (bus drivers) was associated with a lower 2 week prevalence of pain measured at the end of the training period, compared to inactive controls (Zavanela et al. 2012). A longitudinal study of the effect of a six month graded, aerobic exercise intervention on people with chronic widespread pain found that the odds ratio of reporting feeling “much better” or “very much better” compared with the other less favourable replies was 6.2 at 6 months after baseline and 3.6 at 9 months after baseline (McBeth et al. 2012). A study on a group of rheumatoid arthritis patients found that a 16 week strength training programme led to benefits including significant pain reduction, when compared to controls (Flint-Wagner et al. 2009).

In cross-sectional studies, it is not possible to ascertain the direction of a relationship, i.e. does reduced exercise contribute to the development of pain, or does pain limit the ability to do exercise? A review reported that pain and fatigue were both predictors of reduced participation in leisure activities (Backman 2006). One study found that the presence of pain at baseline predicted low self-reported levels of physical exercise activity at 32 month follow-up, although the possibility of the reverse relationship, i.e. low levels of physical activity increasing the risk of pain was not ruled out (McBeth et al. 2010a). A review of 7 studies on the relationship between chronic low back pain and levels of physical activity found no difference between adolescent or younger adult (<65 years old) low back pain patients and healthy controls, but the two studies on people over the age of 65 found that low back pain patients were less active than controls (Griffin, Harmon, and Kennedy 2012).

2.3.4 Sleep quality

Poor sleep quality and chronic pain are highly co-morbid. There is evidence that the relationship between pain and sleep is bi-directional in that sleep deprivation leads to hyperalgesia, and pain impairs sleep (Brand et al. 2010). A review reported that two thirds of individuals with chronic pain also report poor sleep quality, in particular non-restorative sleep (Lavigne et al. 2011).
A case-control study which recruited cases who frequently consulted their GP for musculoskeletal pain problems over a 5 year period, and controls who did not consult for this issue, found that sleep quality measured by questionnaire was significantly worse (Pittsburgh Sleep Quality Index 7 or higher) in cases than controls (Rohrbeck, Jordan, and Croft 2007). A population survey gathered data by telephone on pain symptoms and sleep duration during the past 24 hours, daily for 7 days (Edwards et al. 2008). The study found significant associations between sleep duration less than 6 or greater than 9 hours and next-day pain, and also between previous pain and next-day sleep duration of less than 6 or greater than 9 hours, but the relationship was stronger between dysfunctional sleep and subsequent pain. A survey carried out on students measured sleep quality and the cognitive-emotional elaboration of pain (CEEP) (hypochondria and somatosensory amplification) rather than the presence of pain itself (Brand et al. 2010). Using structural equation modelling, the authors found that CEEP influenced poor sleep both directly and indirectly, whereas poor sleep only influenced CEEP indirectly.

Sleep disturbance is very common in people suffering from fibromyalgia, with up to 99% of them reporting some sort of problem with sleep, particularly non-restorative sleep (Davies et al. 2008). Poor sleep has been found to be associated with low pressure pain threshold at tender points and control sites (Chiu et al. 2005), and low pressure pain thresholds at defined tender point sites is part of the definition of fibromyalgia (Wolfe et al. 1990). A longitudinal study found that in participants with chronic widespread pain (CWP) at baseline, restorative sleep was associated with the resolution of CWP 15 months later (Davies et al. 2008). Although this is the clearest indication of a possible causative relationship between sleep quality and chronic pain, the authors state that restorative sleep may merely be an early marker of recovery from CWP.

2.3.5 Social deprivation

Low social class has been found to increase the risk of developing chronic headache and fibromyalgia (Macfarlane, Jones, and McBeth 1999) as are being unemployed and having a lower income (McBeth and Jones 2007). A study investigating the link between new onset of chronic widespread pain and living in an area of low socio-economic status found that the association was explained by co-morbid psychological factors (Davies et al. 2009b). The prevalence of fibromyalgia in a low socioeconomic status population was found to be similar to that found in
higher status populations (Assumpcao et al. 2009), but conversely another study found musculoskeletal symptoms to be commoner in people living in socially deprived areas (Urwin et al. 1998). A study which used car ownership as a measure of socio-economic status found that the likelihood of new onset neck pain in a 12 month period, in people pain-free at baseline, was the same for car owners and non-owners (Croft et al. 2001). A survey found that socioeconomic class related to employment was related to the prevalence of both chronic regional and chronic widespread pain, in that participants with manual jobs had the highest prevalence, followed by non-manual workers, then higher grade non-manual workers, and finally those with upper level executive jobs had the lowest prevalence (Bergman et al. 2001). The same study found that participants from an area with poor economic conditions and social problems had a higher prevalence of chronic widespread pain than participants from a more affluent area. Together these studies suggest that greater social deprivation, as quantified by a variety of measures, is associated with greater prevalence of pain.

### 2.3.6 Education status

A population survey found that having 9 or fewer years of education was a risk factor for both frequent (>6 days per month) and chronic headaches (≥15 days per month) when compared to having 13 or more years of education (Hagen et al. 2002). A population based study which used a questionnaire to ask about pain location and years in education went on to identify fibromyalgia by physical examination of a sub-set of participants, and then weighted this prevalence back to the whole cohort, found that participants with 9-11 years of education had a significantly higher risk of having fibromyalgia than participants with 12 or more years of education (Wolfe et al. 1995). A large (n=7217) study on fibromyalgia which physically screened all participants divided educational level into “less than elementary”, “elementary”, “secondary” and “high school or more” found an odds ratio of 0.29 for prevalence of fibromyalgia between any two adjacent education levels, i.e. the prevalence fell with increasing level of education (Makela and Heliovaara 1991). A population survey in France found that level of education (having or not having a diploma) was strongly associated with having back pain for at least 30 days in the past 12 months. However, this was almost entirely mediated by physical work factors, e.g. handling heavy loads, and lifestyle factors such as being overweight (Leclerc et al. 2009). A prospective study of employed people
found that each additional year of formal education was associated with a reduced risk of claiming disability pension for back pain at 7 year follow-up. This remained even after adjusting for occupational factors (e.g. physically demanding work, concentration required) and lifestyle factors (e.g. smoking, exercise) (Hagen, Tambs, and Bjerkedal 2006). A telephone survey found that less than 14 years in education significantly increased the likelihood of having pain of a higher intensity, compared to 14 years or more in education (Tripp, VanDenKerkhof, and McAlister 2006). A survey found that musculoskeletal pain and headache were less common in men with a University education than those without, but there was no association for women (Bingefors and Isacson 2004). A population based survey found that participants having education upto the age of 16 had 2.17 odds ratio of having chronic pain compared to participants with higher education (over the age of 18) (Kurita et al. 2012). In summary, fewer years in formal education are associated with a higher prevalence of pain, but this may be mediated by other factors.

### 2.3.7 Smoking

A population-based study found that smoking was associated with persistent low-back pain over a 10 year period (van Oostrom et al. 2011). A population survey found that among people with chronic pain, smokers experienced higher pain intensity than non-smokers (Jakobsson 2008). A study of pain rehabilitation outpatients found that at baseline measurement, smokers had significantly worse physical and emotional functioning than non-smokers, as measured by SF-36 and Multidimensional Pain Inventory (Hooten et al. 2009). A prospective study of public sector workers in Sweden found that people who had ever smoked (currently or in the past) had an increased risk of new onset of sickness absence due to back or neck pain (Skillgate et al. 2009). A longitudinal study on adolescent twins found that smoking levels at baseline were positively correlated with the presence of low back pain at 8-year follow-up, but there was no longer a statistically significant effect when the twin pairs discordant for back pain status were used as controls for one another. The authors considered that this was most likely to be due to “over-matching” of cases and controls, and did not necessarily contradict the main findings of the study. (Hestbaek, Leboeuf-Yde, and Kyvik 2006). A survey of adults without neck pain at baseline found no association between smoking and neck pain during the 12 month follow-up period (Croft et al. 2001).
2.3.8 Drinking alcohol

A survey of community-dwelling adults with orofacial or arthritis pain found that approximately one quarter used alcohol to self-medicate for pain, and that alcohol use was commoner in men than women, and in younger than in older people (Riley, III and King 2009). A prospective study of public sector workers in Sweden found that alcohol consumption had a small (but not statistically significant) protective effect with respect to new onset of sickness absence due to back or neck pain (Skillgate et al. 2009). A longitudinal study which recruited adolescents found that alcohol drinking levels at baseline were not associated with low back pain at 8-year follow-up (Hestbaek, Leboeuf-Yde, and Kyvik 2006). A survey of adults without neck pain at baseline found no association between drinking alcohol and neck pain during the 12 month follow-up period (Croft et al. 2001).

2.3.9 Marital status

A population survey of adults aged 15 – 65 found that people reporting neck pain were more likely to be married than unmarried (Stranjalis et al. 2011). A survey of adults without neck pain at baseline found that those who were separated, divorced or widowed were more likely to have neck pain within the 12 month follow-up period than those who were single or married (Croft et al. 2001). A general population survey which asked about pain in any area of the body found that participants with persistent pain (i.e. are “often troubled with pain” and have had pain within the past 2 weeks) were more likely to be widowed than those with no pain (Crook, Rideout, and Browne 1984). A telephone survey found that being married did not alter the probability of having pain of a higher intensity, compared to not being married (Tripp, VanDenKerkhof, and McAlister 2006). A survey found that musculoskeletal pain and headache were commoner in married or cohabiting compared to single women, but there was no association for men (Bingefors and Isacson 2004). A cross sectional survey found that both men and women who had ever been married were more likely to have low back pain than people who had never been married (Silman et al. 1995).
2.3.10 Number of children

A cross-sectional survey found a linear trend of increased risk of low back pain with increasing numbers of children in married men and women (Silman et al. 1995). A prospective survey of adults without neck pain at baseline found that there was an increasing, linear trend of neck pain within the 12 month follow-up period according to the number of children participants reported having (Croft et al. 2001). The authors theorised that this might be due to mechanical stresses related to raising young children. A one-year prospective study of aircraft assembly workers found an association between limitation with work activities due to back symptoms and caring for children at home (Rossignol, Lortie, and Ledoux 1993).

2.3.11 Musculoskeletal ill health and other co-morbidities

Osteoarthritis is commonly associated with pain. In a large (n=46,394) postal survey, 34% of participants with pain said their pain was due to osteoarthritis (Breivik et al. 2006). A study which recorded health care episodes over a period of 10 years due to osteoarthritis found that the prevalence of physician diagnosed OA rose with increasing age, from 1.5% of the population at ages 20-24 to 60% of the population at ages over 90 (Kopec et al. 2007).

Multiple physical symptoms, help-seeking for health problems and existing non-widespread pain are all associated with a subsequent increased likelihood to develop chronic widespread pain (Gupta et al. 2007b). A study of middle-aged and older men found that co-morbidities increased the likelihood of reporting chronic widespread pain, with increasing probability as the number of co-morbidities increased (Macfarlane et al. 2009). A twin study found that subjects with chronic widespread pain were significantly more likely to report chronic fatigue, irritable bowel syndrome, depression, poor self-rated health and joint pain, although the authors felt that this might reflect different manifestations of a single disorder (Kato et al. 2006). A population based survey found that participants with cardiovascular disease had an odds ratio of 3.84 for chronic pain compared to participants without cardiovascular disease (Kurita et al. 2012).

A study on older people found that a simple count of medications was of comparable effectiveness to more complex indices of co-morbidity in predicting health care use and mortality in the ensuing year (Perkins et al. 2004).
2.3.12 High body mass index (BMI)

A study of older people found that the prevalence of chronic pain was highly associated with obesity (defined as BMI $\geq 30$) even after adjusting for depression and anxiety (McCarthy et al. 2009). A study found that high BMI was associated with knee and low back pain in females, but only with knee pain in males (Pountain 1992). A population-based study found that obesity was associated with persistent low-back pain over a 10 year period (van Oostrom et al. 2011). A survey found that underweight (BMI $< 18.5$) and obese (BMI $\geq 30$) individuals had odds ratios of 1.51 and 1.89 respectively of reporting chronic pain, compared to normal weight individuals ($18.5 >$ BMI $\leq 25$) (Kurita et al. 2012). Conversely, a survey of adults without neck pain at baseline found no association between body mass index and neck pain during the 12 month follow-up period (Croft et al. 2001). In people with chronic pain, a high BMI may be associated with more severe symptoms, for example among clinic patients with fibromyalgia, a high BMI was found to be associated with a high Health Assessment Questionnaire (HAQ) score indicating greater disability (Yunus, Arslan, and Aldag 2002).

2.3.13 Social support

A study on patients with irritable bowel syndrome found that social support was positively related to less severe pain (Lackner et al. 2010). A survey of chronic pain patients found that self-perceived level of social support was inversely proportional to pain intensity (Lopez-Martinez, Esteve-Zarazaga, and Ramirez-Maestre 2008). A longitudinal study which surveyed patients with recently diagnosed rheumatoid arthritis at baseline, after 3 years and 5 years found that a low level of perceived social support was associated with an increase in severity and frequency of painful episodes between baseline and both follow-up points (Evers et al. 2003). A study on rheumatoid arthritis patients asked the participants to complete a visual analogue scale for pain severity and a measure of satisfaction with social support twice daily for 7 days (Holtzman, Newth, and Delongis 2004). Both morning and evening pain severity were negatively associated with degree of satisfaction with social support. The authors stated that this relationship was mediated by the use of coping strategies (cognitive reframing, stoic distancing, emotional expression and problem solving).
2.3.14 Occupation

Many studies of occupational risk for pain consider specific activities or types of work in relation to regional pain. A prospective population study collected data at baseline and follow-up 20 years later on shoulder pain and occupational history, and among those who were free from shoulder pain at baseline, work recorded at baseline as involving repetitive movements and vibration was the highest occupational risk factors for chronic shoulder pain at follow-up (Miranda et al. 2008). A cohort of men enlisting for military service were asked about the occurrence of back pain in the previous 2 years, and whether their work was “mostly sitting”, “not physically heavy”, “medium heavy” or “heavy” (Hellsing and Bryngelsson 2000). At a follow-up 20 years later they were asked about the occurrence of frequent back, neck or shoulder pain and this was found to be significantly associated with carrying out heavy or medium work at baseline, compared to mostly sitting. A study using employed participants asked about manual handling activities at work at baseline, and location (neck/shoulder, low back, upper limb, lower limb) and severity of pain at both baseline and at follow-up 24 months later (Andersen, Haahr, and Frost 2007). Manual handling activities were found to be significantly associated with onset of severe pain in participants free from pain at baseline: repetitive work with neck/shoulder, upper limb and lower limb pain, lifting and pushing/pulling with pain in all regions, lifting ≥50 kg per hour above shoulder height with neck/shoulder, upper limb and lower limb pain, and standing for >30 minutes per hour with pain in all regions. Sitting for >30 minutes per hour was not associated with onset of any severe pain.

Factors not related to manual handling or posture are also included in some studies. A telephone survey of employed participants asked about the occurrence of pain in the back and arms, heavy lifting and repetitive hand movement at work, but also psychosocial factors such as job satisfaction, supervisor support and having to work fast (Waters et al. 2007). Both back pain and arm pain were found to be significantly associated with heavy lifting and repetitive hand movements, and also poor job satisfaction, lack of freedom in deciding how to do the work, unsupportive supervisors, not enough time to do the job, mandatory overtime and stressful work. A study on intensive care nurses found that 90% of them experienced low back pain at least once per month, and this was found to be associated with the frequency of working night shifts (June and Cho 2011).
2.3.15 Genetics and race

Much of the research into pain genetics has focussed on single nucleotide polymorphisms (SNPs), where a single nucleotide within a gene can be of two or more different types. A review concluded that no definite pain susceptibility genes had yet been identified, although this might, in part, be down to difficulties with study design (Limer et al. 2008). One study found that a combination of 3 SNPs proposed to be pain-protective did not vary significantly between people with, and without, chronic widespread pain (Holliday et al. 2009). A study of shoulder pain in post-surgical patients found that catechol-O-methyltransferase (COMT) genotype was associated with pain rating, but only in interaction with catastrophising (George et al. 2008). There is some evidence that some of the excess pain prevalence in females compared to males might have a genetic component, for example sex-related genetic variations of metabolising enzyme systems leading to differences in pain mechanisms between men and women (Holdcroft and Berkeley 1999).

Race can be defined as:

“A local geographic or global human population distinguished as a more or less distinct group by genetically transmitted physical characteristics.” (Farlex 2010).

There are also other definitions, including one from a study of pain and alcohol use which considered race a social category (Riley, III and King 2009).

A study of a native American community found that they had a much lower prevalence of chronic widespread pain and shoulder disorders than had been measured in Caucasian communities (Jacobsson et al. 1996). A study of black and white older people living in New York found that the black women reported significantly more neck and shoulder pain than white men or women (Vogt et al. 2003). In the UK, participants of South Asian origin reported more disabling back pain than other ethnic groups (McBeth and Jones 2007). A study in New Zealand did not report any significant differences in pain prevalence between Maoris and non-Maoris (Taylor 2005). A study in the USA found that Caucasians with knee osteoarthritis reported less knee pain than African-Americans with knee osteoarthritis, but this difference was no longer statistically significant when number of occupational tasks involving the lower limb were taken into account (Allen et al. 2012).
2.3.16 Stressful life events

One such cause of stress is major life events, which may cause psychological distress and could trigger physiological responses to stress, such as altered function of the hypothalamic-pituitary-adrenal axis (McBeth et al. 2007). Such events vary across the lifespan, and may be different for males and females. Examples include childbirth, retirement and bereavement (Holdcroft and Berkeley 1999). One study found that adverse life events were associated with a subsequent increased likelihood to develop chronic widespread pain (Gupta et al. 2007b). A study of middle-aged and older men found that the number of recent life events was strongly associated with the likelihood of reporting chronic widespread pain (Macfarlane et al. 2009).

2.3.17 Sex and age

Sex is a known risk factor for chronic pain. Almost all studies of the prevalence of chronic pain in the population show an excess prevalence in females compared to males (Eggermont et al. 2009; Fillingim et al. 2009; Kato et al. 2006). Females also make more use of health care for painful conditions than males (Skillgate et al. 2007).

Prevalence of chronic pain is known to vary with age (Buskila et al. 2000; Huisstede et al. 2008; Svebak, Hagen, and Zwart 2006). Differences in known risk factors for pain have been found between people of different ages, for example pain beliefs (Gibson 2003), marital status (Gibson 2003) and depression (Turk, Okifuji, and Scharff 1995).

These factors warrant further discussion so each has been covered in a separate section, age in section 2.4 and sex in section 2.5.

2.4 Pain and ageing

2.4.1 Defining “ageing”

Age is usually defined as the period of time since a person’s birth to the present time. However, the changes associated with increasing age (see sections 2.4.4 – 2.4.7) do not all proceed at the same rate, and indeed are not the same for different
individuals. An alternative view of biological ageing is that of increasing frailty, which is defined as the accumulation of largely unrelated co-morbidities (Shega et al. 2012). However, this view of ageing excludes some factors known to be important in the study of pain (see section 2.3), such as pain beliefs and social factors. Chronological age has shortcomings as a measure of ageing, but it gives an indication of ageing within all the domains which are important in the study of pain.

2.4.2 Pain prevalence and age

All population-based studies show that the prevalence of musculoskeletal pain, both regional and widespread, varies with age (Blyth et al. 2001). For some body areas, for example neck, shoulder and low back pain, prevalence reaches a peak in mid-life and declines somewhat in old age, although it remains high (see Figure 2.4), but in other body areas, for example the knee and the hip, pain prevalence continues to increase with increasing age (see Figure 2.5) (Svebak, Hagen, and Zwart 2006). There is some evidence that more severe pain is more prevalent in the oldest age groups. A study which asked about frequent pain in any body area in people aged over 50 years found a peak at ages 60 – 70 and a decline thereafter, but moderate to severe pain prevalence increased continuously with age (Shi et al. 2010). A study on a convenience sample of 124 community-dwelling people over the age of 60 found that over 80% of them had experienced moderate or severe pain in the past month (Brown et al. 2011). It is also generally found that pain prevalence is greater for females than for males, and this appears to persist across age groups (Blyth et al. 2001; Holdcroft and Berkeley 1999).

Chronic widespread pain, as defined by the ACR (Wolfe et al. 1990) is generally found to increase with increasing age (Buskila et al. 2000; Croft et al. 1993; Hunt et al. 1999) but in some studies there is a peak of prevalence in mid-life (Macfarlane et al. 2009). Two examples of regional or localised pain conditions which differ with respect to the age of peak prevalence are shoulder pain and knee pain. Shoulder pain prevalence is commonly found to peak in mid-life, e.g. ages 45 – 64 (Huisstede et al. 2008; Picavet and Schouten 2003; Svebak, Hagen, and Zwart 2006), then decline at older ages (see Figure 2.4). It is often related to soft tissue injuries (Bjelle 1989), which may be linked to occupational and recreational activities (Karels et al. 2007).
The pattern of prevalence with age would support this link, as most people in developed countries are retired by age 65. Many studies of shoulder pain concern occupational risks, for example, office workers (Eltayeb et al. 2009), bus drivers (Perovitch-Najenson et al. 2010) or general working populations (Andersen, Haahr, and Frost 2007; Miranda et al. 2008; Waters et al. 2007). Even among those studies of shoulder pain prevalence which do not directly address occupational factors, many only consider populations of working age (Hasvold, Johnsen, and Forde 1996; Leijon, Wahlstrom, and Mulder 2009; Pernold et al. 2005).

Knee pain prevalence, in contrast, is almost always shown to continue increasing with age (see Figure 2.5) (Andersson et al. 1993; Svebak, Hagen, and Zwart 2006; Thomas et al. 2004). A survey of people over 50 found that hip, knee and ankle pain continued to increase with age, whereas pain in other body areas declined after the age of 69 (Thomas et al. 2004). Knee pain in older individuals is often considered to be associated with degenerative joint disease, indeed, the American College of Rheumatology (ACR) clinical definition of osteoarthritis of the knee could be met by having knee pain, being over 50 years old, having no palpable warmth in the joint, and morning joint stiffness of under 30 minutes (Altman et al. 1986).

**Figure 2.4 – Variation of shoulder pain prevalence with age**

![Shoulder pain prevalence graph](image-url)
2.4.3 Acute pain and age

Acute pain can be viewed as protective, because it can help an individual to avoid tissue damage or limit activity to allow healing. However, this only benefits the individual briefly, and prolonged noxious stimulation can promote plastic changes within the peripheral and central nervous system. As with chronic pain, acute pain includes emotional and behavioural as well as sensory components (Cousins and Power 1999).

Many studies of pain prevalence include pain which has lasted for less than 3 months, but often pain of recent origin is not distinguished from chronic pain. Considering some examples of how pain is measured in population-based studies of pain, one study (Veerapen, Wigley, and Valkenburg 2007) asked about 7 day pain prevalence, and another study (Bingefors and Isacson 2004) asked about pain in the previous 2 weeks, but neither asked about pain duration.

Those studies which broke down pain prevalence by age generally found a similar pattern in pain of unspecified duration to that seen in chronic pain. One study (Thomas et al. 2004) found a mid-life peak and a decline in older age in one month period prevalence of shoulder pain lasting longer than 1 day. Two more studies
found that 7 day period prevalence of knee pain rose with increasing age (Taylor 2005) and that point prevalence of knee pain followed the same pattern (Picavet and Schouten 2003).

Some acute illnesses which are considered as almost universally painful in younger people can be experienced as not painful by older adults. For example, myocardial infarction presents painlessly in about 35 – 42% of older people (Gibson 2003), and angina may be painless in some older individuals (Davies and Sinclair 1995; McCleane 2008). Almost half of older cancer patients receiving end-of-life hospice care did not report pain (Gagliese 2009).

2.4.4 Physiological factors

Degenerative processes occur with ageing (McBeth and Jones 2007) and include changes in the skin and the nervous system (Gagliese and Melzack 2005) and in synovial joints (Kopec et al. 2007; Moskowitz 2009). The evidence for a relationship between knee pain and radiographic evidence of joint degeneration varies, ranging from a poor correlation (Macfarlane, Jones, and McBeth 1999) to radiographic signs as a risk factor for knee pain (Neogi et al. 2009).

There are a number of changes which occur in the central and peripheral nervous system with increasing age. Reductions in the density of both myelinated and unmyelinated nerve fibres have been reported (McCleane 2008), together with increased numbers of damaged fibres. Widespread degeneration is observed in dorsal horn neurons (Gibson and Farrell 2004), including changes in C- and Aδ-fibre function, changes to the descending pain inhibitory system and increased frontal and lateral cortical activation in response to painful stimuli (Gagliese and Melzack 2005). Levels of substance P and calcitonin gene-related peptide (CGRP) (both important nociceptive neurotransmitters) in the spinal cord dorsal horn have been found to be lower in older than in younger rodents (McCleane 2008). This is likely to contribute to alterations in descending pain modulation with age (Gibson and Farrell 2004). Areas of the brain known to be involved in nociceptive processing, such as the hippocampus and anterior cingulate, have shown neuronal degeneration with increasing age (Gibson and Farrell 2004). An imaging study also found that older adults with more severe acute or chronic pain had smaller hippocampal volumes (Zimmerman et al. 2009).
2.4.5 Consequences of pain

A survey found that the presence of disabling pain was higher in people aged over 65 than in younger adults (Jimenez-Sanchez *et al.* 2010). Older people with shoulder pain had worse function than younger people also with shoulder pain (Hill *et al.* 2010). A study comparing the relationship between pain and limitation of mobility found that the relationship was stronger in younger than in older people, but that a greater proportion of older people had pain-related mobility restriction (Mottram *et al.* 2008). A longitudinal study of people over 50 found that increasing age was a predictor of new onset pain interference with activity (Jordan *et al.* 2008). A study of 4 week pain prevalence in people aged over 50 found that those aged over 80 had a much greater prevalence of pain-related interference with activities than the younger age groups (Blyth *et al.* 2007).

2.4.6 Psychological factors

A longitudinal study of people aged over 50, with follow-up surveys at intervals over a period of 14 years, found that depression at baseline gave a univariate odds ratio of 2.05 (95% C.I. 1.87, 2.25) of new onset pain in any body area, when compared to no depression (Shi *et al.* 2010). When the model was adjusted for age, sex, race, education, marital status, smoking and body mass index, the OR was 1.70 (95%C.I. 1.51, 1.91) and was still statistically significant. A study looking at the association between chronic pain severity and depression found a strong correlation in patients aged over 70, $r = 0.51$ $p < 0.005$, but a low, non-significant correlation in adults under 69 years old, $r = 0.01$ (Turk, Okifuji, and Scharff 1995).

Pain beliefs appear to differ between older and younger people. Older people often attribute mild pain to “normal” ageing, but are more likely than younger people to interpret severe pain as a sign of serious illness and seek treatment (Hofland 1992). Older people are more likely than younger people to have an external locus of control (i.e. believe that their pain is not within their own control) (Gibson and Helme 2000). A study on chronic pain patients found that an attitude of stoicism mediated the relationship between age and pain severity (Yong 2006). Coping strategies also vary between age groups. Older people have been found to use more catastrophising and more hoping and praying than younger adults when they have mild pain, although strategies are more similar between age groups for severe pain (Gibson 2003).
2.4.7 Social and lifestyle factors

Different life events are common at different ages, e.g. marriage/partnering, child rearing, retirement and bereavement. These interact with other risk factors in influencing pain perception (Holdcroft and Berkeley 1999). A one-year prospective study of aircraft assembly workers found an association between limitation with work activities due to back symptoms and caring for children at home (Rossignol, Lortie, and Ledoux 1993). Retirement leads to an absence of work-related stresses, both physiological and psychological. This may contribute to the reduction in shoulder pain prevalence at older ages observed by many studies, as this is often linked to occupational causes (Karels et al. 2007). Widowhood has been linked to increased risk of pain in community-dwelling older people (Gibson 2003).

Increasing age may lead to social isolation, particularly if accompanied by physical disability and subsequent reduced mobility. Although maintaining social support may be seen as a positive factor, the presence of social support has been found to both increase and decrease the risk of pain in older people, in different studies (Gibson 2003).

2.4.8 Interaction of ageing with period and cohort effects

It is very difficult to separate out differences in pain prevalence due to ageing, those due to period effects (i.e. the events which occur in a given period of time, such as wars) and those due to cohort effects, which tend to increase homogeneity between members of a birth cohort (e.g. the social environment in which a group of people grow up). A large, longitudinal study which surveyed adults aged 15 – 98 at 5 time points over a 32 year period attempted to address these issues (Ahacic and Kareholt 2010). New participants were recruited at each time point, making it possible to compare individuals of the same age at different times, as well as follow the same participants at different ages and time points. This study found a substantial age effect in pain reporting, amounting to odds increasing x1.5 for each decade older. Although no period or cohort effects were identified, there was an interaction of age and cohort effect such that participants born in the 1940s and later consistently reported pain more frequently than participants born before that time (Ahacic and Kareholt 2010).
2.5 Pain and sex

2.5.1 Sex and gender

Sex is generally defined by male or female reproductive organs and chromosomes of the individual, whereas the gender definitions of masculine and feminine are defined by the individual and by society’s response to that individual (Holdcroft and Berkeley 1999). However, these demarcations are not clear-cut, and interact with one another.

Neither sex nor gender has a single, unambiguous definition (Geary 2010). There is evidence that gender identity is linked to biological as well as social influences, e.g. gonadal hormone dysfunction in some people with gender identity disorder (Geary 2010). Gender may also be considered a continuous variable, ranging from exclusively masculine to exclusively feminine, making dichotomous classification difficult (Greenspan et al. 2007). However, most researchers feel that “sex” refers to biological phenomena and “gender” to social issues (Greenspan et al. 2007), so the term “sex” will be used here.

2.5.2 Pain prevalence and sex

Most studies of pain prevalence in general populations show an excess prevalence in females compared to males (Fillingim et al. 2009). This includes studies of older adults (Leveille et al. 2005). Table 2.2 shows data from some general population based studies of chronic pain prevalence. These studies reported either chronic pain in any area of the body, or chronic widespread pain as defined by the ACR (Wolfe et al. 1990). It can be seen that all the reported prevalences for females (F) were higher than those for males (M), although in some cases the differences were small. The countries in which these studies were carried out are all in Europe or North America and observed sex differences may not be consistent elsewhere. This has been demonstrated in studies of regional pain, for example, 7 day period prevalence of shoulder pain in the UK: males 6.7%, females 8.0% (Walker-Bone et al. 2004); 7 day prevalence of shoulder pain in Iran: males 9.8%, females 19.6% (Davatchi et al. 2008).

The pain prevalence studies listed in Table 2.2 all reported chronic pain. Many studies do not distinguish between chronic and acute pain in their reporting, for
example point prevalence of shoulder pain (Picavet and Schouten 2003) or 1 week period prevalence of knee pain (Veerapen, Wigley, and Valkenburg 2007).

There is evidence that women use healthcare services to a greater extent than men. Data collected over a 12 month period by a UK general practice found that amongst patients aged between 16 and 45 years old (once pregnancy-related consultations were excluded) women were twice as likely as men to consult for acute conditions, although there was no significant difference for chronic conditions (Briscoe 1987). This may contribute to differences in the sex ratios of pain prevalence when measured in clinical as opposed to population studies. A study of Dutch patients consulting their general practitioner about neck or shoulder pain found that 63% were female, i.e. 1.7 times more females than males (Bot et al. 2005b). Another survey of patients in Sweden seeking healthcare for neck and shoulder pain found that 71.3% were women, which is 2.5 times more females than males (Skillgate et al. 2007). By comparison, a Dutch postal survey found that point prevalence of shoulder pain was 1.4 times commoner in females than males (Wijnhoven, de Vet, and Picavet 2006). A UK postal survey reported 7 day period prevalence of shoulder pain was 1.18 times more common in women than men (Walker-Bone et al. 2004).

However, some population studies show sex ratios of pain prevalence comparable to those in studies of health care consultation. A population study in Norway of 2 week period prevalence of neck or shoulder pain found that women were 1.62 times more likely to report pain than men (Hasvold, Johnsen, and Forde 1996). Another Norwegian postal survey found that 30 day period prevalence of shoulder pain was 1.6 times greater in females than males. A study conducted in urban Iran found the 7 day prevalence of shoulder pain to be 1.63 times higher in women than men (Davatchi et al. 2008).

There is some evidence that female sufferers of chronic pain conditions report more severe pain, more frequent pain and longer lasting pain than male sufferers with the same condition (Greenspan et al. 2007; Hurley and Adams 2008). Some medical conditions which are usually painful exhibit a male excess, e.g. gout and migraine without aura, although a greater number of painful conditions have a female excess, such as rheumatoid arthritis, irritable bowel syndrome, headache (all types) and multiple sclerosis (Holdcroft and Berkeley 1999).

Regarding acute versus chronic pain, surgical procedures often lead to acute postoperative pain. A review found that most studies of surgery patients found no
difference between males and females, or a female excess in pain presence or intensity (Fillingim et al. 2009). One study evaluated point prevalence of any pain, 1 year period prevalence of any pain, prevalence of chronic pain in any body area and prevalence of persistent chronic pain in any body area, and found that females reported more pain than males in all categories (Wijnhoven, De Vet, and Picavet 2006).

The majority of people with a diagnosis of fibromyalgia are women. A study which recruited consecutively diagnosed patients via rheumatologists found that only 8.2% were male (Wolfe et al. 2010). Because of this large female excess prevalence, many studies using fibromyalgia patients only use women (Dobkin et al. 2010; Hurtig et al. 2001). A Turkish survey which used house-to-house visits found that women were 2.45 times more likely than men to have fibromyalgia (Turhanoglu et al. 2008). A Cuban study (Reyes-Llerena et al. 2009) used a mobile clinic for examinations and found that women were 3.75 times more likely than men to have fibromyalgia, although the overall prevalence of the condition was low (0.2%) compared to that found in other studies, e.g. 2.4% in Spain (Mas et al. 2008) 10.2% in the UK (Croft, Schollum, and Silman 1994) and 8.8% in Turkey (Turhanoglu et al. 2008). However, a Brazilian study (where 77% of the participants were female) which also used a mobile clinic found that all of the fibromyalgia cases identified were women (Assumpcao et al. 2009). To date, no studies have been published using the new, modified criteria which allow fibromyalgia classification in survey studies (Wolfe et al. 2011).
<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>STUDY DESIGN</th>
<th>AGE RANGE</th>
<th>NUMBER OF SUBJECTS</th>
<th>LOCATION</th>
<th>PAIN CLASSIFICATION AND HOW ASSESSED</th>
<th>TOTAL PREVALENCE</th>
<th>PATTERN BY SEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svebak, Hagen and Zwart (2006)</td>
<td>Population of one county invited to participate, 1 year retrospective. Postal questionnaire.</td>
<td>Over 20.</td>
<td>64690.</td>
<td>Norway.</td>
<td>All body areas &gt; 3 months. Self report of pain or stiffness in muscles or joints.</td>
<td>Prevalence of chronic pain: 44.6%</td>
<td>M – 40.4% F – 48.8%</td>
</tr>
<tr>
<td>Eggermont et al (2006)</td>
<td>Random sample from town lists. Interview and examination.</td>
<td>Over 70.</td>
<td>600.</td>
<td>USA.</td>
<td>Interview questions, all body areas &gt; 3 months.</td>
<td>Chronic pain one or more site(s): 63%</td>
<td>M – 58.1% F – 65.7%</td>
</tr>
<tr>
<td>(Kurita et al. 2012)</td>
<td>Pre-existing national cohort plus data from national registers. Postal or online questionnaire.</td>
<td>Over 16 Age groups 1)16-24 2)25-44 3)45-64 4)65-79 5)80+</td>
<td>14925.</td>
<td>Denmark.</td>
<td>Self report using manikin, pain &gt; 6 months. All body areas.</td>
<td>Point prevalence of chronic pain: 26.8%</td>
<td>M – 22.3% F – 31.3%</td>
</tr>
</tbody>
</table>

Key: M = males, F = females, CWP = chronic widespread pain.
2.5.3 Sex differences in biological risk factors

Physiological factors

The physiological differences between men and women give rise to some sex-specific painful conditions. Dysmenorrhoea and pain related to childbirth can obviously only occur in women. However, this only accounts for a small proportion of the total pain experienced and does not explain, for example, the higher prevalence of back pain (Walker, Muller, and Grant 2004) or shoulder pain (Leijon, Wahlstrom, and Mulder 2009) in females compared to males, at all ages.

There appears to be a link between blood pressure and pain experience, which differs between men and women, but it is not clear what the causal mechanism might be or even the direction of the effect. Blood pressure was found to be inversely related to experimental pain sensitivity in pain-free men but not pain-free women (Bragdon et al. 2002). BMI, systolic blood pressure and depressive symptoms were associated with clinical pain in women but not in men (Leveille et al. 2005).

Neurotransmitters

The transportation and action of neurotransmitters which are important in pain processing has sometimes been found to be different between the sexes. Dopamine has been found to play a part in pain modulation (Wood 2008), and there is animal evidence that estradiol stimulates production of dopamine (Lookingland and Moore 1984). However, these findings have not been directly linked to sex differences in pain perception in humans (Fillingim et al. 2009). N-methyl-D-aspartate (NMDA) receptors are attached to second order neurons in the spinal cord dorsal horn, and they are activated by glutamate. There is animal evidence that oestrogen enhances the excitability of NMDA receptors (McRoberts et al. 2007), which could contribute to the higher temporal summation seen in females (Fillingim et al. 2009).

Sex hormones

Levels of sex steroid hormones are different in men and women. Evidence for the importance of hormones in the perception of pain can be found by looking at
changes in prevalence of painful conditions before and after puberty. The prevalence of migraine is similar in girls and boys pre-puberty, but three times greater in adult women than men (Manson 2010). The prevalence of low back pain was found to be higher in adolescents (aged 15) of both sexes than in 12-year olds (Jones et al. 2003), which may reflect changes in the hormonal milieu of both sexes during puberty. An animal study found that separately administered oestradiol, oestradiol with progesterone, or testosterone all gave rise to decreased heat pain tolerance in gonadectomised female rats, but there were no differences for gonadectomised male rats administered the same hormones (Stoffel, Ulibarri, and Craft 2003).

A study conducted in a specialist menopause clinic found that headache and migraine were common in this group of women, with a 3 month period prevalence of 57% for headache and 29% for migraine (MacGregor and Barnes 1999). A group of women with migraine had a hormone assay carried out to ascertain which stage of the menstrual cycle attacks occurred in; migraines were found to be more frequent, severe and disabling during the menstrual than the luteal or follicular phases, which the authors of the study believed might be due to the presence of high levels of progesterone or its metabolites (Martin et al. 2005). Women suffering from painful conditions such as fibromyalgia or irritable bowel syndrome report increased pain in the phases of the menstrual cycle where oestrogen levels are low or rapidly falling (Vincent and Tracey 2010). A review found that most studies of clinical pain and hormonal status e.g. pregnancy or puberty, found a connection between that status and pain prevalence (McBeth and Jones 2007). Painful inflammatory conditions such as rheumatoid arthritis are commoner in women than men (Andrianakos et al. 2006).

Some experimental pain studies have found that menstrual cycle stage in women influences experimental pain perception, but others have not (Hurley and Adams 2008; Soderberg et al. 2006). A study of thermal pain in healthy women found that heat pain threshold, heat pain tolerance and cold pain ratings were unaffected by the stage of the menstrual cycle, but descending noxious inhibitory controls effect was greater in the ovulatory phase (when oestradiol levels are high and progesterone levels low) than the other menstrual phases (Tousignant-Laflamme and Marchand 2009).

Results from brain imaging show some of the effects which hormones can have on brain activity. One imaging study examined 18 women twice, once during the
follicular phase low levels of progesterone and rising levels of oestrogen) and once during the luteal phase (high then falling levels of progesterone and oestrogen) of the menstrual cycle (Choi et al. 2006). The authors found that in the follicular phase, the prefrontal cortex was activated during the anticipation of a painful stimulus and following its administration, and the putamen, cerebelum and pre-central gyrus were activated during administration of the painful stimulus. In the luteal phase, the parahippocampal gyrus and amygdala were active during anticipation, the thalamus during administration of the stimulus and the parahippocampal gyrus following administration of the stimulus (Choi et al. 2006).

The amygdala and thalamus are most associated with the emotions and the affective component of pain (Vincent and Tracey 2010). Another imaging study on 9 pain-free women found that their heat pain thresholds did not vary significantly between times when their oestrogen levels were high and when they were low, but that activation in the left cerebellum, anterior cingulate and precuneus (associated with anticipation of pain) only occurred at the low oestrogen state (de Leeuw et al. 2006).

**Stress response system**

The hypothalamic-pituitary-adrenal (HPA) system responds to physiological and psychological stressors by increasing the release of cortisol, which leads to adaptive effects including analgesia. Under unstressed conditions, cortisol levels follow a regular circadian pattern. Chronic pain conditions can result in reduced release of cortisol and a reduced response to increasing cortisol levels (McBeth et al. 2007). A study which used male and female chronic pain patients (as well as male and female healthy controls) measured salivary cortisol at 4 time points each day, on awakening, at 12:00, 18:00 and 21:00. It found that levels of cortisol were lower in male patients than female at the 18:00 time point, indicating a reduced stress-response in males (Turner-Cobb et al. 2010). A study which found that HPA dysfunction was linked to subsequent onset of CWP found that menopause status did not alter this relationship, implying a small role for sex hormones (McBeth et al. 2007).
**Genetic factors**

It might be expected that some if not all of the sex-related differences discussed will have a genetic component. In pain studies in laboratory animals, the direction and magnitude of the differences between males and females is highly strain-dependent, showing that genetic influences are very important (although the genes responsible have generally not been identified) (Mogil and Bailey 2010). Laboratory work has shown that estradiol can increase substance P mRNA levels in rat pancreas tissue, indicating a hormonal regulation of gene expression (Villablanca and Hanley 1997). A review of human studies found no definite evidence of genes linked to susceptibility to pain (Limer et al. 2008) so at present there is no evidence of a direct sex-linked genetic component in pain perception in humans.

**Response to analgesics**

Studies of different responses to analgesic drugs between males and females have mainly focussed on opioids. There are 3 different types of endogenous opioid receptors: μ, κ and δ. Animal studies have generally found a more robust response in males to μ-opioid analgesics, and in females to κ-opioid analgesics (Hurley and Adams 2008). However, a study on rhesus monkeys found that females demonstrated a lesser response to κ-opioid analgesia than males, but males and females responded similarly to μ-opioid analgesia (Mogil and Bailey 2010). A PET imaging study on women showed that μ-opioid receptors in several parts of the brain had a higher binding potential when oestradiol levels were high and progesterone low (Vincent and Tracey 2010). However, a review found no or minimal sex differences in response to μ-opioid analgesia in experimental pain (Fillingim et al. 2009).

An animal study found that the anti-nociceptive properties of morphine were more potent in intact male rats and gonadectomised male rats administered testosterone, than in gonadectomised male rats given no hormones; and the effects of morphine were more potent in gonadectomised female rats given no hormones than in gonadectomised female rats administered testosterone, oestradiol or oestradiol plus progesterone (Stoffel, Ulibarri, and Craft 2003). A randomised controlled trial of postoperative pain found that κ-opioid analgesia was more effective for pain relief in women than men (Gear et al. 1999). A mutation of a gene originally identified in mice (MC1R gene in humans) has been found to be associated with enhanced...
response to κ-opioid analgesia in women but not in men (Greenspan et al. 2007). The original work in rodents identified that the effects of κ-opioid analgesia could be blocked in males but not females by NMDA receptor antagonists, indicating a different role for these receptors in pain processing in males and females (Mogil and Bailey 2010). Studies of self-administered opioid analgesia post-surgery have found that women administer less of the drug than men, which is at odds with the fact that women generally report more post-operative pain than men and may be related to other factors, such as greater effectiveness of the drug or larger side-effects in women (Mogil and Bailey 2010).

2.5.4 Sex differences in psychological factors

Women have a higher reported prevalence of anxiety and a higher reported prevalence of depression than men (Breslau, Chilcoat, and Schultz 1998). Both of these are associated with higher pain prevalence (Arola et al. 2010). However, anxiety has been found to be more strongly associated with both experimental and clinical pain in men than in women (Jones and Zachariae 2002), whereas depression is more often co-morbid with pain in women than men (Munce and Stewart 2007). A review of factors influencing experimental pain reported that neither depression nor anxiety had a clear role in mediating sex differences in pain perception (Racine et al. 2012b).

There are reported sex differences in how stressful life events influence pain perception (Spertus et al. 1999). A review found that there were significant associations between both physical and sexual abuse and occurrence of fibromyalgia. Although too few of the studies looked at sex differences for a sub-group analysis to be carried out, both sexual abuse and a diagnosis of fibromyalgia were commoner in women than men (Hauser et al. 2011).

The association between beliefs about pain and the perception of pain has already been discussed (see section 2.3.2). Catastrophising is a maladaptive illness coping strategy which focuses on feelings of helplessness, rumination, and magnification of the problem. A study of adolescents with chronic pain found that females used catastrophising as a coping strategy to a greater extent than males, and greater catastrophising was associated with more intense pain (Keogh and Eccleston 2006). Several studies have shown that catastrophising is associated with sex differences in the perception of experimental pain and the reporting of clinical pain
(Edwards et al. 2004; Osman et al. 2000). An experimental study of DNIC and catastrophising in 35 healthy volunteers found that catastrophising directly relating to the experimental stimulus was somewhat greater in women than men, although this did not reach statistical significance (p=0.09). The same study also found that the relationship between catastrophising and pain ratings was mediated by DNIC in women but not in men (Goodin et al. 2009). Another study found no differences between men and women in the relationship between DNIC and catastrophising (Granot et al. 2008). Sex-related differences in experimental pain ratings using a cold pressor stimulus disappeared when catastrophising was controlled for (Sullivan, Tripp, and Santor 2000). Similarly, sex-related differences in both pain and pain-related disability in patients with knee osteoarthritis were no longer significant when catastrophising was controlled for (Keefe et al. 2000). A review of factors influencing experimental pain reported that both catastrophising and use of coping strategies appeared to be associated with the relationship between sex and pain perception (Racine et al. 2012b).

A review found that women used coping strategies such as positive statements and social support, more than men (Fillingim et al. 2009). Women with chronic pain have been found to seek more social support than men (Greenspan et al. 2007). A telephone study of people with troublesome pain in the previous two weeks found that women sought social support, used behavioural distractions and problem-solving more frequently and were more likely to use simple palliative interventions such as relaxation, massage, and therapeutic heat or cold than men (Unruh, Ritchie, and Merskey 1999).

Self-efficacy refers to a person’s confidence in their own ability to perform a particular behaviour and to overcome barriers to that behaviour (Richard, Dionne, and Nouwen 2011). Self-efficacy for tolerating pain was found to be higher in men than in women (Miller and Newton 2006). This may be linked to gender role expectations, where male gender role expectations generally include an ability to tolerate pain, whereas female gender role expectations are more tolerant of pain reporting (Defrin, Shramm, and Eli 2009; Fillingim et al. 2009). In experimental pain studies, the sex of the experimenter and even his/her perceived attractiveness may influence the results (Fillingim et al. 2009). A study which characterised participants according to their identification with gender norms by asking how important it was to them to be similar to an ideal man or woman, found that high-identifying men tolerated more painful electrical stimulation than high-identifying women, but that there was no difference between low-identifying men and women (Pool et al. 2007).
Groups of men and women had pressure pain threshold tested by either a man or a woman, who were dressed to emphasise their gender roles. The male dressed in jeans and a tee shirt, the female in a sweater, skirt and high heels. The men tested by the male experimenter had higher pain thresholds than those tested by the female experimenter, but there was no difference between the groups of female participants (Gijsbers and Nicholson 2005).

Women use more analgesic drugs than men (Isacson and Bingefors 2002), although there is also evidence that women’s pain is undertreated compared to men’s (Mogil and Bailey 2010). Women are more likely than men to visit a medical practitioner, and more likely to report pain as a symptom (Hurley and Adams 2008). Women may be exposed to certain risk factors for chronic pain to a greater degree than men, e.g. repetitive work, working in the home and child care (Strazdins and Bammer 2004). Women are more likely to be disabled than men suffering from the same painful disease or condition (Greenspan et al. 2007).

Age and sex may interact as risk factors for pain. A study of pain prevalence in all parts of the body found that age was a greater risk factor for women than men, but only for knee and foot pain (Wijnhoven, de Vet, and Picavet 2006).

### 2.6 Neuroanatomy

In order to understand the measurement of responses to sensory stimuli given in subsequent sections of this report, some knowledge of neuroanatomy is useful. The human nervous system comprises the peripheral, central and autonomic nervous systems. This section will discuss the role of the peripheral nervous system (PNS) and central nervous system (CNS) in the perception of pain.

#### 2.6.1 Sensory pathways

The International Association for the Study of Pain (IASP) defines nociception as “the neural processes of encoding and processing noxious stimuli” (Loeser and Treede 2008). Nociception does not necessarily lead to the perception of pain, and likewise pain can occur without nociception.

Nociception and other sensory inputs are detected by receptors. In the skin, thermal and nociceptive receptors are unencapsulated nerve endings and
Meissner’s corpuscles respond to fine touch. Pacinian corpuscles respond to vibratory stimulation. The signals are carried to the spinal cord by first-order neurons, which have their cell bodies in the dorsal horn of the spinal cord grey matter, and synapse with second-order neurons there. In the case of pathways carrying signals from nociceptive, thermal and pressure receptors, the second-order neuron decussates (crosses to the contralateral side of the spinal cord) and ascends within the spinothalamic tract (see Figure 2.6). For pathways carrying light touch signals, the second-order neuron ascends in the dorsal column (see Figure 4) and only decussates at the level of the brain stem. Second-order neurons terminate in the thalamus, where they synapse with third-order neurons, which project to the somatosensory cortex (see Figure 2.7) (Crossman and Neary 2005).

Figure 2.6 – The spinal cord showing tracts

(www.todayschiropractic.com 2010)
2.6.2 The peripheral nervous system

Peripheral sensory nerve fibres carry information from tissues such as the skin, muscles and viscera to the CNS. There are many sub-types of nerve fibres which vary in diameter and myelination (myelin is an insulating layer which increases conduction speed). Large diameter fibres conduct faster than small ones and myelinated fibres conduct faster than unmyelinated. Sensory stimuli are transmitted by C-, Aδ- and Aβ-fibres. Small diameter, unmyelinated C-fibres have conduction speeds under 2.5 m/s, whilst slightly larger diameter, myelinated Aδ-fibres have conduction speeds of 4 to 30 m/s and large, myelinated Aβ-fibres have conduction speeds of 30 to 75 m/s (Westlund 2005).

Sensation in the skin has been more closely studied than other areas (e.g. the viscera). C-fibres in the skin respond vigorously to cutaneous warm sensations, Aδ-fibres to cool sensations (Raja et al. 1999). Large diameter, myelinated Aβ fibres respond to deep pressure and vibration (Popescu 2005). Nociceptors in the skin are the unencapsulated axonal endings of Aδ- and C-fibres (Kiernan and Barr
2005). Many of them respond to several types of stimuli, e.g. mechanical and thermal (mechanothermal nociceptors) or thermal and chemical (polymodal nociceptors), but some are more specialised, e.g. mechanoreceptors or cold receptors (Westlund 2005). Pain within muscles also results from activation of $A\delta$- and C-fibres (Graven-Nielsen and Arendt-Nielsen 2002). Sensory fibres terminate in the dorsal horn of the spinal cord.

2.6.3 The spinal cord

The central nervous system (CNS) comprises the brain and spinal cord.

In the spinal cord, cell bodies are contained within the H-shaped grey matter, with its distinctive anterior and dorsal horns (see Figure 2.6) which are organised into distinct zones (laminae). Sensory cells in the spinal cord are mainly located in the dorsal horns and receive input from peripheral sensory nerves. Glutamate is the primary neurotransmitter in this part of the CNS, but its action is modified by neuropeptides such as calcitonin gene-related peptide (CGRP), substance P and neurokinin A. These peptides require a prolonged period of nociceptive stimulation before they are released (Westlund 2005). N-methyl-D-aspartate (NMDA) receptors in the dorsal horn of the spinal cord are stimulated by glutamate and mediate excitation of noxious stimuli (Wilcox G.L. et al. 2005). The receptor mechanisms for NMDA and neurokinin A are implicated in the phenomenon of temporal summation of pain (also called wind-up) and play a role in central sensitisation (Staud 2006).

Signals are not transmitted passively but are processed within the dorsal horn in a manner dependent upon various local and descending influences. Table 2.3 summarises the processing modes. In mode 1, low intensity stimuli are interpreted as innocuous, and high intensity as noxious. Mode 2 represents descending inhibitory mechanisms operating on the spinal cord, so a high intensity stimulus is not perceived as painful.

In mode 3 dorsal horn excitability is increased, possibly by injury or inflammation, leading to amplification of the afferent input. In mode 4 there is irreversible structural reorganisation in response to an injury to the peripheral or central nervous system. It is possible that the changes in mode 3 could become permanent, i.e. mode 4 (Doubell, Mannion, and Woolf 1999). The change from mode 1 to mode 3 may form the first step in the development of central sensitisation because
peripheral injury can trigger longer-term excitability of spinal cord neurons (Woolf 2011).

Spinal cord nerve fibres (axons) are organised into ascending and descending tracts within the white matter (see Figure 2.6). The most important tracts with regard to pain processing are the spinothalamic tracts, the spinoreticular and the spinohypothalamic tract (Craig and Dostrovsky 1999).

The spinothalamic tract is the major tract transmitting cutaneous nociceptive signals to higher centres (Westlund 2005). Some authors believe that only this tract is involved in central pain mechanisms (Boivie 2003). Axons in the spinothalamic tracts (lateral and anterior, see Figure 2.6) cross over and ascend on the contralateral side to their origin. The laminae from which the spinothalamic neurons originate contain mainly polymodal nociceptive cells with mainly C-fibre input and wide dynamic range (WDR) nociceptive cells receiving input from Aβ, Aδ and C-fibres. They terminate in distinct regions within the thalamus (Craig and Dostrovsky 1999).

The spinoreticular tract is formed from collaterals from spinothalamic neurons, which project to some areas of the brain involved in nociceptive processing, such as the subnucleus reticularis dorsalis (which is involved in descending pain modulation) (Westlund 2005). Some of the nociceptive neurons in the spinohypothalamic tract terminate in the hypothalamus, the periaqueductal gray matter (PAG) and amygdala, and are believed to be involved in the affective component of pain (Westlund 2005).
### Table 2.3 – Sensory processing in the dorsal horn

<table>
<thead>
<tr>
<th>MODE</th>
<th>STIMULUS INTENSITY</th>
<th>PRIMARY AFFERENT</th>
<th>SENSATION</th>
<th>CLINICAL SYNDROME</th>
<th>PHYSIOLOGICAL CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Aα/C</td>
<td>Nociceptive pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Suppressed. Reduced pain sensibility.</td>
<td>High</td>
<td>Aα/C</td>
<td>Innocuous</td>
<td>Hyposensitivity.</td>
<td>Reduced excitation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased inhibition.</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Aα/C</td>
<td>Hyperalgesia</td>
<td>Central neuropathic pain.</td>
<td></td>
</tr>
</tbody>
</table>

(Doubell, Mannion, and Woolf 1999).

#### 2.6.4 The brain

Although no neurological function can be entirely attributed to one part of the CNS, brain areas having major contributions to functions were initially established by the study of specific lesions then later refined by functional imaging techniques.

The techniques of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) are commonly used in brain imaging. fMRI uses the different magnetic properties of oxygenated and deoxygenated blood to determine which areas of the brain are most active, i.e. using most oxygen, whereas PET tracks emissions from a radionuclide analogue of glucose, which is selectively taken up by active tissues. An advantage of fMRI is that an image can be produced in about 2 seconds, so it can capture images of rapidly changing states. This means that several images can be taken in close succession, but these will not be identical.
PET imaging takes about 2 minutes so it cannot be used to capture images in rapidly changing states. A disadvantage of fMRI is that the signal difference it attempts to detect is small compared to drift in scanner sensitivity, so repeat scans may not show an identical result (Gracely and Bradley 2005).

Several areas of the brain have been associated with chronic pain through neuroimaging (Tracey and Bushnell 2009), although there is no known area of the brain which responds only to pain (Davis, Racine, and Collett 2012). Atrophy of and reduced blood flow to the thalamus (see Figure 2.7) has been imaged using PET in pain patients (Tracey and Bushnell 2009); the thalamus has long been associated with neurological pain of CNS origin and was originally thought to be entirely responsible for it (Head and Holmes 1911).

Imaging and recording techniques have confirmed the interaction of several brain areas as a pain matrix. They include cortical areas such as the inferior parietal cortex, anterior cingulate, dorsolateral prefrontal cortices, somatosensory regions, and the amygdala (Westlund 2005), and sub-cortical areas such as several nuclei of the thalamus, peri-aqueductal gray matter (PAG), parabrachial nucleus and hypothalamus (Jones, McBeth, and Power 2010).

The pain matrix can be divided into two for convenience. The lateral pain system comprises the lateral thalamic nuclei, somatosensory regions and inferior parietal cortex, and is fast acting and serves to determine pain location, intensity and duration. The medial pain system comprises the midline thalamic nuclei, dorsolateral prefrontal cortices, anterior cingulate, amygdala and hypothalamus, and is slow acting and is concerned with the affective components of pain (Jones, McBeth, and Power 2010). Figure 2.7 shows some of these areas.

Modulation of afferent stimuli has already been mentioned in the discussion of the spinal cord. The descending modulatory system involves a number of higher centres and originates in the PAG (Popescu 2005). It also includes the anterior cingulate, hypothalamus, midline thalamic nuclei and amygdala. This modulation can be inhibitory or facilitatory (Jones, McBeth, and Power 2010).

### 2.7 Pain sensitivity mechanisms

The view of chronic pain as a disease in its own right is supported by the International Association for the Study of Pain (IASP) (Loeser and Treede 2008).
However, once chronic pain is considered as separate from other disease processes, new explanations as to its initiation and maintenance must be sought. It is accepted that central sensitisation may play a role in chronic musculoskeletal pain (Graven-Nielsen and Arendt-Nielsen 2002). Central sensitisation occurs when afferent activity from a peripheral injury leads to an increase in the excitability of wide dynamic range neurons in the dorsal horn of the spinal cord, which may be made permanent or long-term by plastic changes within the spinal cord (Woolf 2011).

*Experimentally induced central sensitisation*

Central sensitisation has been induced experimentally in healthy volunteers, and in animals, to provide evidence of possible mechanisms and effects. In one study, an area of skin was sensitised by injecting capsaicin (Torebjork, Lundberg, and LaMotte 1992). A level of intraneural electrical stimulation of an Aβ afferent fibre (which innervated the affected area of skin) which was not painful prior to the capsaicin injection was painful after. Aβ afferent fibres do not normally transmit noxious sensation (Staud 2006), this phenomenon is allodynia (see section 2.8.2). This stimulation remained painful even after lidocaine anaesthesia was applied to the affected area of skin. The authors concluded that the effect must be due to changes in central processing, as the lidocaine would have eliminated any purely localised sensitivity (Torebjork, Lundberg, and LaMotte 1992). Another study found that when pinprick stimuli were applied to skin which had previously been injected with capsaicin, the subjective rating of the pain level was higher than for the same stimulus prior to capsaicin injection (Magerl, Wilk, and Treede 1998). An animal study showed that wind-up is reduced by the administration of ketamine (an NMDA antagonist) to the spinal cord dorsal horn neurones of rats (Davies and Lodge 1987). Although peripheral nervous system NMDA receptors have also been identified as being important in nociception (McRoberts et al. 2001), administration of ketamine directly to the spinal cord would make it less likely that peripheral mechanisms were involved. Both these studies were in rats, evidence for NMDA receptor involvement in humans with fibromyalgia is given in section 2.8.5. Muscle soreness was induced using exercise in the first interosseous muscle of the right hand of healthy volunteers, and deep tissue pain was induced in the same muscle using pulses of ultrasound (Bajaj et al. 2000). The wind-up ratio of pain ratings of a single pulse and a train of 5 pulses was calculated for the right (test) and left (control) hands of healthy students, and was found to be significantly higher in the
test than the control hand, both immediately after the exercise protocol and 24 hours later. The same study also tested pressure pain threshold (PPT) over the same muscle, and found that the PPT in the test hand was reduced immediately after the exercise protocol, 24 hours later and 48 hours later compared to immediately before the exercise protocol (Bajaj et al. 2000).

Diffuse noxious inhibitory controls (DNIC) has been described as a mechanism of endogenous analgesia (Pavlakovic and Petzke 2010). Noxious stimulation to one part of the body inhibits dorsal horn nociceptive neurons innervating remote body parts. Although DNIC has been measured in people with chronic pain, it has not been measured in people with experimentally induced central sensitisation. This is likely to be due to methodological difficulties, because DNIC uses a painful conditioning stimulus to induce descending inhibition of pain (see section 2.8.2), and central sensitisation is itself experimentally induced using a painful conditioning stimulus. A review reported that people with central sensitisation experience a) increased pain in response to stimuli which are generally accepted as painful, b) pain in response to stimuli which are not generally accepted as painful (alodynia), c) reduced descending analgesia (DNIC) (Lee, Nassikas, and Clauw 2011).

Distinguishing central and peripheral sensitisation

Peripheral sensitisation is a localised phenomenon where the responsiveness of nociceptors is increased locally, particularly heat stimuli, in response to an injury or inflammation (Latremoliere and Woolf 2009). By this definition, it can only exist close to the site of the injury or inflammation, so QST results obtained at non-painful or unaffected sites are unlikely to be influenced by peripheral sensitisation. An animal study on rats found that UV-B irradiation of the base of the hind paw led to mechanical hyperalgesia in the irradiated area only, which was not relieved by administration of an NMDA receptor antagonist (Bishop et al. 2010).

Some of the QST results reported in section 2.8.5 appear to be due to peripheral sensitisation. For example, a group of patients with knee OA had heat hyperalgesia at the affected knee compared to a control site before and immediately after knee replacement surgery (Martinez et al. 2007).
Central sensitisation and musculoskeletal pain

There is some direct evidence of the role of central sensitisation in fibromyalgia (FMS) in that drugs which block the activation of NMDA receptors can reduce pain. Female FMS patients were randomised in a cross-over design to receive ketamine infusion or placebo (saline) (Graven-Nielsen et al. 2000). Pain at rest was measured using a visual analogue scale. Seventeen of the 29 participants had a reduction in pain at rest of 50% or more, which was also statistically significantly greater than their response to placebo. The remainder either did not respond to the treatment, or they responded to placebo. The inhibition of NDMA receptors by ketamine greatly reduced pain in over half of this group of FMS patients, indicating that central sensitisation is an important mechanism in FMS (Graven-Nielsen et al. 2000). Pregabalin is a α₂δ ligand which inhibits the release of neurotransmitters including glutamate (which stimulates NMDA receptors). A Cochrane systematic review on the use of pregabalin in fibromyalgia patients reported a relative benefit for a 50% decrease in pain of between 1.5 (95% C.I. 1.2, 1.9) and 1.7 (95% C.I. 1.4, 2.1) (Moore et al. 2009).

There is no similar evidence for central sensitisation in other musculoskeletal pain conditions, although some of the QST results reported in section 2.8.5 are consistent with central sensitisation. For example, hip OA patients awaiting hip replacement exhibited lower pressure pain thresholds than healthy controls when tested at the forearm (Wylde et al. 2012), and OA knee patients had lower PPT than controls at a site remote from the knee (forearm) (Gwilym et al. 2009).

2.8 Quantitative Sensory Testing (QST)

Quantitative sensory testing is a collection of psychophysical techniques used to obtain responses to various experimental stimuli, in order to characterise the responses of both healthy individuals and people with known or suspected illnesses or injuries. The responses sought may be verbal, e.g. “sharp” or “blunt”, an action such as pressing a button in accordance with the instructions given, or a physiological response such as the nociceptive flexion reflex (NFR). Stimuli which have been used in published studies include heat, cold, light touch, deep pressure, pinprick, vibration, electrical, chemical and ischaemia (Campbell et al. 2008; Campbell et al. 2011; Fischer 1987; Nebuchennykh et al. 2008; Pud, Sprecher, and Yarnitsky 2005; Ryall et al. 2007; Whitton, Johnson, and Lovell 2005).
2.8.1 What QST techniques are used currently?

Modern QST techniques measure detection thresholds, pain thresholds, pain tolerance and pain ratings. Detection thresholds are the lowest level of a stimulus perceived by the participant, and pain thresholds are the lowest level of stimulus perceived to be painful (Walk et al. 2009). To obtain a pain tolerance measure, participants are asked to endure an increasing stimulus for as long as possible, and the final stimulus intensity is noted (Defrin, Shramm, and Eli 2009; Edwards et al. 2003; Ryall et al. 2007). To obtain pain ratings, participants are asked to rate a stimulus within a range, e.g. 0 – 10 (Kelly, Cook, and Backonja 2005) or 0 – 100, using “anchors”, e.g. 0 = “no pain” and 100 = “worst pain imaginable” (Rolke et al. 2006b). Diffuse noxious inhibitory controls (DNIC) is tested by comparing pain ratings of a test stimulus before, and during or after, application of a conditioning stimulus at a remote body location (Pud, Granovsky, and Yarnitsky 2009). More detail on DNIC is given later in this section. Table 2.4 summarises commonly used sensory stimuli, how they are applied and what tests they are used for. DNIC is not listed because it uses a combination of stimuli.
Table 2.4 – Commonly used quantitative sensory testing techniques

<table>
<thead>
<tr>
<th>How applied?</th>
<th>Heat</th>
<th>Cold</th>
<th>Pressure</th>
<th>Pinprick</th>
<th>Vibration</th>
<th>Electrical</th>
<th>Pain rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peltier thermode</td>
<td>Peltier thermode</td>
<td>Von Frey filament</td>
<td>Von Frey filament</td>
<td>Vibrameter</td>
<td>Adhesive electrodes</td>
<td>Any stimulus</td>
<td></td>
</tr>
<tr>
<td>Hot water bath</td>
<td>Cold water bath</td>
<td>Algometer</td>
<td>Weighted pin</td>
<td>Tuning fork</td>
<td>Sub-epithelial needles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual digital pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tests carried out</td>
<td>Warm detection threshold</td>
<td>Cool detection threshold</td>
<td>Mechanical detection threshold</td>
<td>Mechanical pain threshold</td>
<td>Vibration detection threshold</td>
<td>Electrical detection threshold</td>
<td>Allodynia</td>
</tr>
<tr>
<td>Heat pain threshold</td>
<td>Cold pain threshold</td>
<td>Pressure pain threshold</td>
<td>Wind-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat pain tolerance</td>
<td>Cold pain tolerance</td>
<td>Tender point count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wind-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyposensitivity</td>
<td></td>
</tr>
</tbody>
</table>
Thermal detection thresholds

Thermal detection thresholds include warm and cool detection thresholds, and also thermal sensory limen, which is the smallest distinction between two thermal stimuli which can be distinguished (Rolke *et al.* 2006a). A related measure is the presence of paradoxical heat sensations, where an innocuous cool sensation is perceived as an innocuous warm sensation (Rolke *et al.* 2006a). Hot and cold stimuli may be applied via a test block using the Peltier principle, as mentioned above (Granot *et al.* 2008). Modern devices are computer controlled and log the data back to a computer (Medoc 2012; Somedic 2012). Thermal thresholds may be determined using a method of levels or a method of limits. For example, to ascertain cool detection threshold using a method of levels a cool stimulus is presented and the subject states “yes” if a cool sensation is felt, or using a method of limits, a changing stimulus of decreasing temperature is presented until the subject indicates a cool sensation is felt (Dyck *et al.* 1993). The rate of change of a stimulus using the method of limits may vary, e.g. 1°C per second (Rolke *et al.* 2006b) or 1.5°C per second (Kelly, Cook, and Backonja 2005). Thermal stimuli of different physical sizes may be used, e.g. a thermode 50x25 mm (Pud, Sprecher, and Yarnitsky 2005), 30x30 mm (Granot, Sprecher, and Yarnitsky 2003) or 16x36 mm (Kleinbohl *et al.* 1999).

The method of limits includes a small change in temperature which occurs during reaction time, so warm detection threshold will be higher and cool detection threshold lower than when using the method of levels (Dyck *et al.* 1993). Although the authors of one study stated that the method of levels takes longer to carry out, so the participant may become fatigued and make errors (Dyck *et al.* 1993), another study found that there was only a small difference in the time taken for the two methods (Yarnitsky and Sprecher 1994).

Warm and cool detection thresholds and thermal sensory limen test the integrity of sensory pathways, primarily involving peripheral nerve C-fibres, but also Aδ fibres for cold detection (Raja *et al.* 1999). It has been hypothesised that fibromyalgia patients may have a generalised hypervigilance, leading to lower sensory thresholds than healthy controls (Geisser *et al.* 2003). If this is the case, it could apply to detection as well as pain thresholds. Myelinated nerve fibres such as Aδ undergo greater deterioration due to ageing than unmyelinated fibres such as C-fibres (Gibson and Farrell 2004). The presence of paradoxical heat sensations indicates deterioration in the Aδ-fibres so that the C-fibre response predominates,
and is considered normal when up to one in three cold sensations is detected as warm, at the foot only of participants aged over 40 (Rolke et al. 2006a).

Thermal pain thresholds

Thermal pain thresholds include heat and cold pain thresholds, also heat and cold pain tolerance limits. They are generally tested using the same type of equipment as for thermal detection thresholds. Radiant heat and CO$_2$ laser heat have also been used to test heat pain threshold (Gibson and Farrell 2004). The length of time immersion of a body part in a cold pressor (a vessel circulating cold water at a controlled temperature) can be tolerated has been used as a measure of cold pain tolerance (Desmeules et al. 2003). As for thermal detection thresholds, the methods of levels or the method of limits may be used; however, at least one author has reported that thresholds may be altered by repeated exposure to stimuli in the nociceptive range (Dyck et al. 1993), which would make the method of levels less suitable than the method of limits for testing pain thresholds.

Thermal pain tolerance limits are rarely measured, because there are temperature limits built into the software of the stimulus delivery devices for safety reasons, e.g. 0°C and 50°C for the Medoc TSA, and 5°C and 50°C for the Somedic MSA (Rolke et al. 2006a). It would be potentially unsafe and unethical to alter these allowed temperatures, but as the upper 95% confidence interval for heat pain threshold has been measured at 50°C and the lower 95% confidence interval for cold pain threshold at 0°C (in healthy males) (Rolke et al. 2006a) it is likely that this would lead to ceiling effects in measurement.

Heat hyperalgesia provides evidence for peripheral sensitisation (Rolke et al. 2006a). A well as testing the physiological integrity of the perception pathway (like the detection thresholds), thermal pain thresholds are associated with some of the same factors as clinical pain, for example gender role expectations (Defrin, Shramm, and Eli 2009), pain beliefs and depression (Geisser et al. 2003), which indicates that these measurements reflect at least some aspects of pain processing.
**Mechanical detection thresholds**

The most commonly applied mechanical detection thresholds are light touch and vibration. Light touch is commonly applied using von Frey filaments, which are a set of filaments each of which bends at a different, predetermined force (Baumgartner et al. 2002). A modified method of limits is generally used, with the filaments being applied in an ascending or descending sequence (Rolke et al. 2006a; Tena et al. 2012). Vibration can be applied using a vibrameter, which can vary in frequency (Bartlett et al. 1998), or a tuning fork, which generally only uses one frequency. The Rydel-Seiffer tuning fork has a calibrated scale adjacent to a triangle on each of its arms, when the tuning fork is in motion this triangle appears as 2 intersecting triangles and the measurement nearest the intersection is read (Whitton, Johnson, and Lovell 2005). Vibration detection threshold testing using vibrameter could be forced choice, i.e. the participant decides which of 2 stimuli are vibrating (Bartlett et al. 1998), or using a method of limits, i.e. the stimulus increases until vibration is felt (ascending threshold) or decreases until it is not felt (descending threshold) (Peters et al. 2003). Vibration detection threshold using a tuning fork is a descending threshold, i.e. the participant has to state when they do NOT feel the vibration (Rolke et al. 2006b). Tuning forks of different frequencies may be used (Hilz et al. 1998).

Light touch detection threshold tests the integrity of sensory pathways, primarily involving peripheral Aβ-fibres for the thinner filaments, but also possibly Aδ- and C-fibres for the thicker von Frey filaments (Tena et al. 2012). It has been used to test for hyperalgesia in post-surgical patients (Tena et al. 2012). Vibration detection threshold tests the integrity of sensory pathways involving Aβ-fibres (Lowenstein, Jesse, and Kenton 2008). Myelinated nerve fibres such as Aβ and Aδ undergo greater deterioration due to ageing than unmyelinated fibres such as C-fibres (Gibson and Farrell 2004).

**Mechanical pain thresholds**

The most commonly applied mechanical pain thresholds are cutaneous (sharp) pain and deep pressure pain. A heavy von Frey filament is sometimes used to apply a noxious cutaneous stimulus (Tena et al. 2012), but weighted pins can also be used for this task, using a modified method of limits, as for light touch (Rolke et al. 2006b). Deep pressure (applied to structures beneath the skin, e.g. muscles) is
usually applied using an algometer (Fischer 1987; Pfau et al. 2009), and the fibromyalgia tender point examination can also be carried out using an algometer (Pfau et al. 2009) or manual digital pressure (Croft, Schollum, and Silman 1994). An algometer may be used to determine pressure pain threshold or pressure pain tolerance limit, although the latter was found to be less reproducible than the former (Fischer 1987).

Cutaneous pain (pinprick) threshold primarily tests the sensory pathway involving A\(\delta\) nerve fibres, and pressure pain the pathways involving both A\(\delta\)- and C-fibres (Rolke et al. 2006a). It has been hypothesised that the presence of cutaneous hyperalgesia in the absence of thermal hyperalgesia is evidence for central sensitisation (Baumgartner et al. 2002; Rolke et al. 2006a). Tender point count has been found to be directly related to the number of body areas with pain (Croft et al. 1996), although it is also believed to be a marker of generalised distress (Croft, Schollum, and Silman 1994).

**Pain ratings**

Pain ratings can be applied to any stimulus above pain threshold level. What is required is a scale, e.g. 0 – 100, and “anchor” statements, e.g. 0 = no pain, 100 = the worst pain you can imagine (Baumgartner et al. 2002). Allodynia is assessed by requesting ratings in the same way, but for a normally innocuous stimulus such as a cotton wisp (Baumgartner et al. 2002). Dynamic mechanical allodynia is considered a pathological response, which does not occur in healthy subjects of any age (Rolke et al. 2006a). Ratings can be applied to cutaneous (pinprick) pain (Baumgartner et al. 2002), heat and cold pain (Kelly, Cook, and Backonja 2005), ischaemic pain (Kosek and Hansson 1997), and potentially to any other painful stimulus.

The authors of one study expressed the view that pain ratings at pain thresholds are important in the interpretation of QST data, as they incorporate factors as to the meaning of pain for the individual, rather than just rating a sensation (Kelly, Cook, and Backonja 2005). Pain ratings provide information about sensitivity to low and high intensities of stimulation (Graven-Nielsen and Arendt-Nielsen 2002).
**Wind-up**

Wind-up is also called temporal summation, and occurs when repeated application of the same noxious stimulus results in a higher perceived intensity, due to an increase in the response of dorsal horn WDR neurons (Lautenbacher, Kunz, and Burkhardt 2008). C-fibres appear to be the principal source of sensory input to initiate and maintain this sensitisation (Farrell and Gibson 2007). The commonest stimulus applications used to achieve wind-up are of repeated, brief, painful, thermal stimuli (Lautenbacher, Prager, and Rollman 2007), repeated, painful electrical stimuli (Farrell and Gibson 2007) and repeated, painful, pinprick stimulation (Rolke et al. 2006b). Frequencies used range from as low as 0.2 Hz (Baumgartner et al. 2002) to as high as 2.0 Hz (Farrell and Gibson 2007). The test protocol for wind-up proposed by the German Research Network on Neuropathic Pain appears to be the most widely used at present (Blumenstiel et al. 2011; Geber et al. 2011; Rolke et al. 2006b). The evaluation of wind-up requires the pain rating of a single stimulus (as described above) and the pain rating of a train of repeated stimuli, from which the wind-up ratio can be calculated.

The presence and degree of wind-up may indicate the level of effectiveness of descending inhibitory mechanisms (Farrell and Gibson 2007).

**Diffuse noxious inhibitory controls (DNIC)**

Testing of DNIC requires a conditioning stimulus and a test stimulus, which are applied to different areas of the body, concurrently or consecutively (Pud, Granovsky, and Yarnitsky 2009). The nociceptive input from the conditioning stimulus travels via the spinal cord dorsal horn to higher centres, such as the dorsal reticular nucleus of the medulla. This stimulates the generation of descending inhibitory signals, which are received by dorsal horn wide dynamic range (WDR) sensory neurons which synapse with nociceptive neurons from remote body areas, such as the area receiving the test stimulus (Fields, Basbaum, and Heinricher 2005; Price and McHaffie 1988).

There is no widely accepted test protocol for DNIC; test methods include using a cold pressor to apply a cold stimulus to a large area of skin (Edwards et al. 2003; Granot et al. 2008; Pud, Sprecher, and Yarnitsky 2005), thermode heat pain (Lautenbacher, Prager, and Rollman 2007; Price and McHaffie 1988; Riley, III et al.)
2010), and ischaemic pain (Campbell et al. 2008) as the conditioning stimulus, and thermode heat pain (Edwards et al. 2003; Granot et al. 2008), electrical stimulation (Lautenbacher, Prager, and Rollman 2007; Price and McHaffie 1988) and mechanical punctate stimulation (Pud, Sprecher, and Yarnitsky 2005) as the test stimulus. The large variety of test methods and test stimuli makes comparing results between studies difficult.

Less efficient DNIC mechanisms have been reported in patients with a variety of pain conditions (when compared to healthy controls) e.g. painful osteoarthritis, chronic low back pain and tension-type headaches, so DNIC efficiency is associated with the presence of non-neuropathic pain, although it is not clear whether it precedes or follows it (Arendt-Nielsen and Yarnitsky 2009). One theory is that ongoing chronic pain can “exhaust” the DNIC response, another is that less efficient DNIC predisposes people to chronic pain (Pud, Granovsky, and Yarnitsky 2009).

A potential criticism of some protocols for testing DNIC involves the use of the cold pressor as a conditioning stimulus. This stimulus has been found to activate stress responses in the cardiovascular and autonomic nervous systems, and in the hypothalamic-pituitary-adrenal (HPA) axis, so it has been suggested that stress induced analgesia via systems other than descending inhibition may be responsible for effects attributed to DNIC (Riley, III et al. 2010). Another criticism is that the pain perception of the test stimulus may be reduced by the distraction provided by the conditioning stimulus. A study which employed a distraction task, continuously prompting participants to attend to the conditioning stimulus before asking them to rate the test stimulus at the end of the test, found that healthy males and females showed no difference in DNIC effect, with or without distraction (Staud et al. 2003). However, female fibromyalgia patients showed an additional pain inhibition during distraction. The authors stated that this might be due to the psychological characteristics of fibromyalgia patients.

**Other pain test modalities**

The following test modalities are used less frequently than those applying thermal and mechanical stimuli. Ischaemic pain is induced by limiting blood flow to a body part, e.g. by applying an inflated blood pressure cuff to the arm (Campbell et al. 2008). It can be used as a conditioning stimulus for DNIC (Pud, Granovsky, and Yarnitsky 2009). Electrical stimulation may be applied transcutaneously using
electrode pads on the surface of the skin (Campbell et al. 2008; Rage et al. 2011; Ryall et al. 2007) or sub-epithelially using fine needles (Price and McHaffie 1988). It differs from other QST stimuli in that it bypasses sensory receptors and stimulates all types of nerve fibre (Backonja et al. 2009). Capsaicin is an irritant chemical, which is painful when applied as a cream or injected into the skin, but is primarily used to temporarily sensitise the skin to other stimuli (such as pinprick stimuli) as a model for neuropathic hyperalgesia (Arendt-Nielsen and Yarnitsky 2009; Baumgartner et al. 2002).

**Test locations**

Different test sites may be used, e.g. forearm, thigh (Dyck et al. 1993), lower leg (Kelly, Cook, and Backonja 2005) and breast (Soderberg et al. 2006). In testing patients with a defined painful area, e.g. painful knee osteoarthritis, the painful region may be chosen as one test site, together with a remote, control site (Wylde et al. 2012). This is to allow localised sensory changes due to the presence of pain to be distinguished from generalised changes. When testing a general population, test sites such as the hand and foot, for which normative data exist, may be selected to allow comparison with these norms (Rolke et al. 2006a). A study which compared thermal detection and pain thresholds at 3 upper limb sites (thenar eminence, dorsum of the hand and volar surface of the wrist) and the dorsum of the foot found that all the upper limb sites were more sensitive to warm and cool detection than the foot, but had similar pain thresholds, and that the thenar eminence had the smallest inter-individual variability (Hagander et al. 2000). Age-related differences in QST variables have been found to be more pronounced at the foot than the hand (Rolke et al. 2006a). Many published studies give no justification for the choice of test site (Granot, Sprecher, and Yarnitsky 2003; Moloney et al. 2011; Wasner and Brock 2008).

**2.8.3 Physiological basis of QST**

Physiological experimental work has shown that specific nerve fibre types respond more to some types of stimuli than others. Aβ fibre function is tested by light touch detection and vibration thresholds, Aδ fibres by cold detection threshold, pinprick pain threshold and paradoxical heat sensations, and C fibres by warm detection and heat pain thresholds. Both Aδ and C fibres contribute to cold perception and
pressure pain thresholds (Rolke et al. 2006a). These nerve fibres are connected to higher centres via the spinal cord. Two phenomena of interest which occur (or partially occur) at spinal cord level are wind-up and DNIC, which have already been discussed.

The nociceptive flexion reflex (NFR), also called the RIII reflex, may be used as part of QST although it is not a psychophysical technique. It is evoked by directly applying electrical stimulation to the sural nerve and measuring the corresponding contraction of biceps femoris, so it does not rely on the participant’s response (Yunus 2007). The NFR threshold has been found to be highly correlated to subjective pain reports (Rhudy and France 2007). The definition of the NFR threshold is not universally agreed upon (Rhudy and France 2007). Definitions used in studies include the current which gives an increase in mean electromyographic (EMG) muscle activity of at least 1.5 times the standard deviation above measurements at rest (Campbell et al. 2008), the current which gives an increase in mean EMG muscle activity of at least 1.0 times the standard deviation above measurements at rest (Rhudy et al. 2005), and EMG activity above 20 µV for a period of at least 10 ms in the 70–200 ms post-stimulus interval (Terkelsen et al. 2004).

Imaging can reveal some of the brain activity which occurs during QST. A review stated that QST studies utilising fMRI found increased activity in areas of the brain including the amygdala, prefrontal cortex and cingulate cortex, which are known to be involved in affective and cognitive responses (Gracely and Bradley 2005).

Differences in QST responses in participants suffering a physiological or psychological stress may be due to activation of the hypothalamic-pituitary-adrenal (HPA) stress axis. The hypothalamus releases corticotropin releasing hormone (CRH), which stimulates the pituitary to release adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal gland to release cortisol (Hamilton-West 2010). Prolonged high levels of cortisol are associated with negative health outcomes (Goldberg and McGee 2011). Differences in how groups of individuals respond to stressors may be markers of differences in pain perception. Study participants with chronic widespread pain had lower levels of salivary cortisol at baseline conditions, but higher levels of plasma cortisol after a physical (pressure pain examination) and a chemical (overnight dexamethasone suppression test) stressor, than pain-free controls. This latter finding was partially but not fully explained by levels of psychological distress (McBeth et al. 2005). Some patients
with fibromyalgia show an exaggerated release of ACTH following stressful exercise (Russell and Bieber 2005). The HPA axis is differentially affected by stress in males and females (Holdcroft and Berkeley 1999).

2.8.4 Utility and limitations of QST

QST is one of several methods used in the assessment of sensory processing, others include brain imaging, nerve conduction studies and nerve fibre density assays. Each of these has advantages and limitations.

QST results depend upon method used

The results obtained using QST are dependent upon the test method used. One study found that for cool (CDT) and warm (WDT) detection thresholds, a more rapid rate of temperature change (1°C or 3°C per second, compared to 0.5°C per second) yielded a higher WDT and lower CDT (Dyck et al. 1993). The same study found that a larger skin contact area gave a significantly lower WDT. Another study compared test sites and found differences in CDT and WDT between the hand and foot of young (age 20 – 58), healthy subjects. The test environment and instructions given to the participant can also influence results (Shy et al. 2003). A study which compared the test order as given by the German Research Network on Neuropathic Pain protocol (Rolke et al. 2006b) with identical tests in a different order found that Mechanical Pain Sensitivity (participant’s numerical ratings of the painfulness of pinprick stimuli) was higher when it was carried out after thermal tests such as heat and cold pain thresholds than when carried out before thermal tests, showing that test order can alter the results obtained (Grone et al. 2012). This means that only results obtained using identical test methods can be compared.

It is important that the participant understands the instructions and is alert during the test procedure (Backonja et al. 2009). Results obtained using the method of limits are dependent upon reaction time, so the motor skills and alertness of the subject will influence the result (Hansson, Backonja, and Bouhassira 2007). The alternative method of levels is more time consuming, so the subject may become fatigued and lose concentration (Dyck et al. 1993). The gender of the tester may also have an influence. The authors of a study which tested the difference between same-sex and opposite-sex QST results commented that women had similar results when
tested by both sexes, but men had higher pain thresholds when tested by women than men, but they did not offer any explanation as to why this should be the case (Gijsbers and Nicholson 2005).

The test protocols developed by the German Research Network on Neuropathic Pain (Rolke et al. 2006b) have been used in the present study and will be described in more detail in the Methods section. Normative data is available for healthy subjects using these protocols for the hand, foot and face, and reliability testing has also been carried out. Using a standardised protocol allows results from different studies to be compared.

*QST is subjective compared to other techniques*

QST is not an objective measure. It relies on the subject’s co-operation and thus is open to accusations of deception, but this is true of other techniques e.g. audiometry or psychological testing, which are generally accepted (Backonja et al. 2009). There is insufficient evidence to support the use of QST to provide evidence of sensory deficit for legal cases or to detect malingering (Shy et al. 2003).

Nerve conduction and similar laboratory techniques give results which are independent of the co-operation of the subject, which makes them more objective than QST (Bartlett et al. 1998). Epidermal nerve fibre density (ENFD) gives information on small, cutaneous nerve fibres, and nerve conduction studies provide information concerning large, myelinated nerve fibres and spinal cord dorsal columns (Davis, Racine, and Collett 2012). Another technique uses laser-evoked potentials (LEP), where brain activity is measured via an electroencephalogram (EEG) whilst a painful heat stimulus is applied using a laser (Friederich et al. 2001). LEP also primarily tests large diameter, myelinated nerve fibres (Davis, Racine, and Collett 2012). Brain imaging techniques such as fMRI can indicate whether brain areas known to be associated with pain are active (Davis, Racine, and Collett 2012; Tracey and Bushnell 2009). In response to criticisms of the subjective nature of QST, some studies use the nociceptive withdrawal reflex (Desmeules et al. 2003) as an outcome.
Variability of QST measures

The variability of pain threshold measurements obtained even from healthy individuals using QST makes it difficult to interpret results for an individual person, e.g. for diagnostic use, although this is less of a problem when comparing groups in research studies, provided the sample size is adequate (Hansson, Backonja, and Bouhassira 2007). For example, a study on healthy subjects found that cold pain threshold measured at the foot for women under the age of 40 ranged between 0°C and 31°C (Hansson, Backonja, and Bouhassira 2007).

Advantages of QST compared to other techniques

QST is the only method which tests the whole pain pathway, i.e. sensation, transmission of neural signals, processing of the signals and interpretation (Shy et al. 2003). With QST it is possible to differentiate between peripheral and central sensitisation, which is not possible through other techniques (Rolke et al. 2006a). QST can detect heat hyperalgesia, which occurs due to increased sensitivity of nociceptors as a result of local sensitisation and release of prostaglandins (Meyer et al. 2005). In terms of central sensitisation, QST can also detect allodynia and wind-up, which are both due to an increase in excitability of dorsal horn neurons (Lautenbacher, Kunz, and Burkhardt 2008; Walk et al. 2009), and differences in the DNIC response, which is due to defects in descending pain inhibition mechanisms (Fields, Basbaum, and Heinricher 2005). QST tests the function of large, myelinated fibres, thinly myelinated and unmyelinated nerve fibres, whereas nerve conduction studies test only large, myelinated fibres (Bartlett et al. 1998; Rolke et al. 2006b). Imaging data is more objective than QST but needs to be interpreted with care as there is limited data on what is "normal", and no consensus as to what imaging criteria to use, e.g. presence or absence of a signal, magnitude of a signal (Davis, Racine, and Collett 2012). Unlike QST, LEP cannot detect hyperalgesia (Rolke et al. 2006b).

QST is versatile and has been found useful as a diagnostic aid (Levy, Abraham, and Reid 1989; Shy et al. 2003), to classify study participants (Campbell et al. 2008), or on healthy people to obtain normative data (Rolke et al. 2006a). It is recognised that QST may be useful as an adjunct to the usual examination in diagnosing neurological conditions, rather than as an alternative to it (Hansson, Backonja, and Bouhassira 2007; Shy et al. 2003).
2.8.5 Use of QST in musculoskeletal pain conditions

When discussing thresholds, the terms “higher” and “lower” can be confusing. For example, a person who is less sensitive to temperature change would report a higher temperature at which they could detect warmth, but a lower temperature at which they could detect cool. In this report, any change in detection threshold or pain threshold which involves a reduction in or lower sensitivity will be called an increased or higher threshold, whilst a threshold where the sensitivity is increased or higher will be called a reduced or lower threshold.

Many small studies on fibromyalgia (FMS) patients only use women (Geisser et al. 2003; Hurtig et al. 2001; Kosek, Ekholm, and Hansson 1996; Maquet et al. 2004). Only a small proportion of FMS patients are men, e.g. one study found 12.3% of people with a diagnosis of FMS were male (Haviland, Banta, and Przekop 2011). This could lead to very small numbers of men in small studies, too few to obtain statistically significant results for males. As QST results are known to differ for healthy men and women (Rolke et al. 2006a), the results from female-only studies cannot be generalised to men with FMS.

Fibromyalgia

A high tender point count is part of the definition of FMS (Wolfe et al. 1990); however, generalised hyperalgesia to deep muscle pressure has also been found in this patient group, including points other than defined tender points (Granges and Littlejohn 1993). Pressure pain threshold (PPT) has been found to be lower in women with FMS than in healthy women in several studies: mean 227.8 Pa and 371.3 Pa (Geisser et al. 2003), mean 85.2 kPa and 298.1 kPa (Kosek and Hansson 1997). A study which compared PPT between female FMS patients and healthy females measured at the tender point sites defined in the ACR 1990 definition of fibromyalgia (Wolfe et al. 1990) found them to be lower in the patients at every site, e.g. trapezius mean 90 kPa and 210 kPa, medial knee mean 110 kPa and 350 kPa (Maquet et al. 2004). A study comparing PPT of both men and women with fibromyalgia (grouped together) to healthy controls found a similar difference in pressure pain thresholds: mean 19.3 kg/cm$^2$ and 33.9 kg/cm$^2$ respectively (Granges and Littlejohn 1993).
A study comparing FMS patients to healthy controls found the warm perception (mean 34.6°C and 34.3°C from a 32°C baseline temperature) and cool perception (mean 30.4°C and 30.2°C from a 32°C baseline temperature) thresholds were the same, but cold pain (mean 17.6°C and 10.5°C) and heat pain (mean 41.2°C and 43.9°C) thresholds were both reduced in the FMS group, as was the threshold for the nociceptive withdrawal reflex (median 22.7 mA and 33 mA) (Desmeules et al. 2003). These findings for the difference between FMS patients and controls for warm and cool perception and heat and cold pain thresholds were duplicated by another study, although in this case the values of measurements obtained were not stated (Kosek, Ekholm, and Hansson 1996). Another study found female FMS patients had significantly lower heat pain thresholds than female healthy controls (mean 42.4°C and 47.1°C), and significantly lower heat pain tolerance (mean 47.1°C and 49.3°C) (Geisser et al. 2003). A further study also found that both heat (mean 41.9°C and 45.1°C) and cold pain thresholds (mean 14.5°C and 6.9°C) were lower in female FMS patients than female controls (Smith et al. 2008). Another study further confirmed these results with the finding that female FMS patients had lower heat (mean 41.1°C and 45.2°C) and cold pain thresholds (19.7°C and 8.4°C) than female healthy controls (Hurtig et al. 2001).

A study which applied the whole QST protocol of the German Research Network on Neuropathic Pain (Rolke et al. 2006b) to fibromyalgia patients and healthy controls found that the patients were significantly different to the controls in cold pain threshold (at the foot 5.8°C and 18.7°C), heat pain threshold (at the foot 46.3°C and 41.8°C), PPT (at the foot 584 kPa and 299 kPa), and rated mechanical stimuli as significantly more painful (at the foot 0.41/100 and 2.10/100) (Tampin et al. 2012).

In a study of DNIC using ischaemic pain as a conditioning stimulus, healthy controls (mean 300.7 kPa before, 415.5 kPa during) but not FMS patients (mean 115.4 kPa before, 127.2 kPa during) had increased pressure pain threshold whilst the conditioning stimulus was applied (Kosek and Hansson 1997). A DNIC study found that the electrical pain threshold of female FMS patients was not reduced when a concurrent heat pain conditioning stimulus was applied, whereas for female healthy controls the electrical pain threshold was reduced (measurement values not stated) (Lautenbacher and Rollman 1997). Although it is usually thought that the conditioning stimulus to induce DNIC should be heterotopic, one study used a homotopic stimulus in that progressive immersion and removal of an arm in a cold pressor was both the conditioning and test stimulus (De Souza et al. 2009).
Immersion of the whole arm was the conditioning stimulus, so the pain perceived during arm withdrawal was considered to be subject to DNIC, and a percentage reduction in pain rating between immersion and withdrawal was calculated for female FMS patients and healthy females (mean 20.0% and 71.0% respectively). Counter to the other findings, a further study (which did not report measurement values) which used pain scoring of thermode heat wind-up as a test stimulus and hot water immersion of a hand as the conditioning stimulus, found that neither female FMS patients nor healthy females exhibited DNIC, whereas healthy males did, implying that reduced DNIC was due to being female (Staud et al. 2003). However, this study did not include male FMS patients.

A study found an increased wind-up ratio to pinprick stimulation in women with FMS compared to healthy controls, as measured on both hands and both feet (example: right hand mean 0.470 and 0.254) (Klauenberg et al. 2008). Enhanced wind-up in FMS subjects compared to normal controls had previously been noted, and attributed to enhanced activity of NDMA receptors in the spinal cord dorsal horn (Staud et al. 2003). The substance ketamine is an NMDA antagonist. A study on 29 fibromyalgia patients found that among those who were ketamine responders (17 participants), i.e. their clinical pain reduced by at least 50% after its administration, ketamine reduced temporal summation of painful electrical stimuli (Graven-Nielsen et al. 2000). As temporal summation is a centrally mediated phenomenon, this result is very unlikely to be due to blockade of peripheral NMDA receptors. However, the evidence is weakened by the small size of the sample, the fact that only approximately half of the participants responded to ketamine, and the fact that controls without fibromyalgia were not tested.

Osteoarthritis

Patients with hip OA awaiting arthroplasty had lower mechanical detection (mean 0.5 mN and 16 mN) and rated mechanical pain from a 256 mN von Frey filament higher on a 0-100 scale (log of mean 1.37 and 1.12) over the affected hip area than did normal controls; however, heat pain (mean 44.6°C and 45.7°C) and cold pain thresholds (mean 8.3°C and 12.2°C) were not different (Gwilym et al. 2009). A review reported that OA patients were also found to have reduced vibration threshold, reduced mechanical detection and reduced mechanical pain thresholds compared to controls (Pavlakovic and Petzke 2010). A study comparing patients awaiting total knee replacement to healthy controls found that the patients had
higher mechanical detection threshold, lower pressure pain threshold, and higher warm and cool detection thresholds than controls when tested at the knee, but only the mechanical detection and pressure pain thresholds differed significantly between patients and controls at a remote site (the forearm). Heat pain threshold did not differ between the two groups (Wylde et al. 2012). Measurement values were not reported for this study.

A study which compared patients with OA hip awaiting hip surgery (osteotomy or hip replacement) with healthy controls found that the patients had lower pressure pain thresholds (PPT) than the controls (mean 250 kPa and 330 kPa), and the patients also exhibited less DNIC effect on the PPT due to an ischaemic pain conditioning stimulus than the controls (Kosek and Ordeberg 2000). The same study also followed up both patients and controls between 6 and 14 months after the patients’ surgery, at which time all patients were pain-free, and found that there were now no significant differences in PPTs (mean 300 kPa and 320 kPa) or DNIC between patients and controls. Neither group exhibited a DNIC effect of the ischaemic conditioning stimulus on heat pain threshold either before or after surgery.

A study on patients with OA knee measured mechanical, heat and cold pain thresholds at the hand, affected knee and contralateral knee before and at several time points after (the longest was 4 months post-surgery) knee replacement surgery (Martinez et al. 2007). The authors reported significantly higher heat hyperalgesia (high VAS ratings of heat above pain threshold) at the affected knee compared to the other sites, in the preoperative and early (up to 4 days) post-operative period, but no differences in heat, cold or mechanical pain thresholds or cold hyperalgesia between the sites. By one month post-operatively there were no differences in any QST measures between test sites, and the authors did not compare the results between time points. They concluded the results were likely to be due to peripheral sensitisation as a result of local inflammation (Martinez et al. 2007).

Pain imaging studies all use experimental pain stimuli, because they require images during and without noxious stimulation for comparison (Vincent and Tracey 2010). A study using functional magnetic resonance imaging (fMRI) comparing patients with hip OA with pain-free controls found that the patient group showed greater activation in the anterior cingulate cortex, right dorsolateral prefrontal cortex, left middle-frontal gyrus and left lateral occipital cortex (Gwilym et al. 2009).
**Low back pain**

A study comparing low back pain patients with healthy controls found that mechanical detection thresholds over the low back area were the same in both groups, but that identification of sensory stimuli which required more interpretation i.e. two-point discrimination and recognising letters drawn on the back, were impaired in the patient group (Wand et al. 2010). A study using the QST protocol devised by the German Research Network on Neuropathic Pain (Rolke et al. 2006b) found that the sensitivity to pressure pain of female participants with chronic low back pain was greater than that of female pain-free controls over the painful site only, pressure pain threshold mean 239.3 kPa and 352 kPa, indicating peripheral sensory changes, whereas female fibromyalgia patients had greater sensitivity to cold pain and pressure pain than controls at a non-painful site (dorsum of hand), cold pain threshold mean 21.0°C and 12.2°C, pressure pain threshold mean 238 kPa and 318 kPa (Blumenstiel et al. 2011). However, the group sizes were small (21 with FMS, 23 with low back pain, 20 controls). In addition the low back pain participants were recruited from a general population using their responses to a questionnaire, whereas the fibromyalgia patients were recruited from a clinic, so they were from different populations.

A study on non-specific low back pain patients, FMS patients and healthy controls found that the pressure pain threshold at the left thumb was similar for the back pain and FMS patients, but both these figures were significantly lower than for the controls (mean 0.7 kg, 0.7 kg and 2.7 kg) (Giesecke et al. 2004). The same study found that the number of tender points was similar for low back pain patients and controls, but both these were significantly lower than for FMS patients (mean 3.3, 3.2 and 15.1). The authors considered that a low pressure pain threshold at a point distant from the pain site indicated central pain amplification in the low back pain as well as the FMS patients, but that the high tender point count in the FMS patients alone was more indicative of general distress (Giesecke et al. 2004).

A study on clinic patients with non-specific low back pain found that pressure pain threshold measured at the forehead and thumbnail was correlated to functional status (as measured by the physical function sub-scale of the SF-36 questionnaire), and also accounted for 12% of the variance in pain (as measured by the pain sub-scale of the SF-36) in a regression model (Clauw et al. 1999).
Comparing fibromyalgia with other musculoskeletal pain conditions

There is some evidence that peripheral pain may act to initiate or maintain central sensitisation, providing a mechanism for the development of localised pain into widespread pain or fibromyalgia (Staud 2006). QST studies comparing localised and widespread pain can clarify this relationship. A QST study found that temporomandibular disorder (TMD) patients could be divided into sensitive and insensitive, depending upon tender point count (above and below 10 tender points respectively) (Pfau et al. 2009). The insensitive group resembled healthy controls for cold pain, heat pain and mechanical pain thresholds, whereas the sensitive TMD group resembled FMS patients and were more sensitive to cold, heat and mechanical pain than the controls. However, the TMD patients were all similar to each other in terms of duration of clinical pain, and dissimilar to the FMS patients in this respect. The sensitive group of TMD patients had more widespread pain than the insensitive group, but less than the FMS group, which gives a dose-response relationship between number of pain sites and sensitivity to the QST stimuli. Values for threshold measurements were not reported (Pfau et al. 2009). A study which included FMS, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients found that their pressure pain thresholds were all lower than healthy controls (mean 2360 grams, 2376 g, 2653 g, 3595 g respectively), although there were no significant differences between the patient groups (Garcia-Fernandez et al. 2009).

2.8.6 QST in healthy individuals

QST has been applied to healthy individuals in order to obtain normative data, or as a control for patient groups. As measurements are dependent upon the method used to obtain them, Table 2.5 only includes studies using the German Research Network on Neuropathic Pain methodology (Rolke et al. 2006b) or its component parts. Some of the data collected from healthy participants by Rolke and colleagues is reproduced in Appendix VIII.

Only one study included participants over the age of 80, and that study only measured vibration detection threshold (Martina et al. 1998). Four other studies recruited participants over the age of 70 (Hilz et al. 1998; Lin et al. 2005; Yarnitsky et al. 1995; Yarnitsky and Sprecher 1994), and one of those only measured vibration detection threshold (Hilz et al. 1998). Only 4 of the studies had over 100
participants (Hilz et al. 1998; Lin et al. 2005; Yarnitsky et al. 1995; Yarnitsky and Sprecher 1994), two of those used the same participants (Yarnitsky et al. 1995; Yarnitsky and Sprecher 1994), one only measured vibration detection threshold (Hilz et al. 1998) and 2 others only measured thermal detection thresholds (Lin et al. 2005; Yarnitsky and Sprecher 1994). It may be concluded that there is a lack of published QST data using a variety of stimuli and measurements, carried out on non-clinical groups of people aged over 70.

Studies gathering normative data generally also have exclusion criteria, e.g. no pain-related diagnoses (such as osteoarthritis), not depressed or taking anti-depressant medications (Smith et al. 2008). As older individuals have greater numbers of co-morbidities, this would lead to testing of an atypical group if such exclusions were applied to older people.

Differences in QST results obtained from healthy individuals attributed to age and sex are discussed in more detail in section 2.9.
Table 2.5 – Normative QST data on healthy subjects

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>SUBJECTS</th>
<th>QST DATA AVAILABLE</th>
<th>TEST SITE</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fischer (1987)</td>
<td>24 male, 26 female healthy subjects aged 22-63</td>
<td>Pressure pain threshold.</td>
<td>9 muscular sites inc. gluteus medius, upper trapezius and supraspinatus.</td>
<td>Results by site for male and female.</td>
</tr>
<tr>
<td>Hilz et al (1998)</td>
<td>530 healthy subjects aged 3-79</td>
<td>Vibration threshold (at 128 Hz). N.B. German Research Network vibration test = 64 Hz</td>
<td>Second metacarpal, first metatarsal.</td>
<td>10 years age groups. Sex significant in the over 50s.</td>
</tr>
<tr>
<td>Martin et al (1998)</td>
<td>59 neurology patients aged 14-87, 198 healthy controls aged 19-93</td>
<td>Vibration disappearance threshold at 64 Hz.</td>
<td>4 locations: index finger DIP, hallux IP, ulnar styloid, internal malleolus.</td>
<td>Results reported by 20 year age group in upper and lower extremities.</td>
</tr>
<tr>
<td>REFERENCE</td>
<td>SUBJECTS</td>
<td>QST DATA AVAILABLE</td>
<td>TEST SITE</td>
<td>COMMENTS</td>
</tr>
<tr>
<td>-----------</td>
<td>----------</td>
<td>--------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Whitton, Johnson and Lovell (2005)</td>
<td>45 postherpetic neuralgia patients, 45 controls, aged over 55.</td>
<td>Vibration disappearance threshold.</td>
<td>Right ulnar styloid and first metatarsal head.</td>
<td>Divided into 55-70 and over 70.</td>
</tr>
<tr>
<td>Soderberg et al (2005)</td>
<td>19 women of reproductive age.</td>
<td>Heat/cold perception and pain thresholds tested at 3 different menstrual phases.</td>
<td>Cheek, medial forearm, breast non-dominant side.</td>
<td>Only significant difference over the cycle was for cold perception at breast.</td>
</tr>
<tr>
<td>Rolke ae al (2006b)</td>
<td>18 healthy subjects aged 21-58</td>
<td>All in German Research Network protocol.</td>
<td>Testing left and right cheek, dorsum of hand, dorsum of foot.</td>
<td>Results for men and women, under and over 40.</td>
</tr>
<tr>
<td>Wasner and Brock (2008)</td>
<td>20 healthy subjects mean age 35.4</td>
<td>Hot and cold pain thresholds.</td>
<td>Testing at dorsum of hand, at days 0, 1 and 21.</td>
<td>Results broken down by sex. Repeatability over 3 weeks reported.</td>
</tr>
</tbody>
</table>
2.9 Quantitative sensory testing, sex and age

2.9.1 QST and sex

Over the past two decades a large body of work has been conducted on the differences between the sexes in response to pain (Hurley and Adams 2008). Much of this early work was carried out using experimental pain models in animals and included assessment of sex differences in pain thresholds, pain tolerance and response to analgesic treatments (Hurley and Adams 2008). Differences in pain thresholds between male and female rodents have been studied thoroughly (Ruda 1993). In particular, female rodents were found to have lower pain thresholds than males in experimental models of hot thermal (Sternberg, Smith, and Scorr 2004), chemical (Aloisi, Albonetti, and Carli 1994), inflammatory (Cook and Nickerson 2005) and mechanical (Barrett, Smith, and Picker 2002) nociception. Similar findings in humans are discussed below.

Evidence from reviews

A recent review of sex differences in epidemiological, experimental and clinical data found that women showed increased sensitivity to many experimental pain modalities compared to men (Fillingim et al. 2009). Cold pain showed consistent differences between males and females (Kim et al. 2004), pressure pain (Chesterton et al. 2003), electrical pain (al'Absi et al. 2006) and heat pain (Kim et al. 2004) showed evidence of differences but ischaemic pain (Edwards et al. 2004) did not display statistically significant sex differences. Both pain threshold and pain tolerance measurements (al'Absi et al. 2006) have been found to be generally higher in men than women, and women’s rating of experimental pain was usually found to be higher than men’s (Chesterton et al. 2003). A systematic review of experimental pain studies on human subjects published between 1998 and 2008 summarised the findings as follows: males and females had comparable thresholds for cold pain, mechanical cutaneous pain and ischaemic pain, but females had lower pressure pain thresholds than males; females had lower heat pain thresholds than males in approximately 50% of the studies reviewed, comparable with males for the other 50%; females reported lower pain tolerance than males for heat pain, cold pain and pressure pain, but males and females had similar values for
ischaemic pain tolerance; there were no sex differences for reported pain intensity or unpleasantness (Racine et al. 2012a).

Detection thresholds

A study which measured warm (WDT) and cool (CDT) detection thresholds on males and females found that CDT at the foot differed significantly between the sexes in that the males were less sensitive than the females, whereas CDT at the hand and WDT at both hand and foot were similar for males and females (Yarnitsky and Sprecher 1994). Another study which measured CDT, WDT and VDT at the hand and foot found no differences between the measurements for males and females (Bartlett et al. 1998). Females were found to be more sensitive than males to warm and cool detection, but not vibration detection (Liou et al. 1999). Females were found to be more sensitive to light touch than males (Berquin et al. 2010). A study on healthy children aged 6-16 years old using the full QST protocol of the German Research Network on Neuropathic Pain (Rolke et al. 2006b) found that only WDT showed a sex-related difference, with girls being more sensitive than boys (Blankenburg et al. 2011).

Mechanical stimuli

One study reported the mean pressure pain threshold for men was greater than that for women, at the forearm and trapezius (Goodin et al. 2009). A study using the tender points used for fibromyalgia diagnosis plus 6 control points found that the pressure pain threshold was lower for women than men at all the points tested (Garcia et al. 2007). A population-based study of older people (aged 70 – 97 years) found females had a statistically significantly ($p < 0.001$) higher tender point count than males (Eggermont, Shmerling, and Leveille 2010). A study using existing QST reference data found that although men had higher deep pressure pain thresholds and punctate (pinprick) pain thresholds than women at all ages, the pressure pain thresholds for the sexes converged over age 40 whereas the punctate pain thresholds diverged (Magerl et al. 2010). A small study (n=20) using healthy men and women found that temporal summation of pinprick stimuli was greater in the women than the men (Sarlani and Greenspan 2002).
Thermal stimuli

In a large review by Fillingim and colleagues, 23 studies that examined sex difference in experimental pain were reviewed. The authors concluded that females were more sensitive to heat pain than males (Fillingim et al. 2009). They also reviewed 22 studies of experimental cold pain and concluded that females were also more sensitive to cold pain than males. Moreover, females consistently reported higher pain ratings for standardised heat and cold pain stimuli than males (Fillingim et al. 2009). A large study of heat pain threshold and heat pain tolerance (n=249) found that males had higher heat pain tolerance than females but heat pain threshold was similar for the sexes (Defrin, Shramm, and Eli 2009). Sex differences have also been found in dynamic experimental models of pain, such as temporal summation which is commonly used to evaluate differences in central processing of nociceptive signals. In response to heat pain stimuli, female participants consistently exhibit more pronounced temporal summation than males (Fillingim et al. 1998; George et al. 2007).

DNIC

Approximately half of the studies (6 of 13) on DNIC identified in a review have shown that it is more pronounced in males than females, the other studies report similar results for males and females (Fillingim et al. 2009). A study of DNIC using cold pressor pain as a conditioning stimulus and heterotopic noxious pressure found that DNIC was statistically significantly greater in men than women (Goodin et al. 2009). A review found that DNIC had a larger effect in men than in women for a range of conditioning and test stimulus modalities (Popescu et al. 2010). A study using a pressure pain stimulus and heat pain conditioning stimulus found no differences between men and women (Lautenbacher, Kunz, and Burkhardt 2008). Another study using a cold pressor as the conditioning stimulus and capsaicin application to the gums as a test stimulus found no differences in DNIC between men and women (Baad-Hansen et al. 2005). In summary, the evidence is equivocal as to whether males have a more pronounced DNIC response than females, or whether there is no difference between the sexes.
Brain imaging

Although most experimental pain protocols involve psychophysical testing, brain imaging can provide more objective data. Females were found to have a greater activation of the contralateral prefrontal cortex than males when a painful heat stimulus was applied to the forearm (Paulson et al. 1998). An fMRI study measuring blood oxygen level-dependent signals found that women had greater deactivation than men in certain brain areas such as the somatosensory cortex, insular cortex and dorsolateral prefrontal cortex when painful heat was applied to the dorsum of the foot (Moulton et al. 2006). An imaging study which used experimental visceral pain on healthy volunteers found no sex differences in brain responses (Hobson et al. 2005). A review of brain imaging studies found differences between men and women in which areas of the brain which were most active following painful stimulation, but acknowledged that the methodologies of the studies cited were all so different that it was difficult to draw firm conclusions (Fillingim et al. 2009).

Nociceptive flexion reflex

The nociceptive flexion reflex also provides more objective evidence of response to experimental stimuli, and is explained in more detail in section 2.8.3. A review found that 3 out of 5 investigations showed lower levels of electrical stimulation were required to elicit the RIII reflex in the sural nerve (also called the nociceptive flexion reflex) in women than in men (Fillingim et al. 2009). A study using forearm ischaemia as the conditioning stimulus found that the nociceptive flexion reflex was stronger in men than women (France and Suchowiecki 1999). A review included a meta-analysis of 3 studies which measured DNIC using the nociceptive flexion reflex as an outcome measure, and found DNIC was more pronounced in females than males, contrary to studies using participant reported outcomes which showed DNIC to be more pronounced in males than females, or that there was no difference between the sexes (Popescu et al. 2010).

Summary of QST and sex

To summarise, in many studies, females appear to be more sensitive to experimental stimuli than males, although this is not a universal finding. This may
partially explain the fact that pain prevalence for most types of pain is higher for females than males (see section 2.5.2). However, the conflicting results among studies of sex difference in pain may be due to variation in study design, outcome measures and populations being tested.

2.9.2 QST and age

In parallel to the age-related differences which have been found in clinical pain (see section 2.4.1), differences have also been found in responses to experimental pain. Age-related changes in QST results are more pronounced at the foot than at more proximal sites. A study of a group of participants aged 20 – 86 found that warm perception threshold and vibration threshold were very similar across age groups in the hand, but increased significantly with age in the foot (Bartlett et al. 1998). The most plausible reason for this is that longer nerve fibres to the foot are more prone to degeneration with increasing age (Gibson and Farrell 2004). Spatially small and brief stimuli show the greatest age-related changes, which may be related to diminishing nerve fibre density with increasing age (Gibson and Farrell 2004).

Stimulus detection thresholds and ageing

Most evidence supports differences in stimulus detection thresholds in people of different ages. A study on healthy people aged 23-87 years found that both warm and cool detection threshold increased with age when tested at both the upper and lower limb (Huang, Wang, and Lin 2010). Healthy volunteers aged 20-86 years were found to have warm, cool and vibration detection thresholds which increased with increasing age, measured at both the hand and the foot (Lin et al. 2005). One study found evidence that warm and cool detection thresholds at the upper limb were lower in young (21-35 years) compared to older (63-88 years) participants (Lautenbacher et al. 2005) but another study found that warm detection and electrical detection thresholds did not vary between young (age 22-28 years) and older (age 67-87 years) people (Washington, Gibson, and Helme 2000). Increased vibration detection threshold with increasing age has been reported at the ankle (de Neeling et al. 1994) and at both the hand and foot (Hilz et al. 1998; Martina et al. 1998).
Pain threshold and ageing

Although differences in response to stimuli vary with increasing age depending upon the type of stimulus (Gagliese and Melzack 2005), a review found that most evidence supports an increase in pain threshold with increasing age, except for electrical pain thresholds which remain constant with age (Gibson and Farrell 2004). More studies support increased or unchanged pain thresholds with ageing than decreased thresholds. One study found no change in heat pain threshold but a decrease in pressure pain threshold in older compared to younger people (Lautenbacher et al. 2005) although other studies have found increased thermal pain thresholds with age (Gibson and Farrell 2004). Another study found decreased ischaemic pain thresholds in older than in younger participants (Edwards and Fillingim 2001). A meta-analysis of all relevant pain threshold studies found a statistically significant increase with age, with size effect 0.74 which was equivalent to a 2 – 3 °C increase in older compared to younger participants (age difference was not specified) in heat pain threshold (Gibson 2003). A study which blocked the function of Aδ nerve fibres found that the heat pain thresholds of younger participants increased, whereas those of older participants remained stable, showing that the older people normally relied more upon C fibre function (Chakour et al. 1996). A study found that the nociceptive withdrawal reflex did not vary between groups of participants aged 18 – 32 and 65 – 79 years (Farrell and Gibson 2007). A population-based study of older people (aged 70 – 97 years) did not find any significant difference in tender point count with age (Eggermont, Shmerling, and Leveille 2010). A study on women with fibromyalgia aged 21 – 50 years also did not find an association between age and tender point count (Salli, Yilmaz, and Ugurlu 2012).

Pain rating and ageing

There is a very limited amount of evidence for changes to ratings of painful stimuli with age. A study which used several levels of painful heat found that the rating was lower for less intense stimulation, and higher for more intense stimulation, in older compared to younger people (Harkins, Price, and Martelli 1986).
**Wind-up and DNIC and ageing**

Temporal summation or wind-up is more pronounced in older than younger people (Gibson and Farrell 2004) and the frequency of stimulation required to elicit summation decreases (Gibson 2003). DNIC effect has been shown to decrease with increasing age (Edwards, Fillingim, and Ness 2003; McClean 2008; Riley, III et al. 2010; Washington, Gibson, and Helme 2000), and to be reduced even in middle-aged (40 – 55) adults compared to young adults (Lariviere et al. 2007).

**Pain tolerance and ageing**

Most studies show that pain tolerance decreases with increasing age (Gibson and Farrell 2004). One study found decreased ischaemic pain tolerance in older than in younger participants (Edwards and Fillingim 2001). A meta-analysis of pain tolerance studies found a significant decrease with age, with effect size -0.45 (Gibson 2003). For thermal pain, ratings of painfulness near threshold are greater for older than younger people, but as the intensity of stimulation increases, the ratings become more uniform across age groups. There is very little data on ratings of non-thermal supra-threshold stimuli in older people (Gibson and Farrell 2004).

**Older people with musculoskeletal pain**

There are no studies of QST on older people with musculoskeletal pain.

There are some QST studies on healthy people over the age of 65, as described in section 2.8.6 and listed in Table 2.5 (Hilz et al. 1998; Lin et al. 2005; Martina et al. 1998; Yarnitsky and Sprecher 1994). These all had exclusion criteria to ensure that the subjects were “healthy”, e.g. exclusion of those with “sensory symptoms, sensory signs including absent vibration sense, using drugs which might cause a polyneuropathy” (Martina et al. 1998), “diabetes mellitus, hypertension and stroke” (Lin et al. 2005). Some studies go further in their screening of healthy subjects, e.g. exclusion of subjects with “any acute or chronic pain condition” (Rolke et al. 2006a).

There are QST studies on people of a younger age with musculoskeletal pain, as described in section 2.4.5, although sometimes the age range is not stated, e.g. women with fibromyalgia aged between 30 and 68 (Hurtig et al. 2001), women with fibromyalgia with mean age 48.6 (Geisser et al. 2003), people with
temperomandibular pain with mean age 46.8 (Pfau et al. 2009). These studies used subjects with an established diagnosis.

There is no published QST data on older (>65) people from an unselected, general population.

To summarise, detection and pain thresholds mainly appear to increase with increasing age, which may partially explain why prevalence of some types of pain declines after mid-life (see section 2.4.1). However, the limited evidence indicates that pain tolerance decreases with age, which may partially explain why older people find pain more disabling than younger people (see section 2.4.4).

### 2.10 Summary

Pain can be defined in terms of its location, duration, severity or effects. Several outcomes of pain (e.g. disability) increase as a function of the number of areas of the body where pain is felt, so a pain continuum from “no pain” to “pain everywhere” may be a useful concept. The concept of chronic widespread pain (CWP) has been used in some studies and allows comparison of data with the existing literature.

Pain which is not caused by known disease or injury processes may be due to a susceptibility to pain, such as central sensitisation. Some responses to sensory stimuli are characteristic of central sensitisation, and these can be quantified by Quantitative Sensory Testing (QST). QST studies comparing people with musculoskeletal pain conditions to pain-free controls have generally found the participants with pain to be more sensitive to painful stimuli than those without. Hyperalgesia to cutaneous mechanical (pinprick) pain in the absence of hyperalgesia to heat or cold pain has been linked to central sensitisation. The participants with pain were also generally found to have greater temporal summation (wind-up) and lower descending noxious inhibitory controls (DNIC) than those without pain, both of which would indicate the involvement of central sensitisation.

Pain is almost always found to be more prevalent in females than in males. QST pain thresholds and pain tolerance are generally lower and pain ratings higher in females than males, although the results are equivocal. The moderating effect of sex on the relationship between QST data and the presence of pain has not previously been investigated.
Pain prevalence is generally higher for older than younger people, although for some pain conditions there is a mid-life peak and subsequent slight decline. Most QST studies have found an increase in pain threshold but a decrease in pain tolerance with increasing age. There have been relatively few QST studies using older people, and none have studied older people with chronic musculoskeletal pain.

The QST studies comparing the responses of participants with musculoskeletal pain and pain-free controls have generally had small numbers of participants. They have sampled clinical populations for the participants with pain, and recruitment of pain-free controls has often excluded people with conditions such as diabetes or neurological disorders. There have been no population-based studies comparing QST results between groups with different experience of pain. If central sensitisation is a contributory factor in musculoskeletal pain, its importance may vary with age and/or sex, but none of these studies has included older participants, or looked at age or sex as moderating factors.
3 Aim and objectives

3.1 Aim

The overall aim of the study is to determine the relationship between sensitivity to stimuli as measured by quantitative sensory testing (QST) and the prevalence of chronic pain, and ascertain whether and how this relationship varies with age in adults.

3.2 Objectives

Figure 3.1 – Hypothesised pathway linking pain and sensitivity to stimuli

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indicates a moderator, i.e. modifies the relationship between predictor and outcome

indicates unmediated pathway

indicates mediation pathway

indicates confounding
Figure 3.1 shows the hypothesised pathway upon which the study hypotheses have been based.

The study’s objectives are to test the hypotheses that:

1) Sensitivity to stimuli (as measured by QST) will be associated with a) the presence of chronic widespread pain and b) the number of pain sites. Specifically:
   i) A decrease in hot, cold and mechanical pain thresholds will be associated with a) an increasing number of Manchester pain sites and b) CWP.
   ii) An increase in subjective rating of painfulness of suprathreshold mechanical stimuli will be associated with a) an increasing number of Manchester pain sites and b) CWP.
   iii) Warm, cool, mechanical and vibration detection thresholds and thermal sensory limen will be unchanged regardless of a) an increasing number of Manchester pain sites and b) CWP.
   iv) There will be an increase in the ratio of subjective pain ratings of a train of 10 noxious mechanical stimuli to a single stimulus (wind-up ratio or WUR) with a) an increasing number of Manchester pain sites and b) CWP.
   v) There will be a reduction in the inhibitory effect of a simultaneous conditioning stimulus (DNIC) on WUR with a) an increasing number of Manchester pain sites and b) CWP.
   vi) There will be an increase in the number of tender point sites with a) an increasing number of Manchester pain sites and b) CWP.

2) The relationship between QST results and chronic pain will be moderated by age so that detection thresholds will increase, pain thresholds will increase, subjective pain ratings will increase, WUR will increase and DNIC will decrease with increasing age, and that this will be more pronounced at the foot than the hand.

3) The relationship between QST results and chronic pain will be moderated by sex so that pain thresholds will be lower, pain ratings higher, WUR higher and DNIC lower for women than men. Detection thresholds will be unaffected by sex.

4) The relationships in 1 – 3 above will be independent of the role of social deprivation and musculoskeletal ill-health.
4 Methods

4.1 Overview

This chapter describes the design of the study, the recruitment of participants, and the content of the sub-study assessments.

The techniques used in analysing the data are described. Reliability, ethical approval and assessor training are also discussed.

4.2 Study design

The “Pain Across the Adult Life Span” (PAALS) study used a two-phase, stratified sampling design. Data was collected at baseline, and the number of body areas with pain reported was used to stratify the group. Sub-samples were drawn from each stratum to participate in the sub-study. The PAALS study also administered a follow-up questionnaire 1 year later, but the present study only used the cross-sectional data. The baseline postal questionnaire was sent to every participant in the cohort. The questionnaire included a manikin and questions to determine location and duration of pain. A sub-group of participants was selected to obtain balanced numbers with no pain, some pain and CWP, to maximize the predictive power of data collected in the sub-study. In the sub-study, these participants were invited to undergo physical assessments including quantitative sensory testing (QST). Figure 4.1 summarises the study design.

Figure 4.1 – Study design
4.2.1 Participants

The study participants were recruited from two sources.

ACPRC.

This cohort was originally recruited by the Ageing and Cognitive Performance Research Centre (ACPRC) to take part in a longitudinal study of cognitive changes with increasing age, and participants were aged 42 – 92 years old at recruitment. The first wave of the cohort were recruited following television, radio and newspaper advertisements in 1983/4, subsequent waves were recruited in 1985, 1988, 1989/90 and 1991/92. The recruitment areas were Greater Manchester and Newcastle-upon-Tyne. A total of 6542 participants have been in this cohort, although not all at the same time (Rabbitt et al. 2004). Only cognitively intact participants were allowed to remain, and coupled with death and other causes of dropout 725 participants aged between 68 and 101 years old remained in the ACPRC cohort at the time of baseline data collection in the present study.

Detailed information on lifestyle, hobbies, occupation, physical and social activities, and family history was collected at baseline. Batteries of cognitive tests were administered approximately biennially between 1983 and 2003 (Rabbitt et al. 2009). Depression and life events data were collected and demographic and health information has been kept updated, most recently by telephone interview in 2011. Papers related to cognitive changes with age have been published (including genetic risk factors) (Lind et al. 2009; Luciano et al. 2009; Miyajima et al. 2008; Parker et al. 2000; Payton et al. 2010; Rabbitt et al. 2007; Rabbitt et al. 2011). Members of the cohort have also participated in research not related to cognition, such as dysphagia (Holland et al. 2011; Jayasekeran et al. 2011), the presence of c. difficile in stool samples (Miyajima et al. 2011), age-related anatomical changes in the brain (Rabbitt et al. 2008a; Williams et al. 2010), and the relationship between depression and cognitive decline (Rabbitt et al. 2008b).

The “oldest old” people, as a group, have barriers to participation that the majority of younger people do not. Sensory impairments, multiple co-morbidities and difficulties with transport are just three of the difficulties which can limit involvement of older people in research (Bonk 2010). This is a particular issue when older people are the focus of interest of a study. The existence of a cohort of older people who are cognitively intact and able and willing to participate makes such studies feasible.
It could be argued that these participants are less representative of the populations from which they were drawn than they were when first recruited. Older participants from a longitudinal study were shown to be more able than a cross-sectional population sample in a variety of physical and cognitive tests (Burridge et al. 2012). Less able people were more likely to withdraw from the ACPRC study (Rabbitt et al. 2004). Some of the participants have been taking part in research for almost 30 years. The fact that they are all still alive, active and cognitively intact makes them in some ways atypical. Participants who withdrew from the ACPRC cohort between 1983 and 1994 had lower socioeconomic status and fewer years of education than those who remained (Rabbitt et al. 2004), although those currently remaining are reasonably representative of the population as a whole in terms of educational level and social class (Pendleton 2010).

Epifund.

The Epifund (Epidemiology of Functional Disorders) cohort was recruited in 2001 from the patient registers of 3 General Practitioner practices in North West England, and as a very high proportion of the population of the UK are registered with a GP, this sampling frame was likely to be very representative of people in this geographical area. Initially there were 10,987 participants aged between 25 and 65 years old and the entire cohort was surveyed at baseline in 2001 and two subsequent follow-ups in 2003 (follow-up one) and 2005/6 (follow-up two), as well as smaller, intermediate surveys. Substantial amounts of data were collected and several publications resulted, some of which are detailed below.

Having any pain at baseline was associated with low levels of physical activity 32 months later (McBeth et al. 2010b). New onset of CWP between baseline and 15 months later was associated with poorer physical and mental health-related quality of life (HRQoL) than those who remained pain free from CWP, although the mental HRQoL was attenuated after adjusting for psychosocial factors including anxiety and depression (Nicholl et al. 2009). A positive association between insecure relationship attachment style and presence of CWP was found at follow-up two (Davies et al. 2009a). Having no pain at baseline, 15 months later and 4 years later was associated with low levels of psychological distress and good sleep quality (Jones et al. 2009). Sleep quality at baseline was found to predict resolution of CWP between baseline and 15 months later (Davies et al. 2008).
Data were also collected from sub-groups of the whole cohort at intermediate times. High levels of illness behaviour, anxiety, poor sleep quality and somatic symptoms were found to predict new onset of irritable bowel syndrome (IBS) at 15 months follow-up in participants free from irritable bowel syndrome at baseline (Nicholl et al. 2008a). Participants who consented to have GP consultations recorded after baseline data collection also completed a questionnaire on gastrointestinal symptoms, and a sub-group gave stool and blood samples. Persistence of symptoms after 6 months was associated with multiple risk factors including anxiety, depression, stressful life events, being female and being older (Halder et al. 2010). In a random sample of baseline responders who had pressure pain threshold ascertained, depression and poor sleep quality were found to be associated with low pressure pain threshold (Chiu et al. 2005). Another random sample of participants had sputum and serum cortisol levels measured, as a measure of hypothalamic-pituitary-adrenal stress axis function. High levels of cortisol were associated with presence of CWP or being “at risk” of CWP due to somatic symptoms, independently of psychological distress (McBeth et al. 2005). The gene encoding for the enzyme catechol-O-methyltransferase (COMT) had previously been associated with CWP in some small, published studies, so buccal cells were collected for genotyping from samples of participants pain-free and having CWP at baseline; no association was found between COMT “pain sensitivity” haplotypes and presence of CWP (Nicholl et al. 2010). New onset CWP at 4 year follow-up in participants CWP-free at baseline was not associated with either any traumatic event or specifically an RTA after adjustment for baseline psychological variables and sleep quality (Jones et al. 2011). After the last data collection 2655 participants remained in the Epifund cohort.

There are advantages and disadvantages to using an established cohort in a study, which apply to both the ACPRC and Epifund groups. Recruitment of a large cohort of participants takes considerable time and resources, which could otherwise be spent on other aspects of the study. In addition, historical data is available from existing cohorts, which may be accessed. The participants are experienced in completing questionnaires and undergoing a variety of examinations. As they know what they are committing themselves to, the return rate for questionnaires is likely to be high and the dropout rate is likely to be low. Retention of participants is a particular problem in longitudinal studies (Silman and Macfarlane 2002). Conversely, the drop-out which has already occurred at each stage of data
collection may serve to make the cohort less representative of the population from which it was originally drawn.

### 4.2.2 Power calculation

The sample size calculation for the PAALS study was based on the use of quantitative sensory testing (QST) variables to predict new onset of chronic widespread pain (CWP) at 12 month follow-up in those without it at baseline, and persistence of CWP in those with CWP at baseline. As the predictors were the QST variables, which were collected at the sub-study, the sample size for the sub-study was the number calculated. The total number predicted as needed in the sub-study was 300, which was divided for recruitment purposes into groups with no pain, 1 – 2 pain areas, 3+ pain areas (but not CWP) and CWP, all by the American College of Rheumatology definition (Wolfe et al. 1990). These numbers are given in Table 4.1.

<table>
<thead>
<tr>
<th>No pain</th>
<th>1 – 2 pain areas</th>
<th>3+ pain areas</th>
<th>Chronic widespread pain</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>95</td>
<td>75</td>
<td>48</td>
<td>300</td>
</tr>
</tbody>
</table>

Numbers of pain sites are determined using the American College of Rheumatology definition (Wolfe et al. 1990).

As these numbers had already been determined, a calculation was done to show the predictive power of statistical tests on this number of participants in a cross-sectional study. As the predictor variables in the present study were QST variables and the outcome was number of body areas with pain, a calculation was carried out to find the power of a QST variable in predicting a pain status outcome. There is some published data relating QST variables to pain status. Geisser and colleagues tested heat pain threshold (HPT) in small groups of female fibromyalgia patients (n=25) and female healthy controls (n=25), and obtained mean (S.D.) values of 42.4
(4.4)°C and 46.0 (3.0)°C respectively for these groups. This difference was statistically significant (p=0.01) (Geisser et al. 2003). Not everyone with CWP has fibromyalgia, so these pain categories are not analogous to those used in the present study.

The probability of making a type I error, i.e. of rejecting the null hypothesis when it is correct, is \( \alpha \). The probability that a test will show a significant difference at a given level of significance \( \alpha \) (if a difference actually exists) is called the power of the test. The probability of making a type II error, i.e. of accepting the null hypothesis when it is false, is \( \beta \), and the power of a test is given by \( 1 - \beta \), which is the probability of rejecting the null hypothesis when it is false (Swinscow and Campbell 2002).

The following calculations are after Bland (Bland 1995). The power of a t-test is given by:

\[
\text{power} = 1 - \Phi(z)
\]

where, for \( \alpha = 0.05 \):

\[
z = 1.96 - \frac{\left(\mu_1 - \mu_2\right)}{se_{\text{diff}}}
\]

\( \Phi(z) = \text{probability that a value from the normal distribution will be less than } z \)

\( z = z \text{ statistic} \)

\( \mu_1 = \text{mean of sample one} \)

\( \mu_2 = \text{mean of sample two} \)

\( se_{\text{diff}} = \text{standard error of the difference between the means} \)

The standard error of the difference between the means is given by:

\[
se_{\text{diff}} = \sqrt{\frac{\sigma_1^2}{n_1} - \frac{\sigma_2^2}{n_2}}
\]
\[ \sigma_1 = \text{standard deviation of sample one} \]
\[ \sigma_2 = \text{standard deviation of sample two} \]
\[ n_1 = \text{number of subjects in sample one} \]
\[ n_2 = \text{number of subjects in sample two} \]

Using the larger of the two standard deviations from Geisser et al’s study as an estimate (Geisser et al. 2003), and the sub-study group sizes for the “CWP” and “no pain” groups, the standard error of the difference between the means can be found.

\[ se_{diff} = \sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}} = 0.195 \]

Geisser et al found a difference in mean heat pain threshold of 3.6°C between their pain status groups, but this difference is likely to be smaller between a group with no pain and one with CWP than between groups with no pain and fibromyalgia. Assuming the group with CWP will have a mean heat pain threshold 1°C lower than the group with no pain:

\[ z = 1.96 - \frac{-1}{0.195} = 7.088 \]

When \( z = +3.0 \) or -3.0, \( \Phi(z) = 0.001 \) when looked up in a table for the normal distribution (Bland 1995). So for \( z = 7.088 \), \( \Phi(z) \) will be < 0.001. So,

\[ \text{power} = 1 - \Phi(z) > 0.999 \text{ (99.9%).} \]

Assuming the group with CWP will have a mean heat pain threshold 0.5°C lower than the group with no pain:
This value of z is also > 3.0, so the power is still > 99.9%.

4.2.3 Recruitment

The baseline recruitment strategy was different for the ACPRC and Epifund groups.

The ACPRC group are regularly contacted, correct addresses are maintained, and information collected on those who have died or withdrawn due to dementia. The ACPRC group received the questionnaire as one of their regular mailings, and did not receive any postal prompts or reminders, as is usual for them.

In the Epifund group the participants were checked against the electoral register to find out whether they were still at the recorded address, and information regarding deaths and changes of address was also available from their GP practices. Following the initial questionnaire mailing they were sent a reminder postcard after 2 weeks’ non-response, followed by a second full-length questionnaire after 4 weeks’ non-response, and finally a short questionnaire after 6 weeks’ non-response.

Participants from both groups who returned a questionnaire with a blank page or pages were sent a copy of that page or pages and a request to complete them. Missing responses on an otherwise completed page were treated as a decision not to respond and no further request for information was made.

The sub-study recruitment procedure was similar for the ACRPC and Epifund groups and is summarised in Figure 4.2.
The baseline study questionnaire requested participants’ consent to contact them regarding a further part of the study (see Appendix I). All the ACPRC participants who had consented were contacted by telephone by Maureen Jones, but only a sample of the consenting Epifund participants were contacted by members of the PAALS study team, due to their greater numbers. These were selected from the mailing list in no particular order. The sample was stratified by pain status: no pain, 1-2 pain areas, 3+ pain areas, and CWP (by ACR definition) as shown in Table 6. The purpose of the first phone call was to request permission to send the PAALS Participant Information Sheet (see Appendix II). Some participants withdrew at this stage. After a period of at least a week, a second phone call was made by members of the PAALS study team, and the participant could ask questions regarding the sub-study. If the participant agreed to take part, an appointment was arranged. Some of these participants subsequently cancelled their appointments, or could not attend and could not have them rearranged within the period of the study. The remainder took part in the sub-study assessment.

Participants were not excluded from the sub-study on the grounds of having any co-morbidity. The only exclusion grounds were if the participant was: 1) unable to
stand unsupported for 10 seconds, 2) unable to follow instructions and give responses in English, or 3) unable to tolerate the examination by their own assessment, e.g. due to fatigue.

Most of the sub-study assessments took place in one of two central locations: the Wellcome Trust Clinical Research Facility in central Manchester, and Bollington Leisure Centre, in Bollington, Cheshire. If a participant expressed concerns about travelling to the location, he or she was offered a taxi. If a participant felt that the journey was too onerous even by taxi, he or she was offered a home visit.

4.3 Study content

4.3.1 Design of questionnaire

Self-administered questionnaires are a practical means of obtaining data from a large group of participants, but the design must be considered carefully.

The overall length of a questionnaire must be considered, in that a longer one will be more onerous for the participant to complete. This is important to maximise the number of returns. One study found that length of questionnaire did not affect returns by comparing 8 and 14 page documents (Mond et al. 2004), but another found that responses from women over 70 were significantly higher to a 5 than to a 7 page document (Iglesias and Torgerson 2000). A non-health postal survey sent to participants selected from the electoral register achieved a rather low total return rate of 16%, but found that the return rate for a 15 page questionnaire was significantly higher than for one with 24 pages (Sahlqvist et al. 2011). Another study found that greater questionnaire length did adversely affect return rate, but this was improved following a postal and a telephone prompt (Ronckers et al. 2004). The most important variables in the study should have enough of the questionnaire devoted to them to ensure that enough data is collected so that the hypotheses can be tested. The PAALS questionnaire had 33 pages, and is included in Appendix I.

Other factors are important in the design and administration of questionnaires, such as the appropriate level of language, layout which is easy to follow (Dunn, Jordan, and Croft 2003), clear rubric on completion and return and good follow-up in case of non-return (Wensing and Schattenberg 2005).
The questionnaires sent to the ACPRC group used a larger font size than those sent to the Epifund group, to make it easier for participants with age-related deterioration of vision to read. The PAALS study team received at least one notification from a family member that they had read the questionnaire aloud to a visually-impaired participant.

4.3.2 Data collected in baseline questionnaire

Demographic and lifestyle information. Date of birth and sex are among the pre-existing data for all the participants in the PAALS cohort’s data set, so are available for those who returned the questionnaire and those who did not. The importance of age and sex as risk factors for chronic pain prevalence has already been discussed in the Background chapter. Marital status, number of children, age of leaving full-time education, smoking and alcohol drinking were also asked about (see Appendix I).

Postal address was also in the pre-existing data for participants. The postcode was used to determine the Index of Multiple Deprivation 2010 (Office for National Statistics 2012), which is a measure of deprivation of an area which incorporates income, employment, health deprivation and disability, education skills and training, barriers to housing and services, crime and living environment in its calculation. Social support was assessed by asking whether the participant had a confidante, how often they spoke to them, how much they could confide and whether the person could assist in a crisis (see Appendix I).

Pain location. In written assessments, pain manikins are frequently used because they remove the need for an accurate verbal description of the location. The McGill Pain Questionnaire uses a pain manikin with 2 drawings (front and back) in the long but not the short form (Melzack and Wall 1996). However, manikins then need to be coded in order for the data to be analysed. For regional pain, the size and extent of the area defined e.g. as shoulder pain, makes a great deal of difference to the prevalence obtained (Pope et al. 1997). In defining chronic widespread pain (CWP) or fibromyalgia, the American College of Rheumatology manikin divides the body into 10 sections (Wolfe et al. 1990), see Figure 13, whereas the “Manchester” manikin divides the body into 29 sections, see Figure 14.

Not all written assessments use manikins, some ask questions about pain location similarly to telephone interviews. The way in which the question is asked may make
a difference to the response, for example, one postal survey asked about pain in any muscle or joint, then repeated the question naming each body site. The latter question resulted in higher reported prevalence (Taylor 2005). Another study found that comparable pain prevalence and location data was obtained using a manikin and written questions (van den Hoven, Gorter, and Picavet 2010).

The use of telephone interviews to gather pain location information requires another method. A large, multi-national study used the question “Where is your pain located?” (Breivik et al. 2006). Participants were free to describe where their pain was, but this led to categories such as “joints” which would be impossible to localise. Another study using telephone data collection asked “In the past 3 months how often have you had pain in the …”, inserting the name of one of 8 body areas (McCarthy et al. 2009). This method relies upon the participant’s definition of the location of a body area.

Studies using face-to-face interviews for data collection may use questions or manikins, or both (Minaur et al. 2004; Veerapen, Wigley, and Valkenburg 2007). Some studies e.g. (Eggermont et al. 2009), require the pain location to be confirmed by clinical examination. Some have also combined pain data with objective signs, e.g. joint stiffness or swelling (Davatchi et al. 2008).

Pain location definition makes a difference to findings of pain prevalence. The work of Pope et al. (1997) showed the importance of definition of location in shoulder pain and how they could alter the reported prevalence from 32% to 48%. The lowest figure was in response to the question “During the past month, have you experienced pain in your shoulders lasting more than 24 hours?”, the middle 2 definitions used manikin coding schedules with increasingly large areas considered as ‘shoulder’, and the highest figure was obtained using a pre-shaded manikin.

The definition of chronic pain requires a minimum period of pain duration to be stated. Some studies of chronic regional pain specify 3 months as chronic e.g. (Eggermont et al. 2009), others specify 6 months e.g. (Brattberg et al.1989). The ACR definition of CWP and fibromyalgia specifies 3 months (Wolfe et al. 1990).

In the PAALS study, a four section manikin was included in the baseline questionnaire (see Figures 4.3 and 4.4). This was assessed using a transparency overlay and scored according to the ACR definition of chronic widespread pain (see Figure 4.3) (Wolfe et al. 1990) and the “Manchester” manikin protocol (see Figure 4.4) (Hunt et al. 1999).
Figure 4.3 – ACR pain manikin

Wolfe et al 1990
Figure 4.4 – Manchester pain manikin

Hunt et al 1999
A question regarding chronicity “Thinking about this ache or pain, have you been aware of it for more than 3 months?” was also included in the questionnaire.

Psychological distress. In the PAALS baseline questionnaire, psychological distress was measured using the Hospital Anxiety and Depression (HAD) scale, which measures both anxiety and depression. The HAD is a useful measure for groups of participants with varying levels of co-morbidities because during its validation it was found that the scores obtained on both subscales were not affected by concurrent physical illness (Zigmond and Snaith 1983). The HAD was originally developed for non-psychiatric outpatient hospital clinic use, but is now frequently used in postal surveys. The validity of the Dutch version of the HAD was tested on people aged over 65 years (mean age 74.3 years). Correlations between both sub-scales (anxiety and depression) and also the HAD total, and age, were low (r=0.04, 0.15 and 0.06 respectively), and the dimensional structure of the HAD was similar in this group and a group of people aged 57 – 65 years (Spinhoven et al. 1997).

Two commonly used alternative measures of psychological distress are the SF-36 (which measures participants’ views of their health status) and the Beck Depression Inventory (BDI). A study of coronary angiography patients found that the HADS discriminated anxiety better than the Mental Health subscale of SF-36 (Ulvik et al. 2008). As its name implies, the BDI measures depression but not anxiety. A number of the questions in the BDI relate to physical problems such as fatigue and weight loss, which could have a number of causes, and this makes it less suitable for a study population who may have physical illnesses (Bowling 1997). A study concerning depression in hepatitis patients found that the HAD and BDI performed similarly, although neither agreed well with clinical diagnosis (Golden, Conroy, and O’Dwyer 2007).

A literature review found the HAD had good concurrent validity against Beck’s Depression Inventory, the General Health Questionnaire and Spielberger’s State-Trait Inventory in a variety of populations (men and women, different ages, patients and general populations) (Bjelland et al. 2002). The HAD was developed to be self-administered in the form of a questionnaire and is relatively brief, and measures both the presence and severity of anxiety and depression. The optimum cut-off for “caseness” for both anxiety and depression is generally taken as 8 or over (Bjelland et al. 2002).
Pain cognitions. Pain cognitions were assessed in the present study using two instruments, the Pain Catastrophising Scale (PCS) and the Brief Illness Perception Questionnaire (Brief IPQ).

Catastrophising has been found to be associated with responses to experimental pain stimuli as well as clinical pain, in chronic pain patients (Geisser et al. 2003) and in healthy volunteers (Goodin et al. 2009). The PCS is a 13-item single scale which can be split into 3 factors: rumination, magnification and helplessness. Rumination measures the extent to which the person thinks about pain repeatedly, magnification the degree to which they amplify concerns about the pain, and helplessness the extent to which they feel they have no control over the pain. The helplessness sub-scale incorporates aspects of locus of control and self-efficacy. Validation of this scale found that catastrophising increased perception of both experimental and clinical pain (Sullivan, Bishop, and Pivik 1995). This validation was carried out on college undergraduates and a group of patients with a mean age of 40 years, no validation has been carried out on older people. The PCS is the only measurement scale which specifically measures catastrophising related to pain and has been widely used in studies of both experimental and clinical pain.

The IPQ was developed from the work of Leventhal and others, and is the only instrument based on Leventhal’s self-regulatory model (SRM). The original scale had 5 sub-scales based on the 5 domains of beliefs identified by the SRM and was found to have good repeatability and internal consistency (Weinman et al. 1996). The Revised IPQ (IPQ-R) was produced to improve the scope of the tool and added several additional questions and 3 further sub-scales, the main addition being the concept of illness coherence, a measure of understanding of the condition. It was tested on groups of patients with a variety of medical condition, including chronic pain, and found to have good validity and reliability (Moss-Morris et al. 2002).

The Brief IPQ uses 8 questions (one per sub-scale) covering identity (how the person describes the illness), consequences (the expected effects), timeline (how long it will last), personal control (how the person believes they can control the illness), treatment control (how effective the person thinks treatments are), concern (how concerned they are about the illness), understanding (overall comprehension of the illness) and emotional response, as opposed to over 80 items in the full IPQ-R. This version showed good reliability and concurrent validity when compared to the IPQ-R (Broadbent et al. 2006). The groups on whom validity was tested were either out-patients or students with minor illnesses, and they were younger on
average than participants in the current study, e.g. myocardial infarction patients with mean age 54.7, type 2 diabetes patients with mean age 57.2 years. The brief IPQ has not specifically been validated on older people. However, a version of the IPQ-R which was adapted for use in people with subjective memory complaints (IPQ-M) was tested on people with a mean age of 74.3 years. It was found to have good test-retest reliability and good concurrent validity (Hurt et al. 2010).

A potential problem with this scale is that it uses one question per sub-scale, so any errors in answering one question will affect that sub-scale (van Oort, Schroder, and French 2011) but the effect of this on the scale’s validity is disputed (Broadbent, Kaptein, and Petrie 2011). However, its brevity makes it useful for inclusion in the present study, where the overall length of the questionnaire needs to be considered.

**Physical activity.** The present study used the Rapid Assessment of Physical Activity (RAPA) (Topolski et al. 2006) to measure levels of exercise activity. It is relatively concise, and although it was developed for and validated on adults over 50 years old, it has been evaluated by expert consensus as being suitable for use on all adults (Glasgow et al. 2005). It comprises 9 yes/no questions, 7 concerning aerobic exercise activity and 2 concerning strength and flexibility exercise activity. The RAPA aerobic scale is scored between 0-5, with 0 being sedentary and 5 most active. The RAPA strength and flexibility scale is scored between 0-3, with 0 indicating no strength or flexibility exercise, 1 indicating strength exercise, 2 indicating flexibility exercise, and 3 both types of exercise (Mayer et al. 2008).

Other measures of exercise activity include the Physical Activity Scale for the Elderly (PASE) which was developed to evaluate the total amount of physical activity carried out by an older (over 65), less active population. It has been validated against data from a movement sensor, and found to be repeatable (Washburn et al. 1993). However, a study which recruited adults aged 55 - 75 found that the PASE might not be accurate in subjects under the age of 65 (Washburn et al. 1999). Another measure is the Community Health Activities Model Program for Seniors (CHAMPS) which was designed for use in interventions aiming to increase activity levels, so focuses on the activity which the intervention was designed to change. It contains 41 questions and was validated on 65 - 90 year olds (Stewart et al. 2001).

The present study did not include occupational activity. The Office for National Statistics has produced a model which estimates age of withdrawal from the labour market, i.e. age at which a person is no longer working or actively seeking
employment. The most recent year for which this calculation has been carried out was 2008, at which time the estimated age of withdrawal was 61.5 years old for women and 64 years old for men (Office for National Statistics 2010a). Occupational activity data was thus likely to be absent in older participants, making comparisons across the age range impractical.

Sleep quality. Sleep problems have been found to predict the onset of CWP (Gupta et al. 2007), and restorative sleep to predict its resolution (Davies et al. 2008). The present study used the Estimation of Sleep Problems Scale in the baseline questionnaire. It is a concise instrument (4 items) whose sub-scales are all scored from 0-5, with 0 indicating good sleep quality and 5 the worst sleep quality, but covers the aspects of sleep found to be important in chronic pain (Jenkins et al. 1988), and has been used previously in studies on pain and sleep quality (Chiu et al. 2005; Davies et al. 2008; McCurry et al. 2011). The test-retest reliability and internal consistency were found to be good when tested on air-traffic controllers (age range 25 – 49 years) and post-surgery patients (age range 25 – 69 years) (Jenkins et al. 1988) but it has not been validated in older people. The Pittsburgh Sleep Quality Index (Buysse et al. 1989) is a commonly used instrument, but has 18 items and its length might affect return rates for the baseline questionnaire. The PSQI has been validated in distinguishing “good” and “poor” sleepers, and is repeatable (Buysse et al. 1989). The PSQI was tested in older men (mean age 76.4 years) and found to have adequate internal consistency, reliability and construct validity (Spira et al. 2012). It has been used previously in studies on pain and sleep (Miro et al. 2011). This is a more detailed instrument than the Estimated Sleep Problems Scale, with sub-scales on sleep quality (self-rated), sleep latency (how long it takes to get to sleep), sleep duration, sleep efficiency (hours slept divided by hours in bed), sleep disturbances, use of sleep medication and daytime dysfunction. These can also be combined into a global score. Sleep diaries, such as the Pittsburgh Sleep Diary (Monk et al. 1994), provide more detail about variation in sleep quality on consecutive nights but no overall average measure of sleep quality. More objective means of measuring sleep quality such as actigraphy or somnography would be too resource-intensive to be carried out in the present study.

Co-morbidities. The baseline questionnaire asked about current and past diagnoses of rheumatoid arthritis, osteoarthritis, any other form of arthritis, osteoporosis and diabetes. It also asked about falls and injurious falls in the past 12 months, fractures since the age of 25 and any current medications. There are many co-morbidities which could be considered, but the main purpose of cataloguing them
was to eliminate known likely causes of pain as confounders, so conditions commonly associated with pain were chosen. Osteoarthritis is generally accepted as the most common type of arthritis, although its prevalence is not well established, e.g. a review found prevalences between 0.5% and 36% (Kopec et al. 2007). Pain is part of the classification criteria for defining osteoarthritis e.g. of the hand (Altman et al. 1990), the hip (Altman et al. 1991) and the knee (Altman et al. 1986). Rheumatoid arthritis is less common than osteoarthritis, with a prevalence of between 0.5% and 1.1% in North America and Europe (Tobon, Youinou, and Saraux 2010). Pain, swelling or tenderness of joints is part of the classification criteria for rheumatoid arthritis (Aletaha et al. 2010). There are many other forms of arthritis. A study in the USA found that the prevalence of inflammatory back pain (which includes ankylosing spondylitis) in adults aged between 25 and 49 was 0.8% (Dillon and Hirsch 2011). Fractures can result in chronic pain, a study of people who had fractured the distal radius found that 11% had moderate to very severe pain 1 year post-fracture (Moore and Leonardi-Bee 2008). Osteoporosis makes fractures more common. A study reported that 11.6% of the population of Canada aged over 50 had osteoporosis, and that osteoporosis was associated with 60% of the fractures in people aged over 60 (Garriguet 2011). Falls occur in approximately a third of people over the age of 65 annually (Tinetti 2003) and can lead to painful injuries (Howe et al. 2011). A study in Spain found a prevalence of diabetes (almost half of which was previously undiagnosed) of 13.8% (Soriguer et al. 2012). Diabetes is associated with neuropathy, which can cause pain and also affect sensitivity to sensory stimuli. A list of medications can be used to identify any conditions being treated by drugs which have not already been mentioned; analgesics may alter the reporting of pain. A simple count total of medications being taken is an indication of the number of co-morbidities (Perkins et al. 2004).

**Short questionnaire**

The short questionnaire only asked participants about pain, and included the pain manikin (see Figures 4.3 and 4.4) and the question regarding chronicity, identically to the full baseline questionnaire.
4.3.3 Sub-study assessment

The Clinical Assessment Sheet used in recording the data from the PAALS physical examination is in Appendix II.

_Joints examination._ In addition to asking about its presence on the baseline questionnaire, a more detailed measure of osteoarthritis was carried out in the sub-study. An examination to indicate the likelihood of the presence of osteoarthritis (OA) in 3 common sites was performed. The sites were the hand, knee and hip. The features being investigated are defined in the ACR criteria for clinical diagnosis of OA hand (Altman _et al._ 1990), knee (Altman _et al._ 1986) and hip (Altman _et al._ 1991). This was amalgamated into a score of number of OA areas ranging from 0 – 5 (the hands count as one, left and right hip, left and right knee). In addition, participants were also asked whether they had been diagnosed with certain inflammatory joint conditions: ankylosing spondylitis, psoriatic arthritis, Reiter’s syndrome, or rheumatoid arthritis, either currently or in the past.

_Quantitative sensory testing (QST)._ The present study used the protocol devised by the German Research Network on Neuropathic Pain (Rolke _et al._ 2006b). The tests were all applied to 2 body sites: the thenar eminence, and the dorsum of the foot. The left hand was used, unless the participant currently had pain in the left hand, in which case the right hand was used. If the participant had pain in both hands, the left hand was used. Similarly for the foot, the right foot was used unless the participant currently had pain in it, in which case the left foot was used. If the participant had pain in both feet, the right foot was used. Participants were randomised to be tested on the hand or foot first, to minimise the possible impact of learning effects.

Informed consent was obtained from sub-study participants at the time of their recruitment, and again in writing at the time of the sub-study examination. They were given the opportunity to ask questions, and it was made clear that they could withdraw at any time, including during the examination.

The following definitions are used in describing the sensory tests. Detection threshold measurements are the lowest level of a stimulus which can be detected. Pain thresholds are the lowest level of a stimulus which is perceived as painful. A limen is the smallest difference between two stimuli which can be detected. Allodynia is the perception of a non-noxious stimulus as painful.
The participant was seated for tests on the hand, and lying down or seated with the foot elevated for tests on the foot. The room was kept at a comfortable temperature and disturbances and interruptions kept to a minimum. The participant closed their eyes or looked the other way during tests. The instructions given were in accordance with the Standardised Operating Procedure. For the tests carried out in accordance with the protocol compiled by the German Research Network on Neuropathic Pain, the instructions were as per the published protocol, and have been included in Appendix VI (Rolke et al. 2006b). Instructions were repeated if the participant appeared unclear, or if they requested it.

Thermal tests were all done using the Medoc Thermal Sensory Analyser (TSA II) shown in Figure 4.5. The tests were carried out in the following order: cool detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL) which is detection of alternating cool and warm stimuli, and if these were incorrectly identified as warm this counted as paradoxical heat sensation (PHS) which were recorded, cold pain threshold (CPT) and heat pain threshold (HPT). For safety reasons, a maximum temperature of 50°C and a minimum temperature of 0°C were programmed into the TSA II.

Figure 4.5 – Medoc TSA-II
The block (thermode), which measured 30mm x 30mm, was placed on the hand or foot. It had a Peltier element on the face in contact with the skin, which was capable of changing temperature at a pre-defined rate. A control button was given to the participant. A temperature which the participant felt to be neutral was ascertained, and this was set as the baseline temperature for the tests. For all the thermal tests, the stimuli were ramped at 1°C/s, once the button had been pressed the thermode returned to the baseline temperature at 10°C/s. A method of limits was used for the thermal QST measurements. For the CDT the participant was asked to press the button as soon as the slightest change to cool from baseline was felt. This was repeated twice, each time after a 5 second pause. When measuring WDT the instruction was to press the button when the slightest change to warm from baseline was felt, which was also carried out three times. For the TSL, participants were asked to press the button when a change in temperature was felt, and to say whether it felt warm or cool (PHS). This occurred 6 times, 3 warm and 3 cool. For the CPT and WPT the instruction was to press the button when the first painful sensation was felt, both these were carried out 3 times. A graphical representation of these tests can be seen in Figure 4.10.

Cool detection threshold (CDT) and warm detection threshold (WDT) were calculated by taking the arithmetic mean of the three measurements, then deducting the baseline temperature. Thermal sensory limen (TSL) was calculated as the arithmetic mean of the five differences between the six measurements (all expressed as positive numbers). The paradoxical heat sensation (PHS) variable comprised the number of times the participant incorrectly identified warm or cool stimuli during the TSL procedure. Cold pain threshold (CPT) and heat pain threshold (HPT) were calculated by taking the arithmetic mean of the three measurements.

Mechanical testing used a modified method of limits. Mechanical detection threshold (MDT) testing used a set of von Frey filaments (see Figure 4.6). These were optical fibre filaments set in a plastic handle. Each fibre was of such a diameter and length that it bent at a specific pre-determined force. When applied to the skin at 90°, this is the force which was delivered. There were 12 filaments in total, with bending forces of 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, 64.0, 128.0, 256.0 and 512.0 mN. The contact area of each filament was 0.5mm diameter and rounded to avoid sharp edges which could stimulate nociceptors. The filaments were applied in 5 series of ascending and 5 series of descending stimulus
intensities. The ascending series were terminated when the participant could feel the stimulus (the force was recorded), the descending series were terminated when the stimulus could not be felt (the force was also recorded). This is shown graphically in Figure 4.10.

**Figure 4.6 – von Frey filament**

![The author having a 512 mN von Frey filament applied to the left thenar eminence.](source: original)

Mechanical pain threshold (MPT) testing used a set of weighted punctate probes (see Figure 4.7). These comprised blunt-ended pins with a weight attached, housed in a tube in which they could freely slide. When applied to the skin at 90° the full weight was applied. Each probe had a flat contact area 0.2mm in diameter. There were a set of 7 probes with applied forces of 8, 16, 32, 64, 128, 256 and 512 mN. The probes were applied in 5 series of ascending force and 5 series of descending force. The ascending series were terminated when the participant reported pricking or stinging sensations (the force was recorded), the descending series were terminated when pricking or stinging sensations could not be felt (the force was also recorded). This is shown graphically in Figure 4.10.
Mechanical pain sensitivity (MPS) used the same punctate probes described above and shown in Figure 4.7. Participants were asked to rate each stimulus on a 0 – 100 numerical rating scale, 0 indicating “no pain” and 100 the “most intense pain imaginable”. They were applied in a pseudo-random order, to minimise effects of stimulus order on the rating given, with each stimulus being presented a total of 5 times. There was an inter-stimulus interval of 10 seconds to minimise wind-up. Dynamic mechanical allodynia (ALL) was tested at the same time, in that 3 innocuous stimuli were also presented 5 times each, interspersed between the punctate stimuli. These were: a cotton wisp exerting a force of approximately 3 mN, a cotton bud fixed to an elastic strip exerting a force of approximately 100 mN, and a paint brush exerting a force of approximately 200 – 400 mN. Each innocuous stimulus was applied in a stroke approximately 2 cm in length across the skin, and once again there was an inter-stimulus interval of 10 seconds. The participant was asked to rate these using the same numerical rating scale. This is shown graphically in Figure 4.10. The order in which the stimuli were presented is shown on the Clinical Assessment Sheet in Appendix II.

The wind-up ratio (WUR) test used the 256 mN punctate probe. Participants were asked to rate a single punctate stimulus using the same 0 and 100 numerical rating scale as previously, then shortly afterwards to rate the mean of a train of 10
identical punctate stimuli applied at a rate of 1 per second within an area of 1 cm². This was repeated a total of 5 times and is shown graphically in Figure 4.10.

Vibration detection threshold (VDT) was the only disappearance threshold. It used a 64 Hz Rydel-Seiffer tuning fork (see Figure 4.8). This has a specially designed scale attached to the forks to allow vibration amplitude to be assessed on an arbitrary scale from 0 to 8 (see Figure 4.9). When the tuning fork is in motion, the triangle appears as two triangles, and the scale can be read at the point of intersection. The tuning fork was applied to two bony points close to the sites of the other QST tests: the head of ulna (wrist) and the medial malleolus of the ankle, in each case on the same side of the body as the other tests. The participant was asked to indicate when they could no longer feel vibration. The vibratory stimulus was applied 3 times. This is shown graphically in Figure 4.10.

Mechanical detection threshold (MDT) was calculated by taking the geometric mean of all ten recorded stimuli (five “felt” and five “not felt”). Missing values (e.g. because all filaments were felt) were ignored and the mean of the remaining values calculated. Mechanical pain threshold (MPT) was calculated by taking the geometric mean of all ten recorded stimuli (five “blunt” and five “sharp”). Missing values (e.g. because all punctate probes were “blunt”) were ignored and the mean of the remaining values calculated. Mechanical pain sensitivity (MPS) was calculated by taking the arithmetic mean of the numeric ratings for all 35 applications of punctate probes, i.e. five applications of each of the seven probes. Provided there was at least one rating for each punctate probe, this value was calculated. Dynamic mechanical allodynia (ALL) was calculated by taking the arithmetic mean of the numeric ratings for all 15 applications of the non-noxious stimuli, i.e. five applications of each of the three stimuli. Provided there was at least one rating for each stimulus, this value was calculated. Wind-up ratio (WUR) was calculated by taking the arithmetic mean of the five numeric ratings for each train of 10 stimuli and dividing it by the arithmetic mean of the five numeric ratings for each single stimulus. Vibration detection threshold (VDT) was calculated by taking the arithmetic mean of the three measurements.
Figure 4.8 – Rydel-Seiffer tuning fork

A volunteer having the Rydel-Seiffer tuning fork applied to the left head of ulna.

(source: original)

Figure 4.9 – tuning fork measurement scale

(US Neurologicals 2010)
Figure 4.10 – QST battery

**“A”** depicts cold detection threshold x 3, warm detection threshold x 3, thermal sensory limen x 6, cold pain threshold x 3, heat pain threshold x 3, and paradoxical heat sensations, where cool is incorrectly identified as warm.

**“B”** depicts mechanical detection threshold, 5 descending intensity and 5 ascending intensity series of stimuli.

**“C”** depicts mechanical pain threshold, 5 ascending intensity and 5 descending intensity series of stimuli.

**“D”** depicts mechanical pain sensitivity where stimuli of fixed intensity are pain rated between 0 and 100, and allodynia testing, where innocuous stimuli are pain rated between 0 and 100.

**“E”** depicts wind-up ratio, where a single stimulus and series of 10 stimuli are pain rated between 0 and 100, repeated 5 times.

**“F”** depicts vibration detection threshold at 64 Hz, rated between 0 and 8.

*(Rolke et al. 2006b)*

*Diffuse Noxious Inhibitory Controls (DNIC)* There is no widely accepted protocol for testing DNIC. A test stimulus is required, as is a conditioning stimulus to be applied.
to another part of the body. In the present study, mechanical wind-up applied to the thenar eminence of the hand used for the other QST procedures was chosen as the test stimulus. Punctate stimuli have been used previously as a test stimulus for DNIC (Pud, Sprecher, and Yarnitsky 2005). The conditioning stimulus was heat at the level of the participant’s HPT applied to the thenar eminence of the opposite hand. Thermode-applied heat pain has been used previously as a DNIC conditioning stimulus (Lautenbacher and Rollman 1997). The 256 mN punctate probe (see Figure 18) was used. The painfulness of a single punctate stimulus, then a train of 10 stimuli were rated using a 0 – 100 numerical rating scale, as for the WUR test. The test stimulus was applied once before and once during the application of the conditioning stimulus.

To calculate the DNIC variable, both wind-up ratios were calculated as previously, by taking the arithmetic mean of the five numeric ratings for each train of 10 stimuli and dividing it by the arithmetic mean of the five numeric ratings for each single stimulus. The ratio obtained without a concurrent conditioning stimulus was then divided by the ratio obtained with a concurrent conditioning stimulus, so that a resulting number greater than one indicated a reduction in wind-up when the conditioning stimulus was present (positive DNIC).

Tender point examination. The locations of the tender points examined, and the method (manual pressure using the pulp of the thumb or fingers to 4 kg force) are those detailed in the American College of Rheumatology (ACR) definition of fibromyalgia (Wolfe et al. 1990). A report of pain from the participant, or a spontaneous flinch or vocalisation, was classified as a tender point, just pressure or discomfort was not. The number of test sites which the participant reported to be painful was summated as the “tender point count” variable. Figure 4.11 shows a tender point being tested. As well as identifying participants with fibromyalgia, this examination tests sensitivity to deep pressure.

An alternative way to measure sensitivity to deep pressure is using an algometer. This is a device in which a short shaft is connected to a force meter, pressure being applied through a rubber pad on the end of the shaft. Pressure pain threshold using an algometer is the method of measuring sensitivity to deep pressure specified in the German Research Network on Neuropathic Pain’s protocol (Rolke et al. 2006b). This technique was not used in the current study for two reasons. The first was the difficulty for the assessors in achieving a force of 20kg (the maximum allowed force for safety reasons) when testing participants who were not very sensitive to
pressure pain. The second reason was that some of the very elderly participants might have fragile skin, and a thumb is less likely to damage the skin than an algometer.

Figure 4.11 – Tender point examination

The author carrying out a tender point examination on a colleague.

(source: original)

4.3.4 Sub-study questionnaire

Sub-study participants were asked to complete a short questionnaire at the time they attended for the sub-study assessment (see Appendix IV), which included the following.

Current pain. The measures of pain status in the baseline questionnaire (see section 4.3.2) were repeated because the participant’s pain might have changed between completing the questionnaire and attending the sub-study assessment.
For some participants the interval between completing the baseline questionnaire and attending for sub-study assessment was several months. During that interval changes may have occurred, for example plastic changes in pain-processing areas of the central nervous system (Doubell, Mannion, and Woolf 1999). These changes could affect QST measures (Shy et al. 2003) and also alter the perception of clinical pain.

**Sleep.** Sub-study participants were asked to complete the Pittsburgh Sleep Quality Index. This has been discussed in section 4.3.2. The length of the instrument (18 items) was less relevant as part of the shorter, sub-study questionnaire than would have been the case in the baseline questionnaire.

### 4.4 Assessor training

The assessors carrying out the sub-study data collection received training.

**Recruitment.** Telephone scripts for first and second telephone calls were prepared as part of the standardised operating procedure (SOP). Recruitment was carried out by sub-study assessors, as they were best placed to answer any queries about the procedures. Each assessor practiced using these scripts by “recruiting” colleagues in the PAALS project team before contacting participants.

**Joints assessment.** All assessors received training from a Consultant Rheumatologist in assessing the joints in the hands, knees and hips in accordance with the ACR criteria (Altman et al. 1986; Altman et al. 1990; Altman et al. 1991) for each condition, and practiced the examination on volunteers. They attended at least one clinic with the same Consultant Rheumatologist, where they were allowed (with the patient’s consent) to examine osteoarthritic joints under his guidance.

**Tender point examination.** Assessors received training in locating tender points from a Consultant Rheumatologist, and from the Principal Investigator of the PAALS project, who was experienced in carrying these out. This was followed up using written descriptions (Wolfe et al. 1990) and diagrams of the locations of the points. The assessors practiced applying the correct force (4 kg) with the thumb using a calibrated algometer. The entire tender point examination was practiced on volunteers before being carried out on participants.
QST. The QST procedures were described by the German Network on Neuropathic Pain in their published protocol (Rolke et al. 2006b). This protocol was followed as closely as possible. Assessors practiced on volunteers before carrying out the assessment on participants. A professional contact from Oxford University, who was trained by German Research Network for Neuropathic Pain researchers at their centre in Kiel, and was experienced in using these techniques, visited and observed this practice and provided feedback.

4.5 The author’s contribution to the study

The author of the present study was one member of the PAALS study team. Tasks concerned with data collection were shared between the team members. The author contributed to questionnaire mailing, coding of pain manikins and manual data input, but was not involved in scanning of questionnaires. The author contributed to recruiting sub-study participants and carried out 108 of the 290 sub-study assessments.

With regard to data analysis, the author carried out the analyses in Chapters 5 and 6. The analyses in Chapters 7 and 8 were originally done by Matthew Mulvey, but required substantial amendment by the author when the decision was made to use imputed data. The survey weighting calculations were done by Matthew Mulvey, and the data imputation by Amir Rachid.

4.6 Reliability

Reliability is also called repeatability, and it is the ability of a measurement technique or instrument to make the same measurement consistently. It may be divided into inter-rater reliability, where several different raters make the same measurement within a relatively short space of time, and test-retest reliability, where the measurement is repeated after a certain period of time. The latter incorporates two concepts which cannot easily be separated, which are variability of results within a subject or group of subjects, and variability of measurements done by a single rater (intra-rater reliability).

In the present study, test-retest reliability testing was carried out on tender point examination and QST, and inter-and intra-rater reliability testing on manikin coding.
These results are reported in the rest of this section, along with published reliability data for comparison.

4.6.1 Pain manikin coding

Cohen’s kappa (κ) is a measure of agreement between raters for categorical data based upon the number of agreements and disagreements of category allocation. κ > 0.2 is considered acceptable, κ > 0.4 moderate, κ > 0.6 good and κ > 0.8 very good (Walker and Almond 2010). A study on inter-rater reliability of scoring pain manikins by 8 trained, non-clinical staff found a Cohen’s kappa > 0.60, which indicates good reliability (Lacey et al. 2005).

In the present study, manikin coding reliability was checked using a set of 20 manikins with shading on them, which had previously been scored in a standardised way (the “gold standard”) using the ACR (Wolfe et al. 1990) and Manchester (Hunt et al. 1999) coding schemes. Each of the 4 raters scored all 20 manikins in the morning and afternoon of the same day, which allowed inter-rater (and against the gold standard) and test-retest reliability to be ascertained. This testing procedure was repeated at regular intervals, before and during the data collection phase, a total of 4 times. As Cohen’s kappa is used with categorical variables, coding was divided into regional and widespread pain by both ACR and Manchester definitions (there were no blank test manikins so no “no pain” category).

For clarity, only the lowest κ scores in each category are given in Table 4.2.
### Table 4.2 – κ scores for pain manikin coding

<table>
<thead>
<tr>
<th>Date</th>
<th>Inter-rater*</th>
<th>Against gold standard*</th>
<th>Intra-rater*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>κ</td>
<td>p</td>
<td>κ</td>
</tr>
<tr>
<td>June 2010</td>
<td>0.615</td>
<td>0.0014</td>
<td>0.615</td>
</tr>
<tr>
<td>August 2010</td>
<td>0.828</td>
<td>0.0001</td>
<td>0.828</td>
</tr>
<tr>
<td>October 2010</td>
<td>0.828</td>
<td>0.0001</td>
<td>0.828</td>
</tr>
<tr>
<td>January 2011</td>
<td>0.828</td>
<td>0.0001</td>
<td>0.828</td>
</tr>
</tbody>
</table>

* Lowest score given for each category

Each rater was compared to himself at both time points (intra-rater), against the gold standard, and against the other raters at each time point, as a whole group and pair-wise (inter-rater). It can be seen that the κ scores are all either good or very good by the definitions already given.

### 4.6.2 Tender point examination

Cronbach’s alpha (α) is a measure of internal consistency which was originally developed to evaluate the coherence of a questionnaire measurement scale or subscale. It is used for ordinal level data, i.e. categories which can be placed in ascending or descending order. α ≥ 0.6 is considered acceptable, α ≥ 0.7 fairly good and α ≥ 0.8 good (Walker and Almond 2010). It is sometimes used for test-retest and inter-rater reliability, but its use in this way could be disputed as this is not what it was designed to do. A study on test-retest and inter-rater reliability of tender point examination (as per the ACR criteria) found Cronbach’s α of 0.70 – 0.71 for inter-rater and α = 0.72 – 0.76 for test-retest (over a period of 1 week) reliability (Jacobs et al. 1995). The authors expressed the opinion that manual tender point examination appeared to be no less reliable than assessment using an algometer.
In the present study, tender point examination reliability was measured on 5 occasions before and during sub-study data collection. Four volunteers were each assessed by each of the 3 raters, on 2 consecutive days, to allow intra-rater and inter-rater reliability to be determined. Cohen’s kappa was calculated for each rater between the two days, and between raters on each of the days, and the lowest score obtained in each case is given in Table 4.3. In addition, an independent observer was present for at least one tender point examination by each rater, to ensure that the technique used was in accord with the Standardised Operating Procedure.

Table 4.3 – κ scores for tender point examination

<table>
<thead>
<tr>
<th>Time point</th>
<th>Inter-rater*</th>
<th></th>
<th>Intra-rater*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>κ</td>
<td>p</td>
<td>κ</td>
<td>p</td>
</tr>
<tr>
<td>May 2010</td>
<td>0.306</td>
<td>0.0007</td>
<td>0.358</td>
<td>0.0001</td>
</tr>
<tr>
<td>June 2010</td>
<td>0.091</td>
<td>0.1391</td>
<td>0.327</td>
<td>0.0001</td>
</tr>
<tr>
<td>Early October 2010</td>
<td>0.417</td>
<td>0.0000</td>
<td>0.403</td>
<td>0.0000</td>
</tr>
<tr>
<td>Late October 2010</td>
<td>0.280</td>
<td>0.0000</td>
<td>0.278</td>
<td>0.0000</td>
</tr>
<tr>
<td>February 2011</td>
<td>0.270</td>
<td>0.0004</td>
<td>0.457</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

*Lowest score given for each category

It can be seen from Table 4.3 that all but one of the scores were acceptable (>0.2) and that the p values support the fact that the level of agreement was unlikely to be due to chance. The low inter-rater score at time point 2 was between an experienced rater and one who had just started training. This time point was before any participant assessments had taken place. Further training was undertaken and reliability was reassessed prior to the inexperienced rater assessing participants.
4.6.3 QST

Most QST measures have previously been tested for reliability. Table 4.4 shows some of the reliability studies undertaken on the measures used in the present study, on healthy subjects. It can be seen that a variety of statistical tests were used.

Some studies using QST have included a familiarisation protocol to minimise the difference between first and subsequent testing. However, one study which compared reliability between groups with and without familiarisation found no difference (Wasner and Brock 2008).

The two oldest papers (Yarnitsky et al. 1995; Yarnitsky and Sprecher 1994) reported different data from the same trial. They both reported repeatability between days, not inter- or intra-rater reliability. The sample size was quite large and the subjects were of a good range of ages. The statistical measure reported was Repeatability Coefficient (which they denoted r) which is the value below which the difference between two measurements will lie with a probability of 0.95 (Bruton, Conway, and Holgate 2000). As this is not a frequently used measure it is difficult to compare these results to other studies of reliability. The authors themselves indicated that they found heat pain threshold, cool detection threshold and warm detection threshold repeatable only at the foot, not the thenar eminence.

Two studies used Pearson’s product moment correlation coefficient as the reliability statistic (Agostinho et al. 2009; Geber et al. 2007). Pearson’s product moment correlation coefficient r (also called simply correlation coefficient) is often used to show the degree of inter-relatedness of 2 sets of paired variables, and measures how well a straight line would fit a graph of the points. It may be acceptable for test-retest or inter-rater reliability, provided there is a large enough sample (> 30). As a general rule, r ≥ 0.6 is considered acceptable, r ≥ 0.7 fairly good and r ≥ 0.8 good (Walker and Almond 2010). However, correlation coefficients give no indication of the slope of the line, i.e. whether the repeated measurements relate to one another in a ratio of 1:1 or some other proportion, so it should probably not be used for reliability testing (Bruton, Conway, and Holgate 2000). One study reported scores for r > 0.80 (considered good) for both intra- and inter-rater reliability, although this is a mean for several QST variables, and there were only 18 test subjects (Geber et al. 2007). The other study which reported correlation coefficient (Agostinho et al. 2009) reported repeatability between test days, not raters, and obtained much lower values for r, most below what would be considered acceptable (>0.60). The authors
considered that the between-days variation was small compared to the variability within each measure.

Spearman’s rho ($\rho$) is the non-parametric equivalent of Pearson’s $r$ and is used on ordinal data (Walker and Almond 2010). It is scored between 1 (perfect positive agreement) and -1 (perfect negative agreement) and, like Pearson’s $r$, scores above 0.6 (or below -0.6) are taken to indicate acceptable correlation. One study which used Spearman’s $\rho$ found good reliability for vibration and warm detection thresholds, but poor for cool detection threshold (Lowenstein, Jesse, and Kenton 2008).

The two remaining studies used intra-class correlation coefficient (ICC) as the measure of reliability (Moloney et al. 2011; Wasner and Brock 2008). ICC is defined as between-subjects variability divided by between-subjects variability plus error (Weir 2005). This measure is influenced by both variability of the variable within the sample and sample size, such that large variability and a large sample size will give a smaller ICC. This means that ICC cannot easily be compared between measures. An example of this is intra- and inter-rater ICC for cold pain threshold (CPT) in the study of Moloney et al. There is no a priori reason why CPT should be more reliable than cold or warm detection threshold, or heat pain threshold, except that the high variability between subjects of CPT masks any variation in measurement between raters or at different times of testing. The authors of one study claimed their figures showed “good inter-session reproducibility” (Wasner and Brock 2008). The authors of the other study (Moloney et al. 2011) produced a compound measure to overcome some of the problems associated with ICC. They combined ICC with coefficient of variation (CV) and mean intra-individual difference (MID) to assess response stability, and from this compound measure rated intra- and inter-rater reliability as between fair and good.
### Table 4.4 – QST reliability

<table>
<thead>
<tr>
<th>REFERENCE</th>
<th>SUBJECTS</th>
<th>QST MODES TESTED</th>
<th>METHODOLOGY</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Geber et al. 2007)</td>
<td>18 healthy subjects aged 21-58</td>
<td>All in German Research Network protocol.</td>
<td>Testing left and right cheek, dorsum of hand, dorsum of foot.</td>
<td>Mean Pearson’s correlation $r$ over all parameters Inter-observer $r = 0.86$ Intra-observer $r = 0.84$</td>
</tr>
<tr>
<td>(Lowenstein, Jesse, and Kenton 2008)</td>
<td>27 healthy women mean age 40.</td>
<td>Cold (CDT), warm (WDT) and vibration (VDT) detection thresholds.</td>
<td>Non-dominant volar forearm. Retested after 1 week.</td>
<td>Spearman’s correlation $\rho$ between days (not inter-rater) VDT: $\rho = 0.83$, $p = 0.0001$ WDT: $\rho = 0.73$, $p = 0.0001$ CDT: $\rho = 0.47$, $p = 0.0037$</td>
</tr>
<tr>
<td>(Wasner and Brock 2008)</td>
<td>20 healthy subjects mean age 35.4</td>
<td>Hot (HPT) and cold (CPT) pain thresholds using German Research Network protocol.</td>
<td>Testing at dorsum of hand. Retest after 21 days.</td>
<td>Intra-rater ICC: CPT females = 0.782, males = 0.418; HPT females = 0.952, males = 0.845.</td>
</tr>
<tr>
<td>(Agostinho et al. 2009)</td>
<td>39 healthy and 36 chronic pain patients (only healthy subjects reported on here)</td>
<td>Cold and warm detection (CDT/WDT) and pain (CPT/HPT) thresholds using German Research Network protocol.</td>
<td>Testing at thenar eminence repeated on 2 different days.</td>
<td>Mean Pearson’s correlation $r$ between days (not inter-rater) CDT: $r = 0.43$, $p &gt; 0.05$ WDT: $r = 0.49$, $p &gt; 0.05$ CPT: $r = 0.62$, $p &gt; 0.05$ HPT: $r = 0.51$, $p &gt; 0.05$</td>
</tr>
<tr>
<td>(Moloney et al. 2011)</td>
<td>22 healthy subjects aged 23-50</td>
<td>Cool (CDT) and warm (WDT) detection and cold (CPT) and heat (HPT) pain thresholds.</td>
<td>Dorsum of hand tested by 2 raters on each of 2 occasions 2 weeks apart.</td>
<td>Intra-rater ICC: CDT 0.33, WDT 0.30, CPT 0.87, HPT 0.39 Inter-rater ICC: CDT 0.27, WDT 0.38, CPT 0.88, HPT 0.52</td>
</tr>
</tbody>
</table>

*Here $r$ is repeatability, defined such that there is 95% confidence that two measurements on the same subject would differ by less than $r$. 

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In summary, there is no consensus as to which is the preferred measure for QST reliability, but all the measures have disadvantages to their use. There appears to be a degree of support for reliability in thermal QST, with CPT being the most problematic due to its wide inter-individual variability. There has been limited reliability testing of mechanical QST in healthy individuals, with the study of Geber et al giving only a blanket reliability figure which covers both thermal and mechanical stimuli.

A reliability test of QST was performed as part of the sub-study of the present study. Each of 4 healthy volunteers (3 female, 1 male, age range 22 – 53 years) was assessed by each of the 3 assessors on 2 consecutive days. A short QST battery was used, which tested each technique to be used: warm detection (WDT), cool detection (CDT), cold pain (CPT) and heat pain (HPT) thresholds, mechanical (MDT) and vibration (VDT) detection thresholds, and mechanical wind-up ratio (WUR). Spearman’s rho for between-days variation is given in Table 4.5 (there were insufficient subjects to stratify by rater).

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \rho )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cool detection threshold</td>
<td>0.267</td>
<td>0.402</td>
</tr>
<tr>
<td>Warm detection threshold</td>
<td>0.640</td>
<td>0.025</td>
</tr>
<tr>
<td>Cold pain threshold</td>
<td>0.910</td>
<td>0.0000</td>
</tr>
<tr>
<td>Heat pain threshold</td>
<td>0.615</td>
<td>0.033</td>
</tr>
<tr>
<td>Mechanical detection threshold</td>
<td>0.654</td>
<td>0.021</td>
</tr>
<tr>
<td>Wind-up ratio</td>
<td>0.637</td>
<td>0.026</td>
</tr>
<tr>
<td>Vibration detection threshold</td>
<td>0.578</td>
<td>0.049</td>
</tr>
</tbody>
</table>

It is likely that \( \rho \) for CDT is particularly low because of the small amount of variability between young, healthy subjects. Conversely, CPT, which is likely to have the largest variability, has the highest value of \( \rho \). These figures are similar to those
obtained by other researchers (see Table 4.4) although direct comparisons are difficult when different measures are used.

As an additional reliability check, an independent observer was present for at least three sub-study assessments by each rater, to ensure that the technique used was in accord with the Standardised Operating Procedure.

4.6.4 Osteoarthritis joints assessment

As has already been mentioned, all assessors received training from a Consultant Rheumatologist in assessing the joints in the hands, knees and hips in accordance with the ACR criteria (Altman et al. 1986; Altman et al. 1990; Altman et al. 1991) for each condition, and practiced the examination on volunteers. They attended at least one clinic with the same Consultant Rheumatologist, where they were allowed (with the patient’s consent) to examine osteoarthritic joints under his guidance.

It was not practicable to carry out reliability testing for the joints assessment due to lack of access to suitable models. A range of scores is required in order to carry out reliability testing, not simply all zeroes. Most people do not have osteoarthritis at these sites (Zhang and Jordan 2008), so any potential reliability models would have to be screened first and then called back. This would have required a major amendment to the protocol. It is possible that the participants would decline to take part in a further part of the study. It would also require the sub-study facility and all the assessors to be free on several occasions, disrupting the arrangement of sub-study appointments, so it was not carried out.

4.7 Ethical approval

It is mandatory for health research on human subjects to have ethical approval. The PAALS study was approved by North West 8 Research Ethics Committee (REC) – Greater Manchester East and given the reference number 10/H1013/29. As the study was sponsored by the University of Manchester, it also obtained approval from the University’s Senate Committee on the Ethics of Research on Human Beings. Most of the sub-study assessments were conducted on NHS premises. Central Manchester University Hospitals NHS Foundation Trust R&D Committee gave authorisation for the research to be carried out on Trust premises, and
honorary contracts were issued to sub-study assessors to allow them to work in Trust premises.

4.8 Data analysis

All the statistical analyses reported here were done using Stata version 11 (StataCorp 2009a), and were done on imputed, survey weighted data (see sections 4.7.1 and 4.7.2). Results were considered to be statistically significant where p ≤ 0.05 or if the 95% confidence intervals for β coefficients did not include zero. Corrections for multiple statistical tests used Bonferroni.

4.8.1 Sample weighting

The principles of sample weighting are discussed in Appendix VI. In the regression analyses in Chapters 7 and 8, weighting was used to apply data obtained from the sub-study participants to the whole PAALS cohort. All participants were categorised according to age group (divided into 3 quantiles), sex and pain status (“no pain”, “some pain” or CWP by ACR definition (Wolfe et al. 1990)) at baseline. These factors were chosen as a basis of categorisation because the sub-study participants were selected from the whole cohort stratified by pain status, and age and sex are known to affect many of the factors included in the present study (see sections 2.4, 2.5 and 2.9). These 3 factors led to 18 categories. The sub-study participants’ data was weighted according to how many participants in the whole baseline cohort shared those characteristics (pain status, age group and sex). The sample weights used are given in Appendix VI.

4.8.2 Multiple imputation

Imputation was carried out because the level of missing data meant that relatively few participants with complete data were available for use in the analyses. Of the sub-study participants, only 41% had full data from baseline and sub-study data collection. If the analyses had been carried out using complete cases only, 59% of the participants would have been excluded. The number of missing data items per participant was typically not large, and over 90% of sub-study participants had 4 or fewer missing data items.
The analysis in Chapters 7 and 8 was carried out on imputed data. Imputation was carried out using the chained equation technique (see Appendix IX). Sixty data sets were imputed for the analyses in Chapters 7 and 8 containing only those variables used in those analyses. Two categorical variables (PHS and RAPA strength and flexibility) were dropped from the model due to problems with perfect prediction in the imputation (see Appendix IX).

4.8.3 Principal components analysis

The aim of principal components analysis (PCA) is to consolidate a large number of related variables into as small a number of principal components as possible, whilst still explaining as much of the variance in the model as possible. This is discussed in Appendix VII.

Each component comprised the sum of all the included variable values, each variable being multiplied by a coefficient, of the format

\[ \text{component} = (\text{variable}_1 \times \text{coefficient}_1) + (\text{variable}_2 \times \text{coefficient}_2) + \ldots \]

Rotation of orthogonal axes using the Stata command “rotate, varimax” made the coefficients of variables more distinct, i.e. it made the coefficients as large as possible or as small as possible (see Appendix VII). This meant that each component comprised a large proportion of some variables and a small proportion of others, which made interpretation easier.

If all the components were included in a model, this would include all the information in the original variables. However, reducing the number of components makes interpretation of the final model easier. The aim was to choose as few components as was reasonable whilst retaining as much of the information in the original variables as possible. There are two methods for choosing a cut-off. One is to specify an eigenvalue (e.g. 1) above which components will be included. The other is to use parallel analysis, which allows the effects of random noise within the data to be taken into account (see Appendix VII). The latter was done in the present study, using the Stata command “fapara, pca reps (10)”.

PCA was carried out using cool and warm detection thresholds, thermal sensory limen, paradoxical heat sensations, cold and heat pain thresholds, mechanical detection and pain thresholds, sensory response function, allodynia, wind-up ratio,
and vibration detection threshold, all for hand and foot and DNIC. The components were analysed in a linear regression model to determine which of them were statistically significantly related to Manchester pain count.

4.8.4 Descriptive statistics

Descriptive statistics in the form of percentages in each category, or medians and 95% confidence intervals for numerical variables, were compiled to compare first-time responders to the baseline questionnaire with reluctant responders, i.e. those requiring reminders. They were compared on a number of socio-demographic, behavioural and psychological variables as well as pain status (“no pain”, “some pain” or CWP). The two groups were compared using Kruskal-Wallis or \( \chi^2 \) tests as appropriate. Participants in the sub-study were compared to those who had declined to be in the sub-study using the same set of variables.

Data for each QST variable was reported separately for groups according to pain status (“no pain”, “some pain” or CWP), sex, age (65 and under, over 65 years), and by categories of socio-demographic variables. The measurements were reported as medians and 95% confidence intervals, and differences between the groups were compared using Kruskal-Wallis tests.

4.8.5 Data analysis models

Imputation and sample weighting were carried out as detailed in sections 4.7.2 and 4.7.1 above. Linear regression was carried out for each predictor variable against the outcome of Manchester pain count. The predictor variables were: age, sex, marital status, having children, age left education, social deprivation, physical activity, sleep quality, smoking, drinking alcohol, anxiety (HAD), depression (HAD), pain cognitions (PCS and IPQ), tender point count, DNIC, and the QST variables cold and warm detection thresholds, thermal sensory limen paradoxical heat sensations, cold and heat pain thresholds, mechanical detection and pain thresholds, sensory response function, allodynia, wind-up ratio, and vibration detection threshold, all for hand and foot. Multiple logistic regression was carried out on the same set of predictor variables against the categorical outcome of “no pain”, “some pain” or CWP. This corresponds to Model 1 in Figure 4.12.
The regression analyses were repeated on all the variables listed above except age and sex, and each relationship was adjusted for age and sex. Finally, the regression was repeated for groups of variables, namely socio-demographic, behavioural, psychological, thermal QST and mechanical QST, and each variable was adjusted for the other variables in its group, plus age and sex (referred to as “fully adjusted”). This corresponds to Model 2 in Figure 4.12.

The results of the linear regression models were reported as β coefficients and 95% confidence intervals, and a relationship was considered to be statistically significant if the confidence intervals did not include “0”. The results of the multiple logistic regression were reported as relative risk ratios and 95% confidence intervals, and a relationship was considered statistically significant if the confidence intervals did not include “1”. A final model was constructed for each outcome (Manchester pain count and “no pain”, “some pain” or CWP) using only those variables which were still statistically significantly associated with the outcome when fully adjusted. The final models included an adjustment factor for participants who had changed pain status between baseline and the sub-study.

Only those variables found to be statistically significant in the final regression models were included in the moderation analysis (see Model 3 of Figure 4.12). Analysis of the moderating effects of age and sex on the relationship between QST variables and pain as an outcome was carried out using interaction terms, which were generated by multiplying the predictor variable by the moderating variable. Linear regression was used for Manchester pain count as an outcome, and logistic regression for “no pain”, “some pain” or CWP as an outcome. The other variables from the final regression models were included as confounders.
**4.9 Summary**

A cohort of participants aged between 34 and 101 years old, who had all previously taken part in research, were mailed a questionnaire. This included questions on pain location and duration, psychological distress, pain cognitions, sleep quality, physical activity levels and co-morbidities.

A sub-group were sampled from this cohort and underwent a physical examination. This included screening for osteoarthritis in the hands, knees and hips, a tender point examination and quantitative sensory testing. At the time of this assessment the sub-study participants also completed a questionnaire which included an update
on pain location and duration, further questions on co-morbidities and a more
detailed measurement of sleep quality.

Analyses were carried out on the data using Stata version 11.
5.0 Results – participant response

5.1 Overview

The characteristics of study participants are important because of their potential impact on internal and external validity. Internal validity is the extent to which the results of the study are applicable to the population from which the participants were drawn. External validity (or generalisability) relates to the degree to which the study findings can be applied to other populations.

This chapter examined some of the characteristics of the people who participated in the PAALS study. Response rates to the baseline questionnaire and sub-study were described. Responders and non-responders to the baseline questionnaire were compared by age and sex. Baseline questionnaire responders were compared by age and sex to the population from which they were drawn, using National Census data.

People who responded immediately to the questionnaire were compared to those who required one or more reminders (termed reluctant responders) by age, sex, social, psychological and behavioural measures. People who participated in the sub-study were compared with those who actively decided not to take part in the sub-study using the same set of measures.

Issues of internal and external validity were discussed.

5.2 Baseline questionnaire response

Figure 5.1 shows the baseline mailing strategy. The 3380 subjects in the data set prior to mailing were those from the ACPRC and EPIFUND groups (see section 4.2.1) who had not withdrawn or failed to respond on the most recent previous occasion when data was collected from each group. Data regarding deaths, change of address and dementia were obtained from GP records, the electoral roll and other sources as detailed in Methods section 4.2.3. The number of participants who returned full, short or blank questionnaires is given (see sections 4.2.3 and 4.3.2). Finally, the number of participants who consented to further contact regarding the sub-study is shown. The response rate was 87.8% for all questionnaires and 79.9% for completed, full questionnaires. A majority of those participants who returned full questionnaires agreed to further contact regarding the sub-study (61.8%).
Figure 5.1 – Baseline mailing strategy

Participants in data set
n=3380

Participants mailed
n=2987 (88.4%)

Returned questionnaire
n=2623 (87.8%)\(^b\)

Did not return questionnaire
n=364 (12.2%)\(^b\)

Completed questionnaire
n=2478 (83.0%)\(^b\)

Returned blank questionnaire
n=146\(^a\) (4.9%)\(^b\)

Full questionnaire
n=2386 (79.9%)\(^b\)

Short questionnaire
n=92 (3.1%)\(^b\)

Agreed to further contact
n=1475 (61.8%)\(^c\)

Did not agree to further contact
n=911 (38.2%)\(^c\)

\(^a\) includes 139 full blank and 7 short blank
\(^b\) % of participants mailed
\(^c\) % of full questionnaires returned
As these participants had already taken part in previous research studies, they had been through several stages of self-selection so it was possible that they differed from the population from which they were originally drawn. They were therefore also compared by age and sex to data from the 2001 National Census (Office for National Statistics 2003) in Table 5.1. In this case, the return of any questionnaire, full, short or blank, was counted as a returned questionnaire. This is because the aim of this analysis was to compare people who responded in some way to the study with those who did nothing.

The census data used were for the North West of England; while it is recognised that some of the participants were from the North East of England, the population pyramid for that area did not differ greatly from that of the North West. It can be seen in Table 5.1 that there were a higher percentage of females in the group who did not return questionnaires than in the group that did, although not statistically significantly so. Both groups had a substantially higher percentage of females than in the general population. The distribution of ages within the age bands was statistically significantly different between the groups who did and did not return questionnaires. It can be seen that the group who did not return questionnaires contained a higher proportion of people in the youngest and oldest age bands, whereas the group who did return questionnaires had a higher proportion in the middle two, particularly the second age band. Both the questionnaire returners and non-returners contained more older and fewer younger people than the general population. The youngest participant was aged 34 at the time of baseline data collection, but this does not fully explain these differences.

Table 5.1 – Demographic characteristics of full or short questionnaire responders and non-responders compared to population norms

<table>
<thead>
<tr>
<th></th>
<th>Questionnaire returned n=2623</th>
<th>Questionnaire not returned n=364</th>
<th>p^a</th>
<th>2001 Census North West England</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex n (%) Female</td>
<td>1640 (62.5%)</td>
<td>242 (66.5%)</td>
<td>0.199</td>
<td>52.7%</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-49^b</td>
<td>409 (15.6%)</td>
<td>84 (23.1%)</td>
<td>0.000</td>
<td>45.7%</td>
</tr>
<tr>
<td>50-69</td>
<td>1315 (50.1%)</td>
<td>145 (39.8%)</td>
<td></td>
<td>35.9%</td>
</tr>
<tr>
<td>70-89</td>
<td>810 (30.9%)</td>
<td>103 (28.3%)</td>
<td></td>
<td>17.4%</td>
</tr>
<tr>
<td>90+</td>
<td>89 (3.4%)</td>
<td>32 (8.8%)</td>
<td></td>
<td>1.0%</td>
</tr>
</tbody>
</table>

^aChi squared  ^bYoungest participant aged 34
5.3 Comparison of first time responders and reluctant responders

In the Epifund group, first time responders, who returned the questionnaire immediately, can be distinguished from reluctant responders, who required one or more reminders before they returned the questionnaire. The ACPRC group had a different mailing strategy which did not include reminders (see section 4.2.3); as they did not have the opportunity to be reluctant responders, they are excluded from this analysis.

Reluctant responders can be considered a proxy for non-responders, as they would not have responded without further prompting after the initial mailing. First time and reluctant responders have been compared using age, sex, marital status, pain status, the Hospital Anxiety and Depression Scale (HAD), the Pain Catastrophising Scale (PCS), the Brief Illness Perception Questionnaire (Brief IPQ), the Estimated Sleep Problems Scale (ESPS) and the Rapid Assessment of Physical Activity scale (RAPA) (Table 5.2). By definition, participants returning the short questionnaire were reluctant responders, as the short questionnaire was part of the reminder strategy, and as they had already failed to respond to 2 previous reminders they might be considered an extreme group of reluctant responders. Full questionnaire data was not available for those who returned the short questionnaire, who have been listed by age, sex and pain status only. Twenty seven tests of statistical significance have been applied in Table 5.2. Applying Bonferroni correction, for a significance level of $\alpha=0.05$ a p value of $0.05/27 = 0.0019$ should be applied.

There were a similar percentage of females in the first time responder group (59.2%) and in the reluctant responder group (57.6%). The proportion of females in the group who returned short questionnaires (60.4%) was also very similar, and in all groups there were more females than males. There were a higher percentage of reluctant responders than first-time responders in the youngest age band (30-49), similar percentages in the two groups in the middle age band (50-69) and a lower percentage of reluctant than first-time responders in the oldest age group (70-89), although this did not reach statistical significance ($p=0.009$) at the corrected value. The short questionnaire group had a higher percentage of participants in the youngest age group and smaller percentages in the middle and oldest age groups than either the reluctant or the first-time responders. There were no participants over the age of 90 in the Epifund group.

There were no significant differences in marital status between the groups, whether or not they had children and the age of leaving full-time education. Both groups had
approximately equal percentages in the pain status categories of “no pain”, “some pain" and CWP, using the American College of Rheumatology 1990 definition of chronic widespread pain (CWP) (Wolfe et al. 1990). The scores for the PCS or brief IPQ sub-scales were not significantly different for first time and reluctant responders, although the difference between groups for the emotional response sub-scale had a p value of 0.046 even though they had the same 95% confidence intervals. First-time responders scored lower on the HAD anxiety subscale than reluctant responders, although this did not reach statistical significance (p=0.011) at the corrected value, but there was no difference in HAD depression scores.

There were differences between the groups for drinking alcohol and smoking, although these did not reach statistical significance at the corrected value (p=0.032 and p=0.013 respectively). More first-time responders were either teetotal or drank more than 7 units of alcohol per week than the reluctant responders. More of the reluctant responders were current smokers and fewer were ex-smokers than the first-time responders, although the percentages of participants who had never smoked were similar. All responders scored similarly on sleep quality as measured by all 4 of the subscales of the ESPS. There were no statistically significant differences between the two responder groups on either of the physical activity RAPA subscales.
Table 5.2 – Socio-demographic factors, pain status, psychological status, sleep quality and physical activity for baseline questionnaire first-time and reluctant questionnaire responders (Epifund only)

<table>
<thead>
<tr>
<th>Socio-demographic factors (number (%))</th>
<th>First-time n=904</th>
<th>Reluctant n=913</th>
<th>p</th>
<th>Short questionnaire n=91</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex:</strong> Female</td>
<td>535 (59.2%)</td>
<td>526 (57.6%)</td>
<td>0.497$^+$</td>
<td>55 (60.4%)</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-49</td>
<td>151 (16.7%)</td>
<td>197 (21.6%)</td>
<td>0.009$^+$</td>
<td>26 (28.6%)</td>
</tr>
<tr>
<td>50-69</td>
<td>591 (65.4%)</td>
<td>585 (64.1%)</td>
<td></td>
<td>55 (60.4%)</td>
</tr>
<tr>
<td>70-89</td>
<td>162 (17.9%)</td>
<td>131 (14.3%)</td>
<td></td>
<td>10 (11.0%)</td>
</tr>
<tr>
<td>Marital status:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>69 (7.6%)</td>
<td>84 (9.2%)</td>
<td>0.320$^+$</td>
<td></td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>673 (74.4%)</td>
<td>681 (74.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>90 (10.0%)</td>
<td>90 (9.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>63 (7.0%)</td>
<td>48 (5.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>9 (1.0%)</td>
<td>10 (1.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has children</td>
<td>742 (82.1%)</td>
<td>767 (84.0%)</td>
<td>0.264$^+$</td>
<td></td>
</tr>
<tr>
<td>Does not have children</td>
<td>154 (17.0%)</td>
<td>138 (15.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>8 (0.9%)</td>
<td>8 (0.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>215 (23.8%)</td>
<td>174 (19.1%)</td>
<td>0.032$^+$</td>
<td></td>
</tr>
<tr>
<td>1-7 units per week</td>
<td>381 (42.1%)</td>
<td>593 (65.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;7 units per week</td>
<td>307 (34.0%)</td>
<td>141 (15.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.1%)</td>
<td>5 (0.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>416 (46.0%)</td>
<td>448 (49.1%)</td>
<td>0.013$^+$</td>
<td></td>
</tr>
<tr>
<td>Previous smoker</td>
<td>393 (43.5%)</td>
<td>339 (37.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>89 (9.8%)</td>
<td>116 (12.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>6 (0.7%)</td>
<td>10 (1.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age left education:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤16</td>
<td>470 (52.0%)</td>
<td>459 (50.3%)</td>
<td>0.121$^+$</td>
<td></td>
</tr>
<tr>
<td>17-19</td>
<td>152 (16.8%)</td>
<td>191 (20.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td>223 (24.7%)</td>
<td>220 (24.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>59 (6.5%)</td>
<td>43 (4.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5.2 – Socio-demographic factors, pain status, psychological status, sleep quality and physical activity for baseline questionnaire first-time and reluctant questionnaire responders (Epifund only) (continued)

<table>
<thead>
<tr>
<th>Pain status (number (%))</th>
<th>First-time n=904</th>
<th>Reluctant n=913</th>
<th>p</th>
<th>Short questionnaire n=91</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAIN: No pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>310 (34.3%)</td>
<td>294 (32.2)</td>
<td>0.640$\dagger$</td>
<td>28 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>Some pain</td>
<td>377 (41.7%)</td>
<td>385 (42.2)</td>
<td>33 (36.3%)</td>
<td></td>
</tr>
<tr>
<td>CWP missing</td>
<td>206 (22.8%)</td>
<td>219 (24.0)</td>
<td>28 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>11 (1.2%)</td>
<td>15 (1.6)</td>
<td>2 (2.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological factors (median (95% C.I.))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAD - anxiety (0-21)</td>
<td>5 (5-5)</td>
<td>6 (5-6)</td>
<td>0.011$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- depression (0-21)</td>
<td>3 (3-3)</td>
<td>3 (3-3)</td>
<td>0.532$\dagger$</td>
<td></td>
</tr>
<tr>
<td>IPQ - consequences (0-10)</td>
<td>2 (2-3)</td>
<td>2 (2-3)</td>
<td>0.221$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- timeline (0-10)</td>
<td>4 (4-5)</td>
<td>5 (4-5)</td>
<td>0.102$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- personal control (0-10)</td>
<td>5 (5-5)</td>
<td>5 (5-5)</td>
<td>0.181$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- treatment control (0-10)</td>
<td>5 (4-5)</td>
<td>4 (3-4)</td>
<td>0.255$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- identity (0-10)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>0.026$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- concern (0-10)</td>
<td>3 (3-3)</td>
<td>3 (3-3)</td>
<td>0.104$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- understanding (0-10)</td>
<td>2 (2-3)</td>
<td>2 (2-3)</td>
<td>0.716$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- emotional response (0-10)</td>
<td>2 (2-2)</td>
<td>2 (2-2)</td>
<td>0.046$\dagger$</td>
<td></td>
</tr>
<tr>
<td>PCS - rumination (0-14)</td>
<td>2 (2-3)</td>
<td>2.5 (2-3)</td>
<td>0.322$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- helplessness (0-24)</td>
<td>2 (2-2)</td>
<td>2 (2-2)</td>
<td>0.209$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- magnification (0-12)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>0.068$\dagger$</td>
<td></td>
</tr>
<tr>
<td>Behavioural factors (median (95% C.I.))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPS - trouble getting to sleep (0-5)</td>
<td>1 (1-1)</td>
<td>1 (1-1)</td>
<td>0.711$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- waking during the night (0-5)</td>
<td>2 (2-2)</td>
<td>2 (2-2)</td>
<td>0.969$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- early waking (0-5)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>0.716$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- waking unrefreshed (0-5)</td>
<td>1 (1-1)</td>
<td>1 (1-2)</td>
<td>0.060$\dagger$</td>
<td></td>
</tr>
<tr>
<td>RAPA - aerobic (0-5)</td>
<td>4 (4-5)</td>
<td>4 (4-4)</td>
<td>0.155$\dagger$</td>
<td></td>
</tr>
<tr>
<td>- strength and flexibility (0-3)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.026$\dagger$</td>
<td></td>
</tr>
</tbody>
</table>

$ = \text{Chi squared} \quad \# = \text{Kruskal Wallis}$
5.4 Sub-study participation

Figure 5.2 shows the number of participants at each stage of sub-study recruitment. The stages have been described in Methods (section 4.2.3). At the first and second stages of recruitment, some participants declined to participate and some were not able to be contacted. Being unable to contact a participant occurred more frequently at the first than the second telephone call, whereas withdrawal from the sub-study recruitment process occurred more frequently at the second phone call, after the information sheet had been sent out. Just under 20% of those who agreed to further contact were actually assessed in the sub-study.

A distinction can be drawn between those who merely did not take part in the sub-study because, for example, they consented to be contacted but were not selected, and those who actively opted out of the sub-study. The latter group have chosen not to take part, and are described here as “decliners”. They comprise a) participants who declined to participate at the first phone call (n=50), and b) participants who declined to participate at the second phone call (n=131).

A small group (n=34) of participants were recruited but not assessed in the sub-study. These were people who cancelled an appointment or did not attend, but could not have a satisfactory alternative appointment arranged.

Full questionnaire data was available for both those who participated in the sub-study and those who declined to take part in the sub-study. Table 5.3 compares sub-study participants with those who actively declined to take part, using age, sex, marital status, having children, alcohol consumption, smoking, the age participants left full-time education, pain status, the Hospital Anxiety and Depression Scale, the Pain Catastrophising Scale, the brief Illness Perception Questionnaire, the Estimated Sleep Problems Scale and the Rapid Assessment of Physical Activity scale. As none of the variables were normally distributed, p values have been calculated using Chi-squared for number counts and Kruskal-Wallis one-way ANOVA by ranks for the ordinal variables. Twenty seven tests of statistical significance have been applied in Table 5.3. Applying Bonferroni correction, for a significance level of $\alpha=0.05$ a p value of $0.05/27 = 0.0019$ should be applied.
Figure 5.2 – Sub-study recruitment strategy

Agreed to further contact
n=1475

Randomly selected from list
n=779 (52.1%)

Not selected
n=696

Contacted and declined to participate in sub-study
n=50 (3.4%)

Contacted and sent information
n=513 (34.8%)

Unable to contact
n=216 (14.6%)

2nd contact, declined to participate in sub-study
n=131 (8.9%)

2nd contact, agreed to take part
n=324 (22.0%)

Unable to contact
n=58 (3.9%)

Assessed in sub-study
n=290 (19.7%)

Not assessed in sub-study
n=34 (2.3%)

All percentages are % of number who agreed to further contact
There was a statistically significant difference between the two groups in the age at which they left full-time education (p=0.001), with the decliners more likely to have left education at or before the age of 16. The sub-study decliners had a higher percentage of females (74.0%) than the sub-study participants (61.4%) and more people in the youngest (30-49) and oldest (90+) age groups, but these were not statistically significant at the corrected value (p=0.005 and p=0.011 respectively). Similarly, there was a non-significant difference in alcohol consumption (p=0.011), with the decliners more likely to be teetotal. The groups of sub-study participants and decliners did not differ from one another in relation to gender, marital status, whether they had children, and smoking.

Sub-study decliners were more likely to have “some pain” or “CWP” than sub-study participants, although this did not reach statistical significance at the corrected level (p=0.079). There was a statistically significant difference between the groups in anxiety (p=0.0008), with decliners being more anxious than sub-study participants. The sub-study participants and decliners did not differ in terms of depression, the brief IPQ sub-scales, or the RAPA sub-scales. There was a non-significant difference between the groups for the ESPS sub-scale “waking unrefreshed” (p=0.031), where decliners were more likely to score highly (i.e. have poorer sleep quality) than sub-study participants. There were no differences for the other 3 ESPS sub-scales. All 3 PCS sub-scales showed a non-significant trend for decliners to catastrophise more than participants for magnification (p=0.062), helplessness (p=0.023) and rumination (p=0.026).

No data on the reason for opting-out is available for those who did not consent to further contact on the questionnaire, but where participants withdrew at the later stages of sub-study recruitment, a reason was requested. Of the 181 participants who withdrew during sub-study recruitment, reasons were collected for 140 of them. The commonest reasons were too busy/too much of a time commitment (n=40), illness (n=24), not wanting to take part (n=23) and carer commitments (n=8).
<table>
<thead>
<tr>
<th>Table 5.3 – Socio-demographic factors, pain status, psychological status, sleep quality and physical activity for sub-study participants and those who declined to take part</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Socio-demographic factors (number (%))</strong></td>
</tr>
<tr>
<td><strong>SEX:</strong> female</td>
</tr>
<tr>
<td><strong>AGE:</strong> 30-49</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>50-69</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>MARITAL STATUS:</strong> Single</td>
</tr>
<tr>
<td>Married/cohabiting</td>
</tr>
<tr>
<td>Divorced/separated</td>
</tr>
<tr>
<td>Widowed</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td><strong>CHILDREN:</strong> Has children</td>
</tr>
<tr>
<td>Does not have children</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td><strong>ALCOHOL:</strong> Nil</td>
</tr>
<tr>
<td>1-7 units per week</td>
</tr>
<tr>
<td>&gt;7 units per week</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td><strong>SMOKING:</strong> Never smoked</td>
</tr>
<tr>
<td>Previous smoker</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td><strong>AGE LEFT EDUCATION:</strong> ≤16</td>
</tr>
<tr>
<td>17-19</td>
</tr>
<tr>
<td>≥20</td>
</tr>
<tr>
<td>Missing</td>
</tr>
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</table>
Table 5.3 – Socio-demographic factors, pain status, psychological status, sleep quality and physical activity for sub-study participants and those who declined to take part (continued)

<table>
<thead>
<tr>
<th></th>
<th>Sub-study participants n=290</th>
<th>Sub-study decliners* n=181</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain status (number (%))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAIN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>87 (30.0%)</td>
<td>38 (21.0%)</td>
<td>0.079$</td>
</tr>
<tr>
<td>Some pain</td>
<td>154 (53.1%)</td>
<td>104 (57.5%)</td>
<td></td>
</tr>
<tr>
<td>CWP</td>
<td>49 (16.9%)</td>
<td>39 (21.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Psychological factors (median (95% C.I.))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAD - anxiety (0-21)</td>
<td>5 (4-5)</td>
<td>6 (5-7)</td>
<td>0.0008#</td>
</tr>
<tr>
<td>- depression (0-21)</td>
<td>5 (4-5)</td>
<td>5 (4-6)</td>
<td>0.205#</td>
</tr>
<tr>
<td>IPQ - consequences (0-10)</td>
<td>2 (2-3)</td>
<td>3 (2-3)</td>
<td>0.217#</td>
</tr>
<tr>
<td>- timeline (0-10)</td>
<td>5 (4-5)</td>
<td>5 (4-6)</td>
<td>0.989#</td>
</tr>
<tr>
<td>- personal control (0-10)</td>
<td>5 (5-5.9)</td>
<td>5 (5-7)</td>
<td>0.765#</td>
</tr>
<tr>
<td>- treatment control (0-10)</td>
<td>4.5 (4-5)</td>
<td>5 (4-5)</td>
<td>0.566#</td>
</tr>
<tr>
<td>- identity (0-10)</td>
<td>1 (0-1)</td>
<td>1 (0-2)</td>
<td>0.223#</td>
</tr>
<tr>
<td>- concern (0-10)</td>
<td>3 (2-3)</td>
<td>3.5 (3-4.5)</td>
<td>0.151#</td>
</tr>
<tr>
<td>- understanding (0-10)</td>
<td>2 (2-3)</td>
<td>3 (2-4)</td>
<td>0.272#</td>
</tr>
<tr>
<td>- emotional response (0-10)</td>
<td>2 (2-3)</td>
<td>2 (1.6-3)</td>
<td>0.484#</td>
</tr>
<tr>
<td>PCS - rumination (0-14)</td>
<td>3 (2-3)</td>
<td>3 (2-4)</td>
<td>0.026#</td>
</tr>
<tr>
<td>- helplessness (0-24)</td>
<td>2 (2-2)</td>
<td>3 (2-3.5)</td>
<td>0.023#</td>
</tr>
<tr>
<td>- magnification (0-12)</td>
<td>1 (1-1)</td>
<td>1 (1-2)</td>
<td>0.062#</td>
</tr>
<tr>
<td><strong>Behavioural factors (median (95% C.I.))</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPS - trouble getting to sleep (0-5)</td>
<td>1 (1-1)</td>
<td>1 (1-1.2)</td>
<td>0.351 #</td>
</tr>
<tr>
<td>- waking during the night (0-5)</td>
<td>3 (2-3)</td>
<td>2 (2.4)</td>
<td>0.640#</td>
</tr>
<tr>
<td>- early waking (0-5)</td>
<td>1 (1-2)</td>
<td>2 (1-2)</td>
<td>0.398#</td>
</tr>
<tr>
<td>- waking unrefreshed (0-5)</td>
<td>1 (1-1)</td>
<td>2 (1-2)</td>
<td>0.031#</td>
</tr>
<tr>
<td>RAPA - aerobic (0-5)</td>
<td>4 (4-5)</td>
<td>4 (4-4)</td>
<td>0.282#</td>
</tr>
<tr>
<td>- strength and flexibility (0-3)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.920#</td>
</tr>
</tbody>
</table>

$Chi squared  #Kruskal Wallis  *Decliners are participants who have actively opted-out of the sub-study
5.5 Discussion

The characteristics of study participants are important because of internal and external validity. Internal validity is the extent to which the results of the study reflect the “truth” in the population from which the participants were drawn, whereas external validity (or generalisability) relates to the degree to which the study findings can be applied to other populations (Silman and Macfarlane 2002). Both these are influenced by selection bias, which is a form of systematic error which occurs when the non-participation is related to either the predictors or outcomes. Selection bias does not automatically occur when the characteristics of participants differ from the population from which they were drawn, it only occurs if this alters the relationships being investigated.

5.5.1 Questionnaire returns

A high rate of return of questionnaires is more desirable than a low rate, because a greater number of participants increases the predictive power of the study, and because when fewer people have selected not to participate the responders should represent the population more closely. The PAALS study achieved an overall response rate of 87.8%, and a 79.9% return for completed, full baseline questionnaires. The fact that these were experienced study participants and a reminder strategy (as detailed in Methods section 4.2.3) was in place will probably have contributed to this. Of the 2386 completed, full questionnaires returned, 477 were received after the reminder postcard was sent, 279 after the second questionnaire was sent and 157 after the short questionnaire was sent. The usefulness of reminders was demonstrated by a health survey which received an initial return of 49% of questionnaires, but this was improved by 10% following a postal reminder and by 15% following a telephone prompt (Ronckers et al. 2004). Other surveys have obtained poorer return rates, for example a non-health postal survey sent to participants selected from the electoral register achieved a return rate of 16% (Sahlqvist et al. 2011).

The PAALS cohort has taken part in previous research, so there have been several stages of self-selection and the participants may not be representative of the population from which they were drawn. Table 5.1 compares baseline sex and age data for questionnaire responders and non-responders with data from the 2001 National Census. It can be seen that there is a smaller proportion of responders in
the youngest age category (30-49) than among non-responders, and both these are smaller than the proportion in this age category in the general population. Postal surveys often have a higher response rate from middle-aged adults (up to the age of 65) than younger adults (McBeth et al. 2001). There is also a higher proportion of older (aged 70-89) and very elderly (aged 90+) people among the PAALS responders and non-responders than in the general population. One section of the PAALS study cohort was specifically recruited because of their older age (see Methods section 4.2.1) so this is not unexpected. The PAALS responders and non-responders also have a higher proportion of females than the general population, but this is unsurprising as there are a higher proportion of females than males in the population at older ages compared to younger ages (Office for National Statistics 2003).

It is possible that pain status influenced the decision to participate, e.g. people with lots of pain may feel a pain study is more relevant to them than people with no pain. In studies in Western Europe, the proportion of the population with CWP is generally found to range between approximately 10% (Buskila et al. 2000) and 18% (Nicholl et al. 2008b) in adult populations. However, this does increase with increasing age, and is higher for women than men. A large majority of the PAALS study responders are over the age of 50, the median age is 63. The prevalence of CWP at baseline in the PAALS study was 22.5% for first-time responders and 24.6% for reluctant responders. Croft et al found the prevalence of CWP for participants aged 55-64 to be 17.2% for males and 17.4% for females, aged 65-74 to be 7.2% for males and 20.0% for females, and aged 75+ to be 19.9% for males and 26.3% for females (Croft et al. 1993). Bearing in mind the high proportion of females in the PAALS cohort, these figures are somewhat higher but broadly comparable to data from the PAALS cohort.

Even if the study cohort was not completely representative of the population from which it was drawn, this will only introduce bias if it alters the relationships being investigated (Silman and Macfarlane 2002). The hypothesised pathway being tested by the present study (see Figure 3.1) includes the relationship between sensitivity to sensory stimuli and pain, as moderated by age and sex. There is no a priori reason to suppose that this relationship will be different in the PAALS cohort than in the population from which they were drawn.
5.5.2 First-time and reluctant responders

Very limited data is available for study non-responders, but questionnaire data is available for reluctant responders, who can act as a proxy for non-responders as they would not have responded if a reminder strategy had not been in place. This distinction is only available for the Epifund group due to the different recruitment strategy employed for the ACPRC group (see section 4.2.3).

The comparisons of first-time and reluctant responders in Table 5.2 used Bonferroni correction for multiple testing. Whilst carrying out multiple tests without correction would be expected to produce some false positive results, it is acknowledged that Bonferroni is a severe correction and may lead to false negatives. This would tend to make the groups being compared appear more similar than they actually are. None of the differences between first-time and reluctant responders were statistically significant with this correction, but differences in age, anxiety, IPQ emotional response, smoking and drinking alcohol had p values of less than 0.05.

There were more reluctant responders in the youngest (30-49 years) (21.6%) and fewer in the oldest (70-89 years) age group (14.3%) than first-time responders (16.7% and 17.9% respectively). Non-responders (see Table 5.1) had a higher percentage of people in the youngest age group than either of these (23.1%), and also more in the age 70-89 category (28.3%), so reluctant responders are not a perfect reflection of non-responders. The reluctance of people at the extremes of the age range to participate in research has previously been documented (Silman and Macfarlane 2002).

First-time responders scored lower on the HAD anxiety subscale than reluctant responders. More first-time responders were either teetotal or drank more than 7 units of alcohol per week than the reluctant responders. More of the reluctant responders were current smokers and fewer were ex-smokers than the first-time responders, although the percentages of participants who had never smoked were similar. There was a p value of 0.046 for differences between the groups in IPQ emotional response, although the direction of the difference was not clear as the 95% confidence intervals were the same. For all these non-significant differences the lowest p value obtained was 0.009, which was more than 4.5 times the Bonferroni corrected cut-off value of p=0.0019, so the risk of false negatives was low.
5.5.3 Sub-study participants and decliners

The reason for comparing sub-study participants and decliners was to ascertain whether differences in study variables were associated with a person’s choice to participate or not. People who actively declined to take part in the sub-study were chosen as the comparator group, rather than non-participants, because they were likely to represent an extreme group. People who had simply not been invited to be in the sub-study were more likely to be similar to those who participated in it. The only statistically significant differences between the two groups were the age they left full-time education (p=0.001) and anxiety (p=0.0008). A higher percentage of decliners than sub-study participants left education aged 16 or under. Fewer years in education is associated with higher prevalence of pain (see section 2.3.6). However, there is no significant difference between the two groups in pain status. Anxiety has also been found to be associated with pain prevalence (see section 2.3.2), although it can be seen from the 95% confidence intervals that very few participants in either the sub-study (4-5 95% C.I.) or decliners (5-7 95% C.I.) groups scored highly on the HAD Anxiety scale relative to the total range of scores (0-21), with scores of 8 or above indicating clinically relevant anxiety (Zigmond and Snaith 1983).

As has already been discussed, Bonferroni correction will tend to lead to some false negatives, which will make the two groups seem more similar than they actually are. Differences between the groups in age, sex, alcohol consumption, PCS rumination, PCS helplessness and ESPS waking unrefreshed all had p values of less than 0.05. The difference in age between sub-study participants and decliners may be due to the time commitment to an assessment taking up to 3 hours. The Office for National Statistics estimated the age at which a person is no longer working or actively seeking employment as 61.5 years old for women and 64 years old for men in 2008 (Office for National Statistics 2010a). Younger participants are therefore more likely to be employed, so might find scheduling the assessment difficult. Older participants are more likely to have multiple co-morbidities (Seeman et al. 1989), so could find the assessment more onerous. The greater percentage of females in the decliners group may be linked to more females having caring responsibilities (Office for National Statistics 2010b) and therefore less free time. Alcohol consumption has generally not been found to be associated with pain prevalence (see section 2.3.8). Greater catastrophising (see section 2.3.2) and poor sleep quality (see section 2.3.4) have both been found to be associated with pain prevalence, but it has already been mentioned that pain status was not significantly different between the
groups. For all these non-significant differences the lowest p value obtained was 0.011, which was more than 5.5 times the Bonferroni corrected cut-off value of p=0.0019, so the risk of false negatives was low.

5.5.4 External validity

One method of assessing the potential of a study cohort to produce externally valid results is to compare them with other populations, using measures which are related to the study hypothesis. However, finding comparable published data is not easy because very few studies are carried out on a general population. For example, the HAD measured in fibromyalgia patients and healthy controls (Klauenberg et al. 2008), the brief IPQ measured in diabetic clinic patients (Broadbent et al. 2006) and the PCS measured in patients awaiting knee arthroplasty (Riddle et al. 2011). One study which reported HAD anxiety and depression measured in a general population in Germany (see Appendix X) obtained very similar values to those in the present study. A population-based study on adults over the age of 50 years reported that 25% of them scored 4 or 5 on the RAPA aerobic scale (Mayer et al. 2008), which was fewer than in the present study where the median was 4.

However, no population can represent another in every detail. The question with regard to external validity is: can the results from the present study be applied to other populations? This will be the case if the differences between the populations do not affect the relationships between the predictor and outcome variables.

5.6 Conclusion

The PAALS cohort was dissimilar to the population from which it was drawn in terms of age and sex. This was likely to be due to 2 factors: 1) part of the cohort (the ACPRC group) were recruited because of their older age, and females form a higher percentage of older than younger age groups, and 2) serial non-response over a number of episodes of data collection (see section 4.2.1) because males and people at the extremes of age (very young and very old) are less likely to respond (Silman and Macfarlane 2002). The relationship between sensitivity to stimuli and the presence of pain may be different for men and women, and for people of different ages. This can be taken into consideration by describing the relationships
separately for sex and age groups, or by including age and sex in a multivariate analysis.

There were no statistically significant differences in any of the variables reported between first-time responders and reluctant responders, who were a proxy for non-responders. There were some statistically significant differences between people who participated in the sub-study and those who declined, namely the age they left full-time education and HAD anxiety. Both these variables have been found to be associated with the prevalence of clinical pain (see sections 2.3.6 and 2.3.2 respectively), but pain status was not significantly different between the sub-study participants and decliners. It was important that there were no differences between those participants who were in the sub-study and those who were not which would affect the associations tested in the hypotheses, because the sub-study group were weighted to represent the whole cohort in the regression analyses (see section 4.7 and Appendix VI) as they were the only participants to have quantitative sensory testing data. From the evidence examined here, there would appear to be no such differences.

Whilst there is no a priori reason to suppose that the relationship between sensitivity to sensory stimuli and the presence of pain would be different in different populations, there could be unknown confounders which differ between these populations. The study would need to be replicated in a sample of participants drawn from a different population to test whether this is the case.
6.0 Results – QST summary statistics

6.1 Overview

This section is a precursor to the regression analyses which will fully elucidate the relationships shown in Figure 3.1 and the hypotheses given in section 3.2, intended to introduce the quantitative sensory testing (QST) variables and how they vary with respect to relevant factors. The QST variables are presented descriptively, graphically and in tables. Comparisons are made between pain status groups, age groups, sexes, and by groups according to other socio-demographic factors.

6.2 Correction for multiple testing

Statistical tests such as Spearman’s or Kruskal-Wallis calculate the probability of the null hypothesis being correct, given the observed data or more extreme data values. If this probability is 5% (0.05) then, on average, a positive result purely due to chance will occur one time in every twenty. Bonferroni is a statistical correction for multiple testing. If n independent hypotheses are tested at $\alpha=0.05$, a significance level $0.05/n$ should be applied. This is generally considered a severe correction because tests are rarely independent, so it is unlikely that the null hypothesis will be rejected (Swinscow and Campbell 2002). This makes false negatives likely, where a true association between variables is held not to be present.

6.3 QST data and pain status

Table 6.1 contains descriptive statistics of all the quantitative sensory testing (QST) variables (median and 95% confidence intervals) categorised by pain status. The pain status was derived from the sub-study questionnaire, which was completed on the same day as the QST. The pain categories are “no pain”, “chronic widespread pain” (CWP) as defined by the American College of Rheumatology (Wolfe et al. 1990), and “some pain”, which is any pain other than CWP. Sub-study pain status was missing for 6 participants. As none of the variables were normally distributed, the median was used as a measure of central tendency rather than the mean, and p
values were calculated using Kruskal-Wallis one-way ANOVA by ranks. The p values reported were corrected for ties, i.e. a factor was inserted by Stata because some of the scores had the same rank.

Cool (CDT) and warm (WDT) detection threshold were recorded as the difference from the baseline temperature, which is conventional (Rolke et al. 2006b), whereas cold (CPT) and heat (HPT) pain thresholds were expressed as absolute temperatures. CDT was expressed as a positive number for convenience in the table.

CDT, WDT and thermal sensory limen (TSL) were higher for the foot than the hand for all pain categories, indicating greater thermal detection sensitivity in the hand than the foot, and a slightly higher number of paradoxical heat sensations (PHS) were detected in the foot than in the hand. CPT was lower for the foot than the hand, and HPT was higher for the foot than the hand, both of these indicating greater thermal pain sensitivity in the hand than the foot.

Mechanical stimuli followed a similar pattern to the thermal stimuli. Mechanical detection threshold (MDT) was higher for the foot than the hand, indicating greater detection sensitivity to mechanical stimuli in the hand. Mechanical pain threshold (MPT) was higher in the hand than the foot (except in the CWP category), and higher subjective pain ratings were recorded in the mechanical pain sensitivity (MPS) and allodynia (ALL) testing in the foot than the hand. These indicate that the foot was more sensitive to mechanical pain than the hand. Vibration detection threshold (VDT) was higher in the hand than the foot, showing that the hand was more sensitive to vibratory stimuli than the foot. There was no difference in wind-up ratio (WUR) or descending noxious inhibitory controls (DNIC) between the hand and foot.

Overall, the differences in sensory sensitivity between the hand and the foot were similar across the 3 pain status groups.

The p-values given in Table 6.1 showed the statistical significance of differences between pain status groups for each QST modality. Twenty six tests of statistical significance were applied in Table 6.1. Applying Bonferroni correction, for a significance level of $\alpha=0.05$ a p value of $0.05/26 = 0.0019$ should be applied. Using this criterion, only tender point count showed a statistically significant difference between pain groups.
Kernel density plots give a visual representation of the proportion of the data at a given variable value. A peak occurs at the modal value. The shape of the graph is indicative of the amount of variance within the data; a large peak signifies that most of the data are clustered near the modal value, whereas a small peak and wider spread of data signifies more variance. The kernel density plots in this report were plotted using the Stata command “kdensity”.

Figure 6.1 is a kernel density plot of tender point count by pain status group. It has been included in order to illustrate the differences in variation of tender point count between the pain groups more fully than the medians and 95% confidence intervals in Table 6.1. It can be seen that the modal value for participants with CWP was higher, and that there was greater variance in this variable in the CWP group than in the other two groups. The modal peak was slightly higher and the variance slightly smaller in the “no pain” group than the “some pain” group, although the modal values were similar between these two groups.

Figure 6.1 – tender point count by pain status group, kernel density
Table 6.1 – QST summary data by pain status

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>All with sub-study pain status (n=285)</th>
<th>No pain n=100 (35.1%)</th>
<th>Some pain n=138 (48.4%)</th>
<th>CWP n=47 (16.5%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thermal QST variables (median (95% C.I.))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cool detection threshold (°C) ³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>278</td>
<td>1.4 (1.3-1.6)</td>
<td>1.3 (1.2-1.5)</td>
<td>1.4 (1.3-1.6)</td>
<td>1.4 (1.2-2.1)</td>
<td>0.556</td>
</tr>
<tr>
<td>Foot</td>
<td>275</td>
<td>4.8 (4.1-5.7)</td>
<td>5.1 (4.1-6.2)</td>
<td>4.8 (3.7-6.2)</td>
<td>3.5 (2.2-7.9)</td>
<td>0.793</td>
</tr>
<tr>
<td>Warm detection threshold (°C) ³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>278</td>
<td>1.6 (1.5-1.7)</td>
<td>1.6 (1.4-1.8)</td>
<td>1.7 (1.4-1.8)</td>
<td>1.7 (1.3-1.9)</td>
<td>0.968</td>
</tr>
<tr>
<td>Foot</td>
<td>275</td>
<td>8.5 (7.4-9.2)</td>
<td>8.9 (7.5-10.0)</td>
<td>8.7 (7.4-9.7)</td>
<td>5.7 (4.7-9.2)</td>
<td>0.146</td>
</tr>
<tr>
<td>Thermal sensory limen (°C) ³</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>278</td>
<td>3.3 (3.0-3.5)</td>
<td>3.4 (2.9-3.8)</td>
<td>3.4 (3.0-3.7)</td>
<td>3.1 (2.4-3.6)</td>
<td>0.892</td>
</tr>
<tr>
<td>Foot</td>
<td>278</td>
<td>15.2 (13.1-16.7)</td>
<td>15.7 (12.5-18.1)</td>
<td>16.6 (13.1-18.3)</td>
<td>11.5 (8.3-15.2)</td>
<td>0.061</td>
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<tr>
<td>Paradoxical heat sensations</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>274</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.993</td>
</tr>
<tr>
<td>Foot</td>
<td>271</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
<td>0.184</td>
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<tr>
<td>Cold pain threshold (°C) ³</td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>277</td>
<td>10.7 (9.8-12.3)</td>
<td>11.9 (9.5-14.1)</td>
<td>10.2 (9.4-12.3)</td>
<td>11.7 (7.7-15.0)</td>
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<tr>
<td>Foot</td>
<td>274</td>
<td>7.2 (5.5-8.7)</td>
<td>6.2 (2.2-10.0)</td>
<td>7.2 (4.8-8.7)</td>
<td>9.2 (5.7-14.3)</td>
<td>0.601</td>
</tr>
<tr>
<td>Heat pain threshold (°C) ³</td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>277</td>
<td>44.1 (42.8-44.8)</td>
<td>44.6 (42.9-45.4)</td>
<td>43.9 (41.9-45.0)</td>
<td>43.0 (40.2-45.2)</td>
<td>0.886</td>
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<tr>
<td>Foot</td>
<td>272</td>
<td>47.1 (46.6-47.5)</td>
<td>47.3 (46.2-48.2)</td>
<td>47.3 (46.7-47.8)</td>
<td>46.4 (44.5-47.5)</td>
<td>0.171</td>
</tr>
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</table>

³Detection thresholds and limens are given as a temperature difference (expressed positively here for convenience) but pain thresholds are given as absolute temperatures. All p values Kruskal-Wallis
Table 6.1 – QST summary data by pain status (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>All with sub-study pain status (n=285)</th>
<th>No pain n=100 (35.1%)</th>
<th>Some pain n=138 (48.4%)</th>
<th>CWP n=47 (16.5%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanical QST variables (median (95% C.I.))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender point count</td>
<td>285</td>
<td>3.0 (2.0-3.0)</td>
<td>1.5 (0-2.3)</td>
<td>1.5 (1.0-3.0)</td>
<td>8.0 (6.0-10.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mechanical detection threshold (mN)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>283</td>
<td>0.93 (0.76-1.15)</td>
<td>1.00 (0.72-1.30)</td>
<td>0.86 (0.71-1.15)</td>
<td>0.93 (0.65-1.60)</td>
<td>0.999</td>
</tr>
<tr>
<td>Foot</td>
<td>281</td>
<td>6.50 (5.49-8.00)</td>
<td>6.50 (4.86-9.19)</td>
<td>7.00 (5.28-8.57)</td>
<td>6.28 (4.55-10.06)</td>
<td>0.983</td>
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<tr>
<td>Mechanical pain threshold (mN)</td>
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</tr>
<tr>
<td>Hand</td>
<td>285</td>
<td>90.5 (84.4-108.1)</td>
<td>87.5 (73.5-111.4)</td>
<td>90.5 (68.2-111.4)</td>
<td>119.4 (90.5-177.9)</td>
<td>0.095</td>
</tr>
<tr>
<td>Foot</td>
<td>281</td>
<td>45.3 (39.4-48.5)</td>
<td>48.5 (38.4-59.7)</td>
<td>42.2 (34.5-48.2)</td>
<td>48.5 (32.0-60.3)</td>
<td>0.688</td>
</tr>
<tr>
<td>Mechanical pain sensitivity (0-100)</td>
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</tr>
<tr>
<td>Hand</td>
<td>284</td>
<td>6.5 (5.1-7.2)</td>
<td>6.6 (4.9-8.3)</td>
<td>6.4 (4.7-7.4)</td>
<td>6.5 (2.7-9.5)</td>
<td>0.768</td>
</tr>
<tr>
<td>Foot</td>
<td>278</td>
<td>8.3 (6.8-9.8)</td>
<td>8.0 (6.2-10.4)</td>
<td>8.7 (6.6-11.6)</td>
<td>6.3 (3.5-9.6)</td>
<td>0.165</td>
</tr>
<tr>
<td>Dynamic mechanical allodynia (0-100)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>283</td>
<td>0 (0-0)</td>
<td>0 (0-0.4)</td>
<td>0 (0-0.1)</td>
<td>0 (0-0.2)</td>
<td>0.879</td>
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<tr>
<td>Foot</td>
<td>277</td>
<td>0.7 (0.3-1.1)</td>
<td>1.0 (0.2-1.6)</td>
<td>1.0 (0.3-1.3)</td>
<td>0.1 (0-0.6)</td>
<td>0.136</td>
</tr>
<tr>
<td>Wind-up ratio</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>266</td>
<td>2.4 (2.1-2.6)</td>
<td>2.5 (2.1-2.8)</td>
<td>2.4 (2.1-2.7)</td>
<td>2.2 (1.9-3.1)</td>
<td>0.951</td>
</tr>
<tr>
<td>Foot</td>
<td>262</td>
<td>2.5 (2.2-3.8)</td>
<td>2.6 (2.0-3.0)</td>
<td>2.4 (2.0-2.7)</td>
<td>2.8 (2.0-3.5)</td>
<td>0.659</td>
</tr>
<tr>
<td>DNIC (WUR before ÷ WUR after)</td>
<td>211</td>
<td>1.0 (1.0-1.0)</td>
<td>1.0 (1.0-1.0)</td>
<td>1.0 (1.0-1.0)</td>
<td>1.0 (1.0-1.0)</td>
<td>0.659</td>
</tr>
<tr>
<td>Vibration detection threshold (0-8)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>282</td>
<td>6.7 (6.3-7.0)</td>
<td>6.7 (6.3-7.0)</td>
<td>6.7 (6.3-7.0)</td>
<td>7.0 (6.3-7.0)</td>
<td>0.176</td>
</tr>
<tr>
<td>Foot</td>
<td>282</td>
<td>5.3 (5.0-5.7)</td>
<td>5.3 (5.0-5.7)</td>
<td>5.3 (5.0-5.7)</td>
<td>5.3 (4.0-6.0)</td>
<td>0.779</td>
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</tbody>
</table>
6.4 QST data and age

Table 6.2 contains descriptive statistics of all the quantitative sensory testing (QST) variables (median and 95% confidence intervals) categorised into two age groups: 65 and under or over 65 years old. As described previously, a significance level of $p = 0.0019$ was applied.

Looking at the differences between the two age groups, there were statistically significant differences for CDT, WDT, TSL, MDT and ALL in both the hand and the foot, and CPT, HPT and VDT for the foot only. The CDT, WDT, TSL, MDT, CPT, HPT and VDT showed reduced sensitivity to stimuli in the older compared to the younger group, but ALL showed increased sensitivity in the older group. There were no differences between the age groups for PHS, tender point count, MPT, MPS, WUR or DNIC at the hand or the foot.

Kernel density plots were drawn for all the QST variables having statistically significant differences between the two age groups. Figures 6.2 – 6.4 are three examples, showing plots of CDT for hand and foot, and HPT and VDT for the foot only by age group. The other graphs are in Appendix III.

In Figure 6.2, the modal temperature values for CDT in the hand were very similar for the two age groups, but the peak proportion was higher for the younger age group. In the foot, the modal CDT temperature value was lower than in the hand (indicating reduced sensitivity) in both groups, but lower for the older than the younger age group. The prevalence peaks for the foot were lower than for the hand, and the data more widely spread.
In Figure 6.3, the modal value for HPT in the foot was at a higher temperature for
the older than the younger age group, indicating reduced sensitivity. The peak
prevalence was lower and spread of data greater for the younger than the older age
group.

In Figure 6.4 the modal perception values for VDT in the foot were lower (indicating
reduced sensitivity) in the older than in the younger age group. The peak
prevalence was higher in the younger age group and the spread of data was greater
in the older age group.
Figure 6.3 – Foot HPT by age group, kernel density

Figure 6.4 – Foot VDT by age group, kernel density
Table 6.2 – QST summary data by age group

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Age 65 and under</th>
<th>n</th>
<th>Age over 65</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thermal QST variables (median (95% C.I.))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cool detection threshold (°C)(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>127</td>
<td>1.2 (1.1-1.4)</td>
<td>154</td>
<td>1.6 (1.4-1.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Foot</td>
<td>127</td>
<td>3.0 (2.5-4.0)</td>
<td>151</td>
<td>6.8 (5.7-8.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Warm detection threshold (°C)(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hand</td>
<td>127</td>
<td>1.4 (1.3-1.7)</td>
<td>154</td>
<td>1.7 (1.6-1.9)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Foot</td>
<td>127</td>
<td>6.8 (5.5-7.5)</td>
<td>151</td>
<td>9.6 (8.8-11.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Thermal sensory limen (°C)(^a)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>127</td>
<td>2.7 (2.3-3.2)</td>
<td>154</td>
<td>3.7 (3.4-4.4)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Foot</td>
<td>128</td>
<td>11.1 (9.5-12.3)</td>
<td>153</td>
<td>18.5 (16.6-20.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Paradoxical heat sensations (0-6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>127</td>
<td>0 (0-0)</td>
<td>150</td>
<td>0 (0-0)</td>
<td>0.145</td>
</tr>
<tr>
<td>Foot</td>
<td>126</td>
<td>0 (0-1)</td>
<td>148</td>
<td>0 (0-1)</td>
<td>0.697</td>
</tr>
<tr>
<td>Cold pain threshold (°C)(^a)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Hand</td>
<td>126</td>
<td>10.8 (9.3-13.5)</td>
<td>154</td>
<td>10.5 (9.7-12.6)</td>
<td>0.835</td>
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<td>126</td>
<td>9.9 (7.2-12.6)</td>
<td>151</td>
<td>4.9 (1.8-7.2)</td>
<td>0.0003</td>
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<tr>
<td>Heat pain threshold (°C)(^a)</td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>126</td>
<td>43.7 (42.2-44.9)</td>
<td>154</td>
<td>44.5 (42.7-45.5)</td>
<td>0.774</td>
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<tr>
<td>Foot</td>
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<td>46.6 (45.3-47.1)</td>
<td>150</td>
<td>47.0 (47.0-48.3)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

\(^a\) Detection thresholds and limens are given as a temperature difference (expressed positively here for convenience) but pain thresholds are given as absolute temperatures. All p values Kruskal-Wallis
<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Age 65 and under</th>
<th>n</th>
<th>Age over 65</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender point count</td>
<td>128</td>
<td>2.0 (1.0-3.0)</td>
<td>160</td>
<td>3.0 (2.0-4.0)</td>
<td>0.209</td>
</tr>
<tr>
<td>Mechanical detection threshold (mN)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>127</td>
<td>0.66 (0.53-0.76)</td>
<td>159</td>
<td>1.3 (1.1-1.7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Foot</td>
<td>128</td>
<td>4.4 (3.7-5.3)</td>
<td>156</td>
<td>10.2 (8.1-13.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mechanical pain threshold (mN)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>127</td>
<td>111.4 (84.4-128.3)</td>
<td>161</td>
<td>84.4 (73.5-97.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Foot</td>
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<td>157</td>
<td>45.3 (34.3-52.0)</td>
<td>0.593</td>
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<td>Mechanical pain sensitivity (0-100)</td>
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<tr>
<td>Hand</td>
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<td>5.5 (4.1-7.1)</td>
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<td>6.8 (5.3-9.0)</td>
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<td>Foot</td>
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<td>Dynamic mechanical allodynia (0-100)</td>
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</tr>
<tr>
<td>Hand</td>
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<td>0 (0-0)</td>
<td>159</td>
<td>0.1 (0-1.0)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Foot</td>
<td>125</td>
<td>0 (0-0.3)</td>
<td>155</td>
<td>1.4 (1.0-2.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Wind-up ratio</td>
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</tr>
<tr>
<td>Hand</td>
<td>117</td>
<td>2.4 (2.1-2.7)</td>
<td>152</td>
<td>2.4 (2.1-2.6)</td>
<td>0.826</td>
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<tr>
<td>Foot</td>
<td>119</td>
<td>2.4 (2.0-2.7)</td>
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<td>2.6 (2.2-3.0)</td>
<td>0.251</td>
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<tr>
<td>DNIC (WUR before ÷ WUR after)</td>
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<td>123</td>
<td>1.0 (1.0-1.0)</td>
<td>0.237</td>
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<tr>
<td>Vibration detection threshold (0-8)</td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>126</td>
<td>7.0 (6.7-7.0)</td>
<td>159</td>
<td>6.3 (6.0-6.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Foot</td>
<td>127</td>
<td>6.0 (5.7-6.3)</td>
<td>158</td>
<td>4.7 (4.0-5.0)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
6.5 QST data and sex

Table 6.3 contains descriptive statistics of all the QST variables by sex. As described previously, a significance level of $p = 0.0019$ was applied.

There were statistically significant differences between males and females for WDT, TSL, HPT and MDT at the hand and the foot, MPT at the hand only, and tender point count. Females had lower values than males for WDT, TSL and HPT at the hand and foot, meaning females were more sensitive than males to the detection of thermal stimuli and to heat pain. Females had a lower MDT at the hand and foot, a lower MPT at the hand and a higher tender point count than males, showing that females were more sensitive to detection of mechanical stimuli, cutaneous mechanical pain and pressure pain than males. There were no significant differences between males and females for CDT, PHS, CPT, MPS, ALL, WUR, DNIC or VDT.

Kernel density plots were drawn for all the QST variables having statistically significant differences between the two sexes. Figure 6.5 shows WDT for hand and foot. It can be seen that for the hand, the modal value was very similar for males and females, but there was greater spread of data for the males. For the foot, the modal value was lower for females than males, but the degree of spread of data was similar for the two sexes. Figure 6.6 shows tender point count. The modal value was higher and the spread of data greater for females than for males. Kernel density plots for the other QST measures showing statistically significant differences between males and females are in Appendix III.
### Table 6.3 – QST summary data by sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Males</th>
<th>n</th>
<th>Females</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thermal QST variables (median (95% C.I.))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cool detection threshold (°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>111</td>
<td>1.4 (1.2-1.7)</td>
<td>170</td>
<td>1.4 (1.3-1.6)</td>
<td>0.315</td>
</tr>
<tr>
<td>Foot</td>
<td>110</td>
<td>5.1 (4.2-7.3)</td>
<td>168</td>
<td>4.6 (3.6-5.8)</td>
<td>0.119</td>
</tr>
<tr>
<td>Warm detection threshold (°C)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>111</td>
<td>1.8 (1.6-2.1)</td>
<td>170</td>
<td>1.5 (1.3-1.6)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Foot</td>
<td>110</td>
<td>10.1 (9.2-11.3)</td>
<td>168</td>
<td>7.1 (5.8-8.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Thermal sensory limen (°C)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>111</td>
<td>3.6 (3.4-4.2)</td>
<td>170</td>
<td>3.0 (2.6-3.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Foot</td>
<td>112</td>
<td>18.1 (16.2-19.4)</td>
<td>169</td>
<td>13.3 (11.6-15.3)</td>
<td>0.001</td>
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<tr>
<td>Paradoxical heat sensations</td>
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<tr>
<td>Hand</td>
<td>109</td>
<td>0 (0-0)</td>
<td>168</td>
<td>0 (0-0)</td>
<td>0.773</td>
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<tr>
<td>Foot</td>
<td>107</td>
<td>1 (0-2)</td>
<td>167</td>
<td>0 (0-0)</td>
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<tr>
<td>Cold pain threshold (°C)</td>
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<tr>
<td>Hand</td>
<td>110</td>
<td>9.7 (7.9-11.6)</td>
<td>170</td>
<td>11.9 (10.2-14.2)</td>
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<td>Foot</td>
<td>109</td>
<td>4.9 (1.9-7.6)</td>
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<td>8.5 (6.2-10.8)</td>
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<tr>
<td>Heat pain threshold (°C)</td>
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<td>110</td>
<td>45.8 (44.9-47.2)</td>
<td>170</td>
<td>42.1 (41.2-44.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Foot</td>
<td>108</td>
<td>48.0 (47.5-48.6)</td>
<td>167</td>
<td>46.3 (45.4-47.0)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*Detection thresholds and limens are given as a temperature difference (expressed positively here for convenience) but pain thresholds are given as absolute temperatures. All p values Kruskal-Wallis*
Table 6.3 – QST summary data by sex (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Males</th>
<th>n</th>
<th>Females</th>
<th>p</th>
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<tr>
<td><strong>Mechanical QST variables</strong> (median (95% C.I.))</td>
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</tr>
<tr>
<td>Tender point count</td>
<td>112</td>
<td>1.0 (0-2.0)</td>
<td>176</td>
<td>4.0 (3.0-5.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mechanical detection threshold (mN)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>112</td>
<td>1.23 (0.94-1.87)</td>
<td>174</td>
<td>0.75 (0.62-0.93)</td>
<td>0.0004</td>
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<tr>
<td>Foot</td>
<td>111</td>
<td>9.19 (7.29-13.32)</td>
<td>173</td>
<td>5.28 (4.32-6.50)</td>
<td>0.0001</td>
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<tr>
<td>Mechanical pain threshold (mN)</td>
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</tr>
<tr>
<td>Hand</td>
<td>112</td>
<td>119.4 (97.9-147.0)</td>
<td>176</td>
<td>73.5 (61.8-90.5)</td>
<td>0.0001</td>
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<tr>
<td>Foot</td>
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<td>45.3 (36.8-55.7)</td>
<td>175</td>
<td>42.2 (36.9-48.5)</td>
<td>0.749</td>
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<td>Mechanical pain sensitivity (0-100)</td>
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<td>Hand</td>
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<td>6.9 (5.4-8.3)</td>
<td>176</td>
<td>5.6 (4.9-7.3)</td>
<td>0.893</td>
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<td>Foot</td>
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<td>Dynamic mechanical alldynia (0-100)</td>
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<td>0 (0-0)</td>
<td>176</td>
<td>0 (0-0.2)</td>
<td>0.499</td>
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<tr>
<td>Foot</td>
<td>106</td>
<td>1.2 (0.4-1.9)</td>
<td>174</td>
<td>0.4 (0.1-1)</td>
<td>0.019</td>
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<td>Wind-up ratio</td>
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<tr>
<td>Hand</td>
<td>104</td>
<td>2.4 (2.0-2.7)</td>
<td>165</td>
<td>2.4 (2.1-2.6)</td>
<td>0.603</td>
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<tr>
<td>Foot</td>
<td>101</td>
<td>2.4 (1.9-2.8)</td>
<td>164</td>
<td>2.6 (2.3-2.9)</td>
<td>0.114</td>
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<td>DNIC (WUR before ÷ WUR after)</td>
<td>81</td>
<td>1.0 (1.0-1.0)</td>
<td>133</td>
<td>1.0 (1.0-1.0)</td>
<td>0.208</td>
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<td>Vibration detection threshold (0-8)</td>
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<td>Hand</td>
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<td>175</td>
<td>6.7 (6.3-7.0)</td>
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<tr>
<td>Foot</td>
<td>110</td>
<td>5.3 (4.7-5.7)</td>
<td>175</td>
<td>5.3 (5.0-5.7)</td>
<td>0.133</td>
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</tbody>
</table>
Figure 6.5 – Hand and foot WDT by sex, kernel density

Figure 6.6 – Tender point count by sex, kernel density
### 6.6 QST data and socio-demographic variables

Table 6.4 shows the QST data for current smokers, ex-smokers and people who have never smoked, also for non-drinkers of alcohol, people who drink up to 7 measures of alcohol per week, and people who drink more than that amount. As described previously, a significance level of $p = 0.0019$ was applied.

None of the QST measures reached this level of statistical significance for either smoking status or alcohol consumption.

Table 6.5 shows the QST data by marital status (single, married/cohabiting, divorced/separated and widowed), and by whether or not participants have children. As described previously, a significance level of $p = 0.0019$ was applied.

There were statistically significant differences in CDT at the foot and MPT at the hand for participants of different marital status. It can be seen that CDT measured at the foot was similar for single and married/cohabiting participants, slightly lower for divorced/separated participants, and much higher for widowed participants, who were therefore the least sensitive to thermal stimulus detection. MPT at the hand showed more variation between groups, being highest for married/cohabiting, next lowest for divorced/separated, then single, and lowest for widowed participants, showing a gradient of increasing sensitivity to mechanical cutaneous pain. The difference in sensitivity between the hand and foot on all QST measures has already been discussed, and in the case of marital status, there appeared to be larger differences between hand and foot for CDT, WDT, TSL and PHS in participants who were widowed than in the other groups.

Figures 6.6 and 6.7 are kernel density plots for the 2 QST variables found to differ significantly between marital status groups. Figure 6.6 shows CDT for the foot. It can be seen that the modal value was highest for divorced/separated participants, then married/cohabiting, then single, then widowed. There was a noticeably greater spread of data for the widowed participants. Figure 6.7 shows MPT for the hand. The modal value was lower for widowed participants, whereas the modal values for the other groups were much more similar to each other.

None of the QST measures reached the required level of statistical significance for differences between groups of participants having or not having children.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Non smoker (n = 147)</th>
<th>Ex-smoker (n = 124)</th>
<th>Current smoker (n = 16)</th>
<th>p =</th>
<th>Non drinker (n = 75)</th>
<th>≤ 7 units per week (n = 126)</th>
<th>&gt;7 units per week (n = 88)</th>
<th>p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal QST variables (median (95% C.I.))</td>
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<td>Cool detection threshold (°C)*</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>1.4 (1.2-1.6)</td>
<td>1.4 (1.2-1.6)</td>
<td>1.8 (1.1-3.2)</td>
<td>0.826</td>
<td>1.6 (1.4-2.1)</td>
<td>1.4 (1.2-1.6)</td>
<td>1.3 (1.1-1.6)</td>
<td>0.071</td>
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<td>Foot</td>
<td>4.7 (3.7-6.1)</td>
<td>5.0 (4.1-6.2)</td>
<td>2.6 (1.8-7.8)</td>
<td>0.426</td>
<td>6.0 (4.1-7.4)</td>
<td>4.4 (3.5-5.9)</td>
<td>4.8 (3.5-5.8)</td>
<td>0.737</td>
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<tr>
<td>Warm detection threshold (°C)*</td>
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<tr>
<td>Hand</td>
<td>1.6 (1.5-1.7)</td>
<td>1.6 (1.3-1.9)</td>
<td>1.7 (1.4-2.7)</td>
<td>0.726</td>
<td>1.8 (1.6-1.9)</td>
<td>1.6 (1.5-1.8)</td>
<td>1.5 (1.3-1.7)</td>
<td>0.090</td>
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<td>8.5 (7.2-9.2)</td>
<td>9.0 (7.3-10.9)</td>
<td>7.8 (6.3-10.7)</td>
<td>0.372</td>
<td>8.8 (6.3-11.3)</td>
<td>8.3 (7.2-9.3)</td>
<td>8.8 (6.9-9.8)</td>
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<td>Thermal sensory limen (°C)*</td>
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<tr>
<td>Hand</td>
<td>3.2 (2.9-3.5)</td>
<td>3.4 (3.0-4.0)</td>
<td>4.3 (2.6-6.9)</td>
<td>0.449</td>
<td>3.8 (3.2-4.8)</td>
<td>3.2 (2.8-3.6)</td>
<td>3.1 (2.6-3.5)</td>
<td>0.056</td>
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<td>13.5 (11.7-17.0)</td>
<td>16.6 (13.9-18.2)</td>
<td>14.6 (8.3-19.1)</td>
<td>0.500</td>
<td>16.3 (12.8-19.2)</td>
<td>13.6 (11.8-17.0)</td>
<td>15.5 (12.3-18.1)</td>
<td>0.759</td>
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<td>Paradoxical heat sensations</td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0.368</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
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<tr>
<td>Foot</td>
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<td>0 (0-1.0)</td>
<td>0.5 (0-2.2)</td>
<td>0.987</td>
<td>0 (0-1.0)</td>
<td>0 (0-1.0)</td>
<td>0.5 (0-1.0)</td>
<td>0.762</td>
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<tr>
<td>Cold pain threshold (°C)*</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>10.7 (9.7-12.8)</td>
<td>10.5 (8.9-13.1)</td>
<td>14.7 (4.9-23.9)</td>
<td>0.551</td>
<td>11.9 (9.3-15.1)</td>
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<td>8.9 (6.7-11.9)</td>
<td>0.043</td>
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<td>6.4 (3.7-8.8)</td>
<td>11.5 (4.7-21.2)</td>
<td>0.397</td>
<td>7.5 (4.6-11.3)</td>
<td>7.8 (5.7-10.5)</td>
<td>5.5 (1.8-8.8)</td>
<td>0.526</td>
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<tr>
<td>Heat pain threshold (°C)*</td>
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<tr>
<td>Hand</td>
<td>43.1 (41.9-44.9)</td>
<td>44.8 (44.0-46.1)</td>
<td>40.4 (37.0-44.8)</td>
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<td>43.6 (41.8-45.0)</td>
<td>42.8 (41.9-44.8)</td>
<td>45.4 (44.2-46.4)</td>
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<td>47.3 (46.8-47.9)</td>
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<td>46.9 (46.1-48.1)</td>
<td>46.9 (45.7-47.6)</td>
<td>47.4 (46.8-48.2)</td>
<td>0.437</td>
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</table>

*Detection thresholds and limens are given as a temperature difference (expressed positively here for convenience) but pain thresholds are given as absolute temperatures.
All p values Kruskal-Wallis
Table 6.4 – QST data by smoking and drinking status (continued)

<table>
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<th>Variable</th>
<th>Smoking</th>
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<th>Drinking alcohol</th>
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<tr>
<td></td>
<td>Non smoker (n = 147)</td>
<td>Ex-smoker (n = 124)</td>
<td>Current smoker (n = 16)</td>
<td>p =</td>
<td>Non drinker (n = 75)</td>
<td>≤ 7 units per week (n = 126)</td>
<td>&gt;7 units per week (n = 88)</td>
<td>p =</td>
</tr>
<tr>
<td>Tender point count</td>
<td>2.0 (1.0-4.0)</td>
<td>3.0 (1.0-4.0)</td>
<td>4.0 (0-8.4)</td>
<td>0.851</td>
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<td>2.5 (1.0-3.4)</td>
<td>2.0 (0-3.7)</td>
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<td>Mechanical detection threshold (mN)</td>
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</tr>
<tr>
<td>Hand</td>
<td>0.76 (0.66-0.92)</td>
<td>1.16 (0.93-1.35)</td>
<td>2.14 (0.49-3.51)</td>
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<td>1.30 (0.97-2.06)</td>
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<td>8.57 (6.50-11.31)</td>
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<tr>
<td>Hand</td>
<td>90.5 (78.8-110.0)</td>
<td>97.0 (76.5-123.2)</td>
<td>84.4 (56.4-135.6)</td>
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<td>81.6 (64.0-103.4)</td>
<td>97.0 (78.8-119.0)</td>
<td>104.0 (83.7-120.6)</td>
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<td>45.3 (36.8-64.0)</td>
<td>39.4 (20.3-132.1)</td>
<td>0.626</td>
<td>48.5 (38.3-61.4)</td>
<td>39.4 (32.0-46.4)</td>
<td>45.3 (42.1-60.3)</td>
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<tr>
<td>Hand</td>
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<td>5.3 (3.5-19.8)</td>
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<td>0.063</td>
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<tr>
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<tr>
<td>Hand</td>
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<td>0 (0-1.0)</td>
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<td>1.0 (0-2.1-4)</td>
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<td>0.167</td>
<td>1.0 (0-1.4)</td>
<td>1.1 (0-3.1-5)</td>
<td>0.3 (0-1.1-0)</td>
<td>0.252</td>
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<tr>
<td>Wind-up ratio</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
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<td>2.8 (2.4-3.2)</td>
<td>2.8 (1.6-6.8)</td>
<td>0.022</td>
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<td>2.6 (2.3-2.8)</td>
<td>2.0 (1.7-2.7)</td>
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<td>2.8 (2.5-3.5)</td>
<td>1.8 (1.6-2.2)</td>
<td>0.053</td>
<td>3.0 (2.2-3.7)</td>
<td>2.5 (2.0-2.8)</td>
<td>2.4 (2.0-2.6)</td>
<td>0.171</td>
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<td>DNIC (WUR before ÷ WUR after)</td>
<td>1.0 (1.0-1.0)</td>
<td>1.0 (1.0-1.0)</td>
<td>1.0 (0.7-1.8)</td>
<td>0.899</td>
<td>1.0 (1.0-1.0)</td>
<td>1.0 (1.0-1.0)</td>
<td>1.0 (1.0-1.2)</td>
<td>0.249</td>
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<tr>
<td>Vibration detection threshold (0-8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>6.8 (6.7-7.0)</td>
<td>6.7 (6.3-7.0)</td>
<td>6.0 (6.0-7.3)</td>
<td>0.411</td>
<td>6.3 (6.0-7.0)</td>
<td>6.7 (6.4-7.0)</td>
<td>7.0 (6.3-7.0)</td>
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<tr>
<td>Foot</td>
<td>5.3 (5.0-5.7)</td>
<td>5.0 (4.7-5.3)</td>
<td>5.7 (5.4-6.9)</td>
<td>0.028</td>
<td>5.0 (4.0-5.7)</td>
<td>5.3 (5.0-5.7)</td>
<td>5.3 (5.0-5.7)</td>
<td>0.383</td>
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Table 6.5 – QST data by marital status and having children

<table>
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<th>Variable</th>
<th>Marital status</th>
<th>Having children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single (n = 16)</td>
<td>Married/cohabiting (n = 195)</td>
</tr>
<tr>
<td></td>
<td>Divorced/ separated (n = 23)</td>
<td>Widowed (n = 53)</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Thermoal QST variables (median (95% C.I.))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cool detection threshold (°C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>1.8 (0.8-2.7)</td>
<td>1.4 (1.2-1.5)</td>
</tr>
<tr>
<td>Foot</td>
<td>4.9 (2.2-7.4)</td>
<td>4.2 (3.6-5.1)</td>
</tr>
<tr>
<td></td>
<td>1.2 (0.9-1.6)</td>
<td>2.2 (1.6-5.5)</td>
</tr>
<tr>
<td></td>
<td>1.6 (1.3-1.7)</td>
<td>9.1 (6.3-12.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm detection threshold (°C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>1.5 (1.2-1.7)</td>
<td>1.6 (1.4-1.7)</td>
</tr>
<tr>
<td>Foot</td>
<td>7.6 (5.4-11.0)</td>
<td>8.8 (7.3-9.4)</td>
</tr>
<tr>
<td></td>
<td>1.6 (1.2-2.3)</td>
<td>4.5 (3.8-9.2)</td>
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<td>1.6 (1.5-2.3)</td>
<td>9.5 (7.8-12.0)</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td>Thermal sensory limen (°C)</td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>3.1 (2.4-4.4)</td>
<td>3.2 (2.8-3.7)</td>
</tr>
<tr>
<td>Foot</td>
<td>17.5 (9.0-19.7)</td>
<td>14.2 (12.2-16.6)</td>
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<td></td>
<td>3.2 (1.8-4.2)</td>
<td>8.7 (6.2-15.8)</td>
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<td></td>
<td>3.5 (3.0-4.8)</td>
<td>18.3 (15.4-20.9)</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Paradoxical heat sensations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Foot</td>
<td>0 (0-1.8)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td></td>
<td>0 (0-0)</td>
<td>2.0 (1.0-3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold pain threshold (°C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>9.6 (4.2-16.3)</td>
<td>10.4 (9.3-12.1)</td>
</tr>
<tr>
<td>Foot</td>
<td>4.9 (0.6-10.3)</td>
<td>7.4 (4.1-8.9)</td>
</tr>
<tr>
<td></td>
<td>16.4 (10.8-20.5)</td>
<td>12.4 (5.2-22.1)</td>
</tr>
<tr>
<td></td>
<td>11.8 (9.2-15.1)</td>
<td>6.2 (1.5-11.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat pain threshold (°C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>44.4 (38.5-47.0)</td>
<td>45.0 (43.9-45.7)</td>
</tr>
<tr>
<td>Foot</td>
<td>46.7 (44.6-48.8)</td>
<td>47.1 (46.5-47.7)</td>
</tr>
<tr>
<td></td>
<td>42.0 (38.9-44.0)</td>
<td>46.3 (41.7-48.3)</td>
</tr>
<tr>
<td></td>
<td>42.1 (41.2-44.5)</td>
<td>47.3 (46.3-48.3)</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Detection thresholds and limens are given as a temperature difference (expressed positively here for convenience) but pain thresholds are given as absolute temperatures. All p values Kruskal-Wallis
Table 6.5 – QST data by marital status and having children (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Marital status</th>
<th>Having children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single (n = 16)</td>
<td>Married (n = 195)</td>
</tr>
<tr>
<td>Tender point count</td>
<td>5.0 (1.0-10.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Mechanical QST variables (median (95% C.I.))</td>
<td>Mechanical detection threshold (mN)</td>
<td>Mechanical pain threshold (mN)</td>
</tr>
<tr>
<td>Hand</td>
<td>0.97 (0.38-1.58)</td>
<td>0.93 (0.71-1.15)</td>
</tr>
<tr>
<td>Foot</td>
<td>5.10 (3.75-8.00)</td>
<td>6.50 (4.74-8.00)</td>
</tr>
<tr>
<td>Hand</td>
<td>78.8 (50.7-174.7)</td>
<td>111.4 (90.5-119.4)</td>
</tr>
<tr>
<td>Foot</td>
<td>52.1 (40.9-97.0)</td>
<td>45.3 (37.9-48.5)</td>
</tr>
<tr>
<td>Hand</td>
<td>6.2 (1.8-17.5)</td>
<td>6.1 (4.7-7.0)</td>
</tr>
<tr>
<td>Foot</td>
<td>8.3 (1.7-20.2)</td>
<td>8.0 (6.2-9.4)</td>
</tr>
<tr>
<td>Hand</td>
<td>0 (0-1.2)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Foot</td>
<td>0 (0-3.1)</td>
<td>0.4 (0.1-1.0)</td>
</tr>
<tr>
<td>Hand</td>
<td>2.3 (1.4-4.3)</td>
<td>2.3 (2.0-2.6)</td>
</tr>
<tr>
<td>Foot</td>
<td>2.8 (1.8-3.9)</td>
<td>2.3 (1.9-2.6)</td>
</tr>
<tr>
<td>Hand</td>
<td>1.0 (0.8-1.5)</td>
<td>1.0 (1.0-1.0)</td>
</tr>
<tr>
<td>Foot</td>
<td>6.3 (6.0-7.3)</td>
<td>6.7 (6.7-7.0)</td>
</tr>
<tr>
<td>Hand</td>
<td>4.7 (4.0-6.3)</td>
<td>5.3 (5.0-5.7)</td>
</tr>
</tbody>
</table>
Figure 6.6 – Foot CDT by marital status, kernel density

Figure 6.7 – Hand MPT by marital status, kernel density
Table 6.6 shows the QST data by social deprivation index and age the participant left full-time education. Social deprivation was evaluated using the Office for National Statistics’ Index of Multiple Deprivation 2010 (Office for National Statistics 2012). This divides England into 32,482 areas and numbers each one in order from the most socially deprived (1) to the least socially deprived (32,482) area. The whole PAALS study cohort was divided into quartiles and cut-off points were determined for each quartile. These were: 28 to 6365, 6421 to 24803, 24810 to 28708, and 28812 to 32425. For the sub-study group, the maximum score was 32241 (least deprived) and the minimum was 186 (most deprived). As described previously, a significance level of $p = 0.0019$ was applied.

There were statistically significant differences in CDT, TSL and MDT at the hand, and WUR at the foot, between different social deprivation index groups. There were definite trends for all 4 of these variables, with the least deprived participants having the lowest or low values and the most deprived having high or the highest values.

Figures 6.8 and 6.9 are kernel density plots for 2 of the QST variables found to differ significantly between social deprivation index groups. Figure 6.8 shows CDT for the hand by social deprivation index. The modal value was highest for the 2nd quartile, then the 1st (least deprived) quartile, and very similar for the 3rd and 4th (most deprived) quartiles. The spread of data appeared smallest for those in the 2nd quartile, similar for those in quartiles 1 and 3, and greatest for those in the 4th quartile. Figure 6.9 shows WUR for the foot by social deprivation index. The modal values increased in order of social deprivation quartile, as did the degree of data spread. Kernel density plots for the other QST measures showing statistically significant differences between social deprivation index groups are in Appendix III.

None of the QST measures reached the required level of statistical significance for age of leaving education.
Table 6.6 – QST by social deprivation index and age left education

<table>
<thead>
<tr>
<th>Variable</th>
<th>Social deprivation index</th>
<th>Age left education</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; (least deprived) quartile (n = 74)</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; quartile (n = 53)</td>
</tr>
<tr>
<td>Cool detection threshold (°C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hand 4.5 (3.2-5.9) 1.4 (1.1-1.7)</td>
<td>Foot 8.7 (6.5-9.4) 1.4 (1.2-1.8)</td>
</tr>
<tr>
<td>Warm detection threshold (°C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hand 7.9 (6.1-9.7) 1.4 (1.1-1.7)</td>
<td>Foot 13.5 (9.7-18.2) 1.4 (2.1-3.1)</td>
</tr>
<tr>
<td>Thermal sensory limen (°C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hand 17.8 (13.4-19.1) 3.6 (3.4-4.9)</td>
<td>Foot 13.5 (9.7-18.2) 2.6 (2.1-3.1)</td>
</tr>
<tr>
<td>Paradoxical heat sensations</td>
<td>Hand 0 (0-0) 0 (0-1.0)</td>
<td>Foot 0 (0-0) 0 (0-1.0)</td>
</tr>
<tr>
<td>Cold pain threshold (°C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hand 6.4 (1.9-9.8) 10.2 (6.0-12.3)</td>
<td>Foot 7.3 (2.4-10.8) 9.9 (8.8-12.4)</td>
</tr>
<tr>
<td>Heat pain threshold (°C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hand 45.9 (44.9-47.8) 44.1 (42.5-45.7)</td>
<td>Foot 47.4 (46.8-48.1) 44.1 (42.5-45.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Detection thresholds and limens are given as a temperature difference (expressed positively here for convenience) but pain thresholds are given as absolute temperatures.

All p values Kruskal-Wallis
Table 6.6 – QST by social deprivation index and age left education (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Social deprivation index</th>
<th>Age left education</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st (least deprived) quartile (n = 74)</td>
<td>2nd quartile (n = 53)</td>
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<td>Tender point count</td>
<td>2.0 (0.6-3.0)</td>
<td>2.0 (0-4.0)</td>
</tr>
<tr>
<td>Mechanical detection threshold (mN)</td>
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<tr>
<td>Hand</td>
<td>0.58 (0.45-0.93)</td>
<td>0.66 (0.47-0.94)</td>
</tr>
<tr>
<td>Foot</td>
<td>6.06 (4.51-8.74)</td>
<td>6.06 (3.70-8.07)</td>
</tr>
<tr>
<td>Mechanical pain threshold (mN)</td>
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<td></td>
</tr>
<tr>
<td>Hand</td>
<td>111.4 (90.5-137.2)</td>
<td>97.0 (64.0-130.5)</td>
</tr>
<tr>
<td>Foot</td>
<td>45.3 (42.2-64.0)</td>
<td>39.4 (27.9-52.5)</td>
</tr>
<tr>
<td>Mechanical pain sensitivity (0-100)</td>
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</tr>
<tr>
<td>Hand</td>
<td>6.6 (4.3-8.4)</td>
<td>5.1 (2.7-8.0)</td>
</tr>
<tr>
<td>Foot</td>
<td>9.7 (6.5-14.0)</td>
<td>7.5 (4.8-11.7)</td>
</tr>
<tr>
<td>Dynamic mechanical allodynia (0-100)</td>
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</tr>
<tr>
<td>Hand</td>
<td>0 (0-0.2)</td>
<td>0 (0-0.3)</td>
</tr>
<tr>
<td>Foot</td>
<td>1.0 (0.3-1.3)</td>
<td>0.2 (0-1.4)</td>
</tr>
<tr>
<td>Wind-up ratio</td>
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<tr>
<td>Hand</td>
<td>1.9 (1.6-2.5)</td>
<td>2.1 (1.6-2.7)</td>
</tr>
<tr>
<td>Foot</td>
<td>1.8 (1.5-2.5)</td>
<td>2.2 (1.8-2.6)</td>
</tr>
<tr>
<td>DNIC (WUR before ÷ WUR after)</td>
<td>1.0 (1.0-1.3)</td>
<td>1.0 (1.0-1.3)</td>
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<td>Vibration detection threshold (0-8)</td>
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<tr>
<td>Hand</td>
<td>6.7 (6.3-7.0)</td>
<td>6.7 (6.3-7.0)</td>
</tr>
<tr>
<td>Foot</td>
<td>5.0 (5.0-5.8)</td>
<td>5.3 (4.6-6.0)</td>
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</table>
Figure 6.8 – Hand CDT by social deprivation, kernel density

Figure 6.9 – Foot WUR by social deprivation, kernel density
6.7 Discussion

6.7.1 Comparison of QST data with existing literature

QST data has been collected previously on healthy volunteers and on individuals with musculoskeletal pain conditions. Data for the whole of the German Research Network on Neuropathic Pain protocol was collected from 180 healthy, pain-free volunteers aged 17 – 75 years old (Rolke et al. 2006a). The results were subdivided by age into < 40 and ≥40 years, and also by sex. The sub-study participants in the present study were aged 34 – 97 years (only one was under 40 years old), so it was most appropriate to compare the participants who had “no pain” on the day of QST assessment to the ≥40 group in the study of Rolke and colleagues. The data for CDT, WDT, TSL, PHS, CPT, HPT, MDT, MPT, ALL, WUR and VDT were so similar as to be practically indistinguishable. Only MPS (pain ratings) differed, in that the participants in the present study rated the stimuli as more painful than the participants of Rolke and colleagues’ study.

The QST data collected on people with musculoskeletal pain which could be directly compared to data from the present study are most commonly thermal detection or pain thresholds (see section 2.8.5). One such study measured CDT, WDT, CPT and HPT on fibromyalgia patients with a mean age of 49 years (Desmeules et al. 2003), another study made the same measurements on female fibromyalgia patients aged 30 – 68 years (Hurtig et al. 2001). A comparison showed that participants in the present study who had CWP on the day of QST assessment had quite similar results for CDT and HPT, but a lower WDT and lower CPT than the fibromyalgia patients in both the other studies. This showed that participants in the present study with CWP were more sensitive to warm detection, and less sensitive to cold pain than the fibromyalgia patients in both the other studies (Desmeules et al. 2003; Hurtig et al. 2001). This may be because fibromyalgia is a more extreme form of musculoskeletal pain than CWP (see section 2.2.4), or because patients have different characteristics to participants from a general population (see 6.7.2 below).

Appendix VIII contains tables giving the actual numerical values, with data from the present study from Table 6.1 presented for comparison.
6.7.2 QST and pain status

It might be seen as surprising that tender point count was the only QST measure which varied between pain status groups, given the evidence of differences in sensitivity to stimuli between individuals with musculoskeletal pain and controls found in previous studies (see section 2.8.5). Bonferroni is recognised as being a severe correction which may lead to false negatives. However, none of the relationships between variables other than tender point count and pain status even approach this level of significance. There are a number of factors which might explain this.

The previous studies on QST and musculoskeletal pain were conducted on patients, e.g. fibromyalgia patients (Desmeules et al. 2003; Geisser et al. 2003), osteoarthritis patients (Gwilym et al. 2009), and low back pain patients (Blumenstiel et al. 2011). PAALS study participants were drawn from a general population. People in the population who have pain do not always consult a health care professional regarding that pain. A study which compared survey data of 12 month period prevalence of pain in adults with health consultations for pain over the same period found that the ratio of consultation to prevalence (for any body area) was 0.29 (Andersson et al. 1999). As a result, the characteristics of patients are different from people with the same condition who did not consult. For example, a study of non-psychiatric medical outpatients reported that 31% had depression as measured by the Hospital Anxiety and Depression scale (HAD) (Zigmond and Snaith 1983), whereas a population survey found 23% of participants to have depression using the same criteria (Hinz and Brahler 2011). It is likely that other characteristics differ between patient groups and the general population, and some of these could be confounders of the relationship between QST variables and pain status.

As well as being associated with the number of body areas where pain is present, tender point count is also associated with depression, fatigue and poor sleep quality, and is considered a measure of general distress (Croft, Schollum, and Silman 1994). A longitudinal study found that a high tender point count at baseline predicted new onset of CWP, although a low pressure pain threshold at baseline did not (Gupta et al. 2007a). Tender point count has also been described as a combined measure of pain sensitivity and distress (Harth and Nielsen 2007), so it is not a straightforward measure of pressure pain threshold and its relationship with the presence of pain may be different from that of the other QST variables.
The median age of the participants in the PAALS sub-study was 68 years old, and the range was 34-97. The patients in the studies discussed in section 2.8.5 were all younger than this. For example, women with fibromyalgia aged 30-68 and healthy controls aged 21-61 (Hurtig et al. 2001), women with fibromyalgia and controls aged 30-60 (Smith et al. 2008), mean and standard deviation of age of fibromyalgia patients 50.6 (9.5), low back pain patients 43.4 (8.6) and healthy controls 38.3 (7.6) (Blumenstiel et al. 2011). In this purely descriptive section, age has not been adjusted for and may have acted as a confounder.

6.7.3 QST and age

Two or three age groups were needed to ensure that there were sufficient participants in each group for analysis to be carried out. Two groups were chosen because a justifiable dividing point was available. A cut-off point of 65 years old was chosen for three reasons. First, it is close to the median age of the sub-study group (68 years old), which means that there were sufficient numbers of participants in each age group for data analysis. Second, it is the current state retirement age in the UK and is often used to distinguish between adults and older adults. Third, changes in sensory function and pain perception have been observed between similar age groups. For example, Bartlett and colleagues found that the decrease of vibration detection threshold (measured at the foot) with age was no longer linear above the age of 65 (Bartlett et al. 1998). Also, the prevalence of painful conditions which show a mid-life peak in prevalence, such as chronic shoulder pain (Svebak, Hagen, and Zwart 2006) and CWP (Mas et al. 2008), are consistently seen to decline after the 6th or 7th decade of life.

All the detection thresholds, namely CDT, WDT, TSL, MDT (at the hand and foot) and VDT (at the foot only) showed that the older group were less sensitive to detection of stimuli than the younger group. As has already been discussed in section 2.4.3, one of the physiological changes which occurs with ageing is a reduction in nerve fibre density of both myelinated and unmyelinated fibres (McCleane 2008) and those remaining nerves are more likely to show signs of degeneration than in younger individuals (Gibson and Farrell 2004). This will reduce the ability of peripheral nerve fibres to transmit sensory information. A study found that participants became less sensitive to vibration detection with increasing age, and that these changes were more pronounced at the lower than the upper limb (Hilz et al. 1998).
The two thermal pain thresholds, HPT and CPT, were significantly different for the two age groups, HPT being hotter and CPT colder for the older group. This is in agreement with findings from previous research reported in section 2.9.2. The older age group had significantly higher ALL meaning they reported higher pain ratings in response to innocuous stimuli than the younger age group. The authors of a large (n=180) QST study on healthy volunteers stated that allodynia is “normally absent” (Rolke et al. 2006a); however, their participants were all under the age of 75, and it is possible that age-related changes made allodynia commoner in the older group in the present study.

There were non-significant trends for MPT at the hand to be higher and MPS (pain ratings) to be lower at both the hand and foot in younger than older participants, and VDT at the hand to be lower in older than younger participants. The p-value for differences in MPT at the hand with age was 0.006. It has already been mentioned that Bonferroni is a severe correction for multiple testing, so this could be a false negative. Previous research has shown that differences in pain threshold with age for mechanical stimuli is equivocal (Gibson and Farrell 2004), so an age-related difference in MPT would not necessarily be anticipated.

The remaining QST measures showed no difference between the two age groups. There was a very small amount of variance of PHS in the sub-study group as a whole, particularly measured at the hand, so it is relatively unlikely that any differences would emerge. Also, PHS are considered to be normally absent (Rolke et al. 2006a). As was discussed under “QST and pain status”, tender point count is a measure of general distress, and if the two groups were equally distressed, a difference in tender point count would not be anticipated.

There is no existing research on the effect of ageing on ratings of supra-threshold (i.e. painful) mechanical stimuli, although for thermal stimuli the rating appears to be lower for less intense stimulation, and higher for more intense stimulation, in older compared to younger people (Gibson and Farrell 2004). This finding for thermal stimuli might also be true for mechanical stimuli. Given that the MPS measure in the present study is a mean of all the pain ratings for the different weights of pinprick stimuli (see section 4.3.3), this would cancel out any difference which might exist between the age groups for low intensity and high intensity stimuli separately. From previously published data, it would be anticipated that WUR would be higher and DNIC lower for older than for younger people (see section 2.9.2). The amount of variance in the DNIC variable for the whole sub-study group was very small,
making it less likely that any significant differences between groups would be found. A study which did not statistically test the differences between age groups found that mechanical WUR was higher for younger than older people, both for males and females, in contrast to the studies cited in section 2.9.2 (Rolke et al. 2006a). However, in contrast to the present study, their age groups were divided into <40 and ≥40 years old.

It is likely that at least some of the same factors believed to be relevant to the differences in the experience of clinical pain between people of different ages will be relevant in explaining the differences in experimental sensory variables, especially experimental pain (see sections 2.4.3, 2.4.5 and 2.4.6). Hypothesised factors from the literature explaining age-related differences in QST measurements include stoicism/reluctance to report (Huang, Wang, and Lin 2010), changes in density of sensory receptors in the skin (Lin et al. 2005), decline in the function of nerve fibres carrying nociceptive signals, especially Aδ fibres (Chakour et al. 1996), degenerative changes in the central nervous system (Lariviere et al. 2007; Martina et al. 1998), and changes in central pain modulation mechanisms (Edwards and Fillingim 2001). It is unlikely that the lack of difference between age groups for any of the QST measures not showing a difference is due to confounding by sex, as 62% of the older age group were female and 61% of the younger age group were female.

### 6.7.4 QST and sex

Females and males were found to have significantly different results for WDT, TSL and MDT, with females having the smaller values i.e. being more sensitive to detecting stimuli. The results from previous research regarding sex differences in detection thresholds also indicate that females are more sensitive to warm, cool and mechanical detection, but not vibration (see section 2.9.1). The two sex groups also differed significantly with regard to tender point count, MPT and HPT. Although there are no published comparisons of tender point counts in males and females from a general population, females are generally found to have a lower pressure pain threshold than males (see section 2.9.1) and to have higher levels of psychological distress than males (see section 2.5.4), so the finding of females having a higher tender point count than males in the present study is in keeping with other published data.
The findings that HPT was significantly different between the sexes, with females having a lower HPT than males, but CPT was not significantly different is in agreement with evidence summarised in a review (Racine et al. 2012a). However, the significant difference between males and females for MPT found in the present study, with females having a lower MPT than males, is in disagreement with the evidence in the same review.

There were also some non-significant trends. Differences could be seen between the sexes for CDT at the foot and TSL at the hand, both showing females to be more sensitive to detecting stimuli, and males showed more PHS at the foot than females. Females had higher CPT at both the hand and the foot, showing that they were more sensitive to cold pain than males. Females had lower MPS (pain ratings) than males at the hand and the foot, which seems at odds with the statistically significantly higher MPT in males.

It is likely that at least some of the same factors believed to be relevant to the differences in the experience of clinical pain between males and females will be relevant in explaining the differences in experimental sensory variables, especially experimental pain (see sections 2.5.3 and 2.5.4). Many studies on sex differences in QST describe those differences, but do not suggest possible mechanisms (France and Suchowiecki 1999; Lautenbacher, Kunz, and Burkhardt 2008; Popescu et al. 2010; Rolke et al. 2006a; Sarlani and Greenspan 2002).

### 6.7.5 QST and drinking alcohol/smoking

Seven units of alcohol was chosen as the cut-off point because once the non-drinkers had been removed, it was the median weekly alcohol consumption of the remaining participants. No statistically significant differences were found between the groups of non-drinkers, people who drank 7 or fewer units of alcohol per week, and people who drank more than 7 units of alcohol per week, for any of the QST measures. There were some non-significant differences. Non-smokers had the lowest MDT at the hand and current smokers the highest. The p-value for differences in MDT at the hand with smoking status was 0.014. It has already been mentioned that Bonferroni is a severe correction for multiple testing, so this could be a false negative. There were some differences between groups in WUR at the hand and foot, and MDT at the hand, but no definite direction of trend. There is no existing evidence regarding QST and alcohol consumption. However, there
appears to be little or no connection between alcohol consumption and clinical pain (see section 2.3.8).

No statistically significant differences between the groups of current smokers, ex-smokers and people who had never smoked were found for any of the QST variables. There were non-significant trends for detection thresholds (CDT, WDT, TSL and MDT) at the hand, with drinkers in the highest category (>7 units per week) having the lowest values, and teetotallers having the highest. Drinkers in the highest category also had the highest MPT at the hand and teetotallers the lowest MPT. There is no existing evidence regarding QST and smoking, but there is some evidence for an association between smoking and clinical pain (see section 2.3.7). The small number (n = 16) of current smokers means that the power for detecting statistically significant differences between the smoking status groups was probably low.

6.7.6 QST and marital status/having children

There were statistically significant differences between the marital status groups for CDT and MPT. There is no a priori reason why those variables and no others should demonstrate differences between the groups. There is no published data regarding QST and marital status, and the evidence regarding marital status and clinical pain outlined in section 2.3.9 is equivocal.

Participants in the “widowed” category were of an older age than those in the other marital status categories. For the sub-study only, the median ages were: “married/cohabiting” – 66 years old; “single” – 62 years old; “divorced/separated” – 64 years old; “widowed” – 82.5 years old. This could lead to some confounding by age. There were non-significant differences between groups for CDT at the hand and foot, TSL and WDT at the foot and MDT at the hand, where the widowed group were less sensitive to detecting stimuli than the other groups, and the widowed group also scored highest on ALL. This was in accord with the differences already observed for age (see Table 6.2).

The different marital status categories also differed in sex distribution. For the sub-study only, percentage female was: “married/cohabiting” – 52%; “single” – 69%; “divorced/separated” – 78%; “widowed” – 87%. This could lead to some confounding by sex. A regression analysis with adjustment for confounding would be needed to see whether any significant relationships between QST variables and
marital status remained. It should be noted that the small number of participants in some of the groups, especially "single" (n = 16) means that the power for detecting statistically significant differences between the marital status groups was probably low.

No statistically significant differences between the groups of participants with children and participants with no children were found for any of the QST variables. There is no published evidence regarding having children and QST, but there is limited data showing a positive association between having children and clinical pain (see section 2.3.10).

6.7.7 QST and social deprivation/age of leaving education

There were statistically significant differences between the social deprivation index groups for CDT, TSL, MDT and WUR. There is no a priori reason why those variables and no others should demonstrate differences between the groups. There were some non-significant differences. Both CPT and HPT measured at the hand showed a trend towards participants with greater social deprivation being more sensitive to thermal pain. WUR at the hand increased with increasing social deprivation, mirroring the statistically significant difference seen for WUR measured at the foot. There is no existing data regarding QST and social deprivation, but low social class has been found to be associated with chronic pain (see section 2.3.5).

Participants were not equally distributed in terms of age and sex across the social deprivation categories. For social deprivation index group 1 (least deprived), 56% of participants were female; in group 2, 56% were female; in group 3, 64% were female; and in group 4 (most deprived), 68% were female. The median ages of participants in each group were as follows: group 1 (least deprived) - 67 years old; group 2 – 67 years old; group 3 – 80 years old; and group 4 (most deprived) – 62 years old. These differences are not as pronounced as for marital status categories, but there may still be confounding by age and sex.

No statistically significant differences between the groups of participants leaving education at different ages were found for any of the QST variables. However, there were some non-significant differences. Tender point count and MDT at both the hand and the foot decreased with increasing age of leaving education. There is no published data regarding QST and age of leaving education, but there is a body of evidence linking fewer years in education with the presence of pain (see section
2.3.6), although this is likely to be a surrogate measure for other, unidentified factors.

6.7.8 Differences between hand and foot

Tables 6.1 to 6.6 all show the differences between measurements at the hand and the foot for each QST variable. The hand was more sensitive than the foot to all the sensory detection variables: CDT, WDT, TSL, MDT and VDT. Greater numbers of PHS were recorded at the foot than the hand, although the numbers were low for both hand and foot. A study which used healthy volunteers found that up to one PHS was normal at the foot of participants aged over 40 years old (Rolke et al. 2006a). This age range would include all but one of the PAALS sub-study participants. CPT and MPT were lower and HPT, MPS and ALL slightly higher for the foot than the hand. All these differences demonstrate that the foot is less sensitive to detecting low intensity stimuli but more sensitive to painful stimuli than the hand. WUR and DNIC did not differ between the foot and the hand. The study mentioned above also found that WUR did not differ by body site, probably due to differences in pain ratings being similar for the single and multiple stimuli (Rolke et al. 2006a). The same is likely to be true of DNIC.

Published data shows differences between QST measurements at the hand and foot. One possible reason for the differences between the measurements at the hand and the foot is the differing distances which the sensory signals have to travel, i.e. that the foot is further from the brain than the hand. A study which used healthy volunteers aged 20-86 years old and measured CDT, WDT and VDT at the hand and the foot found that height was significantly associated with VDT at the foot, in that increasing height made the participant less sensitive to vibration at the foot (Bartlett et al. 1998). Another study which tested CDT, WDT, CPT and HPT on healthy participants aged 20-58 years old at several sites (dorsum of the hand, thenar eminence, volar surface of the wrist and dorsum of the foot) found that all the upper limb sites were more sensitive to warm and cool detection than the foot, but there were no differences between test sites for HPT and CPT (Hagander et al. 2000). A large study (n=530) of VDT on participants of a wide range of ages (3-79 years old) found that the increase in VDT seen with age was more pronounced at the lower than the upper limb (Hilz et al. 1998).
The differences between measurements at the hand and the foot were not the same for both sexes or for both age groups. The differences between measurements at the hand and foot for CDT, WDT, TSL, CPT, HPT, MDT, MPT and VDT were different for the two age groups. The differences between measurements at the hand and foot for CDT, WDT, TSL, CPT, MDT, and MPT were different for females and males. A study which measured QST variables at 3 sites, dorsum of the hand, dorsum of the foot and face, found interactions between test site and age for CDT, WDT, TSL, CPT, HPT, MDT, VDT and pressure pain threshold (PPT), and interactions between test site and sex for CPT, HPT, MDT, MPT, and PPT (Rolke et al. 2006a). With the exception of PPT (which was not measured in the present study) the interactions between QST variable and test site found between age groups in the present study and by Rolke and colleagues were the same, except for MPT in the present study. The interactions between QST variable and test site and sex found in the present study were not so similar to those found by Rolke and colleagues. The authors gave no suggestion as to why these interactions between QST and test site should occur with age or sex differences, or why they should occur for some variables and not others (Rolke et al. 2006a).

6.7.9 Limitations of this analysis

The limitations of QST as a set of techniques has already been discussed (see section 2.8.4), and the steps taken to ensure reliability (so far as is possible) in the present study have also been described (see sections 4.5.2 and 4.5.3).

There was a technical difficulty recording the TSL for a small number of participants, 5 when measuring TSL at the foot and 4 when measuring TSL at the hand. The difficulty arose during the warm detection part of the TSL measurement cycle (see section 4.3.3). If the participant pressed the button when the temperature was above approximately 49.6°C, the temperature continued to rise to 50°C, and both these temperatures were recorded. However, a total number of 6 measurements were still recorded, but instead of these being 3 warm detection and 3 cool detection, there would be 4 warm detection and 2 cool detection measurements. A member of the PAALS study team contacted the equipment manufacturer (Medoc) and was told that there were no plans to alter that particular software feature, and no post-hoc correction could be applied to the data. So these TSL measurements were treated as missing data.
When calculating the wind-up ratio, if the participant had rated the single pinprick as “0” the denominator was zero and the ratio incalculable. Previous authors who encountered this problem decided to treat the wind-up variable as missing data when at least 3 of the 5 single pinpricks were rated as zero, although no justification for this decision was given (Geber et al. 2011). In the present study it was decided to include data where any of the single pinpricks was rated as non-zero, i.e. the mean of the 5 measurements would not be zero, to maximise the data available for analysis. In the present study, 9 participants rated all 5 of the single pinpricks as zero at the foot, and 13 participants rated all 5 as zero at the hand. It can be seen in Table 6.1 that there are fewer WUR measurements than the other QST measures, with the exception of DNIC. DNIC is calculated as a ratio of 2 ratios, so if either of the 2 denominators were zero it was incalculable, and it has the fewest number of measurements recorded for any of the QST variables. A total of 45 participants scored one or both denominators as zero.

A small number of participants did not have thermal QST data (9 participants), MDT (4 participants) or MPT (2 participants) recorded due to equipment problems. Missing data has not been addressed in this descriptive results chapter. Because only simple relationships between a single predictor and the outcome have been considered, it has not been possible to adjust for confounding. As the QST variables were only measured on the sub-study group (n = 290), only this relatively small number of participants has been used in this chapter.

6.8 Conclusion

The lack of differences in QST variables (except tender point count) with pain status was in contrast to existing evidence given in section 2.8.5. Some of the possible reasons for this have been discussed in section 6.7.2. However, differences in several QST variables were found between the age and sex groups. Depending upon the distribution of age and sex within each pain group, this indicates the potential for confounding by age and sex. Some differences in QST variables were also found between marital status and social deprivation categories, which may be partially or wholly explained by age and sex differences. Because this is a descriptive chapter, other factors such as depression, which are known to be associated with both clinical pain and QST (see section 2.3.2), have not been adjusted for.
Some sources of missing data have been discussed in section 6.7.9, but there are also data missing from the baseline questionnaire. This becomes a much bigger problem when more variables are added to an analysis. The use of regression in Chapter 7 will allow weighting of the sub-study results to the whole study cohort, increasing the power to find any significant relationships. It will also allow multivariate analysis, i.e. the relationship between QST variables and pain whilst adjusting for other variables such as age and sex. Missing data is an issue in regression analysis, because only complete data sets are used in the analysis. The more variables which are included in the model, the greater the likelihood that the data for an individual participant will have missing items. This problem is addressed in subsequent results chapters by using imputation (see Appendix IX).
7 Results – Association between QST variables and pain

7.1 Overview

The analyses in this chapter tested hypothesis 1, which addressed the relationship between quantitative sensory test variables and the presence of pain. Change in pain status between baseline and sub-study data collection was taken into account and controlled for in the final analysis models because some variables were collected at baseline, and some at the sub-study. The data was imputed to compensate for missing data at baseline and sub-study and sampling weights applied to allow the whole study cohort to be represented in analyses using sub-study data.

Socio-demographic, behavioural, co-morbidity and psychological factors, together with QST variables, were regressed against Manchester pain count. The same factors were logistically regressed against pain status as a categorical variable, with categories “no pain”, “some pain” and CWP as defined by the ACR (Wolfe et al. 1990). The linear regression and logistic regression analyses were repeated, adjusted for age and sex, and repeated again adjusted for groups of related factors (“fully adjusted”). Final models were assembled with Manchester pain count and ACR pain status as outcomes using only those factors found to be statistically significantly associated with pain in the “fully adjusted” analyses. Principal components analysis was carried out on the QST variables, but none of the components were statistically significantly related to Manchester pain count so no component model was constructed.

The final model using Manchester pain count as an outcome included the variables sleep quality, tender point count, cool detection threshold (CDT) at the foot, thermal sensory limen (TSL) at the foot, mechanical pain threshold (MPT) at the hand, number of medications, number of sites with osteoarthritis, and the IPQ sub-scales timeline, consequences and identity. This model had an $R^2$ value of 0.4594, i.e. 46% of the variance in Manchester pain count was accounted for in the model. The final model using pain categories “no pain”, “some pain” and CWP as an outcome included the variables sleep quality, tender point count, CDT at the foot, number of medications, number of sites with osteoarthritis, MPT at the hand, and IPQ timeline.
7.2 Objectives

The present study was designed primarily to investigate the association between QST variables and the presence of pain, and the effects of moderating factors (age and sex) on this relationship, as shown in the hypothesised pathway in Figure 3.1. The study hypotheses were developed from this pathway. This Results chapter presents data which tests hypothesis 1 (see section 3.2), namely:

1) Sensitivity to stimuli (as measured by QST) will be associated with a) the primary outcome, an increasing number of pain sites, and b) the secondary outcome, the presence of CWP. Specifically:
   i) A decrease in hot, cold and mechanical pain thresholds.
   ii) An increase in subjective rating of painfulness of suprathreshold mechanical stimuli.
   iii) Warm, cool, mechanical and vibration detection thresholds and thermal sensory limen will be unchanged.
   iv) An increase in the ratio of subjective pain ratings of a single noxious mechanical stimulus to a train of 10 stimuli (WUR).
   v) A reduction in the inhibitory effect of a simultaneous conditioning stimulus (DNIC) on WUR.
   vi) An increase in the number of tender point sites.

In addition, pain cognitions (measured by the IPQ and PCS), psychological state (measured by the HAD), level of physical activity (measured by the RAPA) and sleep quality (measured by the PSQI) were regressed against the primary and secondary outcomes. These are the mediating factors shown in Figure 3.1, and these regressions tested the second half of the mediation pathway.

7.3 Comparison of pain status at baseline and sub-study measurement

The presence of pain was measured in the same way in the baseline questionnaire (see Appendix I) and the sub-study questionnaire (see Appendix IV), using a pain manikin and questions including pain duration. This was to allow pain to be assessed both at the time baseline data was collected and on the day that QST was carried out. This will have led to some discrepancies, since the data collected at baseline will be related to baseline pain status, whereas the data collected at the sub-study will be related to sub-study pain status.
The categories into which sub-study participants were recruited were based upon the ACR pain classification (see Figure 4.3) (Wolfe et al. 1990). The categories were “no pain”, “1-2 painful areas”, “3+ painful areas (but not CWP)” and “CWP”.

Table 7.1 shows that 154 (53.1%) of the 290 sub-study participants remained in the same pain status group on the day of the sub-study assessment as they had been on the baseline questionnaire. Sixty six (22.8%) participants had more pain at the time of the sub-study than at baseline, and 67 (23.1%) had less pain at sub-study than at baseline. Of the 87 participants with no pain at baseline, 28 (41.8%) had pain at sub-study, but of the 203 participants with pain at baseline only 43 (21.2%) had no pain at sub-study. Of the 133 participants who moved into another pain status group, 95 (71.4%) moved up or down by one group only. Three sub-study participants did not fill in a valid pain manikin at the time of the sub-study assessment, and they were excluded from subsequent analyses.

Spearman’s $\rho$ is a test for correlation which can be carried out on non-parametric data (see section 4.5.3); a test of correlation between pain status at baseline and sub-study yielded $p = 0.0000$, showing that it is unlikely that they are independent measures.

It was decided to create a dichotomous variable to record whether a participant’s pain status had remained the same between baseline and sub-study, or changed. This would allow the effect of a change in pain status to be assessed in the final model.
Table 7.1 – Baseline and sub-study ACR pain status

<table>
<thead>
<tr>
<th>Number of painful areas</th>
<th>None (baseline)</th>
<th>1 – 2 (baseline)</th>
<th>3+ (baseline)</th>
<th>CWP (baseline)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (sub-study)</td>
<td>58 (66.7%)</td>
<td>24 (27.9%)</td>
<td>14 (20.6%)</td>
<td>5 (10.2%)</td>
<td>101</td>
</tr>
<tr>
<td>1 – 2 (sub-study)</td>
<td>15 (17.2%)</td>
<td>36 (41.9%)</td>
<td>9 (13.2%)</td>
<td>3 (6.1%)</td>
<td>63</td>
</tr>
<tr>
<td>3+ (sub-study)</td>
<td>10 (11.5%)</td>
<td>23 (26.7%)</td>
<td>31 (45.6%)</td>
<td>12 (24.5%)</td>
<td>76</td>
</tr>
<tr>
<td>CWP (sub-study)</td>
<td>3 (3.4%)</td>
<td>3 (3.5%)</td>
<td>12 (17.6%)</td>
<td>29 (59.2%)</td>
<td>47</td>
</tr>
<tr>
<td>Missing (sub-study)</td>
<td>1 (1.1%)</td>
<td>0 (0%)</td>
<td>2 (2.9%)</td>
<td>0 (0%)</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>87 (100%)</td>
<td>86 (100%)</td>
<td>68 (100%)</td>
<td>49 (100%)</td>
<td>290</td>
</tr>
</tbody>
</table>

The percentages total to 100% for each pain category at baseline.

7.4 Relationships between QST and Manchester pain count

The data set used for the analysis in this results section was obtained by imputing (see section 4.7) the baseline and sub-study data for sub-study participants, so that each of them had full data, then sample weighting the imputed data set to allow the whole study cohort to be represented using only data collected from sub-study participants. Weighting the data in this manner is explained more fully in section 4.7. Paradoxical heat sensations (see Table 6.1) and RAPA strength and flexibility (see Table 5.2) were not included in the analysis because of the very small range recorded in these variables. This led to the formation of zero cells during the imputation process (see Appendix IX) which prevented them from being adequately imputed.

The results of the linear regression analyses were given as non-standardised $\beta$ coefficients (with 95% confidence intervals) for each individual predictor variable against the outcome of Manchester pain count at sub-study. Each predictor was
regressed univariately and then adjusted for age and sex. The “fully adjusted”
column has been adjusted for all the other variables in that table, plus age and sex.
All coefficients were rounded to four decimal places or one significant figure,
whichever had more digits. If the 95% confidence interval of the $\beta$ coefficient
included zero, this was interpreted as the predictor not being significantly related to
the outcome at $\alpha = 0.05$.

7.4.1 Socio-demographic factors

Table 7.2 shows age and sex regressed against Manchester pain count. These are
moderators in the model being tested in the present study (see Figure 3.1), but it is
also informative to see their direct association with the pain variable. This table also
contains socio-demographic variables which have been shown in previous research
to be associated with the presence of chronic pain (see section 2.3).

In Table 7.2, sex and marital status (being divorced/separated, but not single or
widowed, compared to being married/cohabiting) had a statistically significant
relationship to Manchester pain count when unadjusted, but not when adjusted for
age and sex or the other variables in the table. Social deprivation was significantly
related to Manchester pain count when unadjusted and adjusted for age and sex,
but not when fully adjusted. Age, having children, and age of leaving education
were not statistically significantly associated with an increasing number of pain
sites.

7.4.2 Behavioural factors, co-morbidity and psychological factors

Tables 7.3 and 7.4 contain the variables measuring the mediators in the
hypothetical model shown in Figure 3.1: physical activity, sleep quality,
psychological state and pain cognitions. Testing their relationship to the pain
variable tests the second part of the mediation pathway. The other variables in
Table 7.3 are behavioural factors which have been found to be associated with the
presence of chronic pain (see section 2.3) and markers of co-morbidity which are
confounders in the hypothetical model. Of the behavioural and co-morbidity factors
in Table 7.3, only sleep quality (as measured by the Pittsburgh Sleep Quality Index),
number of medications and 2-3 osteoarthritis (OA) sites compared to no OA were
statistically significantly associated with an increasing number of pain sites, even
when adjusted for age and sex or fully adjusted. The other behavioural variables (physical activity, smoking, alcohol consumption and having a confidante) were not significantly associated with Manchester pain count, with or without adjustment.

Of the psychological factors in Table 7.4, anxiety, depression, all 3 subscales of the Pain Catastrophising Scale (PCS) (magnification, rumination and helplessness), and the consequences, identity, timeline, emotional response and concern subscales of the Illness Perception Questionnaire (IPQ) were statistically significantly associated with an increasing number of pain sites, and these relationships persisted after adjusting for age and sex. Although slightly attenuated, the IPQ consequences, timeline and identity subscales remained statistically significantly associated with an increasing number of pain sites when fully adjusted.
Table 7.2 – Socio-demographic factors (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted for age and sex</th>
<th></th>
<th>Fully adjusted*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td><strong>Socio-demographic factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (34 – 97 years)</td>
<td>-0.0463</td>
<td>-0.1156 to 0.0231</td>
<td>-</td>
<td>-</td>
<td>-0.0585</td>
<td>-0.1380 to 0.0209</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>1.6992</td>
<td>0.0232 to 3.3752</td>
<td>-</td>
<td>-</td>
<td>0.8185</td>
<td>-1.0698 to 2.7067</td>
</tr>
<tr>
<td>Marital status (married is reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3.2014</td>
<td>-0.8123 to 7.2150</td>
<td>2.9000</td>
<td>-1.0213 to 6.8211</td>
<td>1.9895</td>
<td>-2.6224 to 6.6013</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>4.2333</td>
<td>0.3957 to 8.0708</td>
<td>3.8908</td>
<td>-0.0223 to 7.8039</td>
<td>3.1327</td>
<td>-0.5352 to 6.8005</td>
</tr>
<tr>
<td>Widowed</td>
<td>2.6166</td>
<td>-0.0743 to 5.3075</td>
<td>2.8896</td>
<td>-0.3976 to 6.1767</td>
<td>2.5687</td>
<td>-0.6092 to 5.7467</td>
</tr>
<tr>
<td>Having children (no is reference)</td>
<td>-2.0071</td>
<td>-4.6878 to 0.6736</td>
<td>-1.8146</td>
<td>-4.5372 to 0.9080</td>
<td>-0.9390</td>
<td>-3.8656 to 1.9875</td>
</tr>
<tr>
<td>Age left education (13 – 25 years)</td>
<td>-0.2315</td>
<td>-0.5802 to 0.1172</td>
<td>-0.2393</td>
<td>-0.5884 to 0.1098</td>
<td>-0.1295</td>
<td>-0.4766 to 0.2177</td>
</tr>
<tr>
<td>Social deprivation (186 – 32241)</td>
<td>-0.0001</td>
<td>-0.0002 to -0.00003</td>
<td>-0.0001</td>
<td>-0.0002 to -0.00003</td>
<td>-0.00006</td>
<td>-0.0001 to 0.00002</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other variables in this table
Table 7.3 – Behavioural factors & co-morbidity (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted for age and sex</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
<td>β coefficient</td>
</tr>
<tr>
<td><strong>Behavioural factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity (RAPA aerobic)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(sedentary is reference) 1 (least)</td>
<td>-1.6063</td>
<td>-5.5464 to 2.3338</td>
<td>-1.6136</td>
</tr>
<tr>
<td>2</td>
<td>-0.8128</td>
<td>-4.8378 to 3.2121</td>
<td>-0.8404</td>
</tr>
<tr>
<td>3</td>
<td>-2.9238</td>
<td>-6.5577 to 0.7101</td>
<td>-2.6180</td>
</tr>
<tr>
<td>4 (most)</td>
<td>-2.2812</td>
<td>-5.7657 to 1.2032</td>
<td>-2.0335</td>
</tr>
<tr>
<td>Smoking (non-smoker is reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>-0.3210</td>
<td>-2.0591 to 1.417</td>
<td>0.0633</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.7214</td>
<td>-4.1498 to 5.5926</td>
<td>0.8189</td>
</tr>
<tr>
<td>Alcohol (units of alcohol) (range 0 – 60)</td>
<td>-0.0575</td>
<td>-0.1684 to 0.0534</td>
<td>-0.0409</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0-21)</td>
<td>0.8026</td>
<td>0.5992 to 1.0060</td>
<td>0.7908</td>
</tr>
<tr>
<td>Having a confidante</td>
<td>-0.3937</td>
<td>-4.5028 to 3.7154</td>
<td>-0.5097</td>
</tr>
<tr>
<td>Number of medications (range 0-17)</td>
<td>0.5337</td>
<td>0.3288 to 0.7387</td>
<td>0.6092</td>
</tr>
<tr>
<td>Number of OA sites (0 reference)</td>
<td>1.2403</td>
<td>-0.2742 to 2.7548</td>
<td>1.9218</td>
</tr>
<tr>
<td></td>
<td>6.0591</td>
<td>2.0084 to 10.1098</td>
<td>6.4474</td>
</tr>
<tr>
<td></td>
<td>9.3542</td>
<td>2.8235 to 15.8849</td>
<td>10.6165</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other variables in this table, plus age and sex

RAPA = Rapid Assessment of Physical Activity  PSQI = Pittsburgh Sleep Quality Index  OA = osteoarthritis
Table 7.4 – Psychological factors (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted for age and sex</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ coefficient</td>
<td>95% confidence intervals</td>
<td>$\beta$ coefficient</td>
</tr>
<tr>
<td><strong>Psychological factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAD anxiety (range 0-21)</td>
<td>0.6090</td>
<td>0.3773 to 0.8406</td>
<td>0.5937</td>
</tr>
<tr>
<td>HAD depression (0-21)</td>
<td>0.5522</td>
<td>0.3096 to 0.7948</td>
<td>0.5669</td>
</tr>
<tr>
<td>IPQ consequences (0-10)</td>
<td>1.0856</td>
<td>0.7261 to 1.4058</td>
<td>1.0557</td>
</tr>
<tr>
<td>timeline (0-10)</td>
<td>0.7261</td>
<td>0.5337 to 0.9184</td>
<td>0.7203</td>
</tr>
<tr>
<td>personal control (0-10)</td>
<td>0.1386</td>
<td>-0.1277 to 0.4049</td>
<td>0.1855</td>
</tr>
<tr>
<td>treatment control (0-10)</td>
<td>-0.0588</td>
<td>-0.2795 to 0.1618</td>
<td>-0.0121</td>
</tr>
<tr>
<td>identity (0-10)</td>
<td>1.0143</td>
<td>0.7009 to 1.3277</td>
<td>0.9872</td>
</tr>
<tr>
<td>understanding (0-10)</td>
<td>-0.2044</td>
<td>-0.5147 to 0.1058</td>
<td>-0.1802</td>
</tr>
<tr>
<td>emotional response (0-10)</td>
<td>0.8781</td>
<td>0.5853 to 1.1708</td>
<td>0.8536</td>
</tr>
<tr>
<td>concern (0-10)</td>
<td>0.7760</td>
<td>0.4705 to 1.0816</td>
<td>0.7397</td>
</tr>
<tr>
<td>PCS rumination (0-14)</td>
<td>0.6217</td>
<td>0.3236 to 0.9198</td>
<td>0.5899</td>
</tr>
<tr>
<td>magnification (0-12)</td>
<td>1.0808</td>
<td>0.6602 to 1.5015</td>
<td>1.0376</td>
</tr>
<tr>
<td>helplessness (0-24)</td>
<td>0.5457</td>
<td>0.3029 to 0.7885</td>
<td>0.5240</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other variables in this table, plus age and sex
HAD = Hospital Anxiety and Depression scale    IPQ = Illness Perception Questionnaire    PCS = Pain Catastrophising Scale
7.4.3 Thermal and mechanical QST

Tables 7.5 and 7.6 show the QST variables regressed against Manchester pain count. These are the predictor variables in the hypothetical model shown in Figure 3.1. Of the thermal QST variables in Table 7.5, cool detection threshold (CDT) at the foot and thermal sensory limen (TSL) at the foot were statistically significantly associated with an increasing number of Manchester pain sites, both only when fully adjusted. The β coefficient for CDT at the foot was -0.1639, which was equivalent to a decrease in CDT (i.e. reduced sensitivity) of about 0.17°C for each additional pain area. The β coefficient for TSL at the foot was -0.1371, which was equivalent to a reduction in TSL (i.e. greater sensitivity) of about 0.14°C for each additional pain area. These vary in opposite directions because CDT is a negative temperature (below baseline), whereas TSL has been calculated as a positive difference in temperatures. The other thermal QST variables (warm detection threshold, heat and cold pain threshold, and paradoxical heat sensations, all measured at hand and foot, and cool detection threshold and thermal sensory limen, measured at the hand only) were not statistically significantly associated with an increasing number of pain sites.

Of the mechanical QST variables in Table 7.6, increasing tender point count was statistically significantly associated with an increasing number of Manchester pain sites, when unadjusted, when adjusted for age and sex and when fully adjusted. The β coefficient in the fully adjusted model was 0.6565, which was equivalent to about 0.7 additional tender points for each additional pain area. Increasing mechanical pain threshold at the hand was statistically significantly related to increasing Manchester pain count when adjusted for age and sex and when fully adjusted. The β coefficient in the fully adjusted model was 0.0142, meaning that MPT increased by about 0.01 mN for each additional pain area. The other mechanical QST variables (vibration detection threshold, mechanical detection threshold, mechanical pain sensitivity, allodynia and wind-up ratio at the hand and foot, mechanical pain threshold at the foot only, and descending noxious inhibitory controls (DNIC)) were not related to Manchester pain count.
### Table 7.5 – Thermal QST factors (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted for age and sex</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
<td>β coefficient</td>
</tr>
<tr>
<td><strong>Thermal QST factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foot cool detection threshold (range -0.6 to -32.0°C)</td>
<td>-0.0525</td>
<td>-0.1659 to 0.0609</td>
<td>-0.1109</td>
</tr>
<tr>
<td>Foot warm detection threshold (range 0.6 - 20.0°C)</td>
<td>-0.1121</td>
<td>-0.3072 to 0.0830</td>
<td>-0.0105</td>
</tr>
<tr>
<td>Foot thermal sensory limen (range 1.3 - 50.0°C)</td>
<td>-0.0722</td>
<td>-0.1455 to 0.0012</td>
<td>-0.0370</td>
</tr>
<tr>
<td>Foot cold pain threshold (range 0 – 27.4°C)</td>
<td>0.0138</td>
<td>-0.0739 to 0.1015</td>
<td>-0.0110</td>
</tr>
<tr>
<td>Foot heat pain threshold (range 33.2 – 50.0°C)</td>
<td>-0.2375</td>
<td>-0.5024 to 0.0274</td>
<td>-0.1467</td>
</tr>
<tr>
<td>Hand cool detection threshold (range 0.3 – 31.9°C)</td>
<td>-0.1180</td>
<td>-0.3914 to 0.1553</td>
<td>-0.1656</td>
</tr>
<tr>
<td>Hand warm detection threshold (range 0.2 – 18.0°C)</td>
<td>0.1836</td>
<td>-0.2849 to 0.6520</td>
<td>0.3423</td>
</tr>
<tr>
<td>Hand thermal sensory limen (range 0.8 – 22.2°C)</td>
<td>0.0626</td>
<td>-0.1758 to 0.3010</td>
<td>0.1288</td>
</tr>
<tr>
<td>Hand cold pain threshold (range 0 – 27.3°C)</td>
<td>0.0856</td>
<td>-0.0227 to 0.1939</td>
<td>0.0700</td>
</tr>
<tr>
<td>Hand heat pain threshold (range 33.0 – 50.0°C)</td>
<td>-0.2386</td>
<td>-0.4683 to -0.0089</td>
<td>-0.1987</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other variables in this table, plus age and sex  
*Detection threshold expressed as difference from baseline
Table 7.6 – Mechanical QST factors (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted for age and sex</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
<td>β coefficient</td>
</tr>
<tr>
<td><strong>Mechanical QST factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender point count (range 0-18)</td>
<td>0.6715</td>
<td>0.5112 to 0.8318</td>
<td>0.6838</td>
</tr>
<tr>
<td>Foot mechanical detection threshold (range 0.37 – 512 mN)</td>
<td>0.0158</td>
<td>-0.0101 to 0.0418</td>
<td>0.0175</td>
</tr>
<tr>
<td>Foot mechanical pain threshold (range 8.0 – 512 mN)</td>
<td>0.0044</td>
<td>-0.0074 to 0.0162</td>
<td>0.0053</td>
</tr>
<tr>
<td>Foot mechanical pain sensitivity (range 0 – 74.4)</td>
<td>0.0076</td>
<td>-0.0623 to 0.0775</td>
<td>0.0168</td>
</tr>
<tr>
<td>Foot allodynia (range 0 – 51.3)</td>
<td>-0.0672</td>
<td>-0.1703 to 0.0359</td>
<td>-0.0304</td>
</tr>
<tr>
<td>Foot wind-up ratio (range 0.9 – 23.3)</td>
<td>-0.0442</td>
<td>-0.3029 to 0.2146</td>
<td>-0.0917</td>
</tr>
<tr>
<td>Foot vibration detection threshold (range 0 – 8)</td>
<td>-0.1014</td>
<td>-0.5249 to 0.3222</td>
<td>-0.3602</td>
</tr>
<tr>
<td>Hand mechanical detection threshold (range 0.25 – 78.8 mN)</td>
<td>0.1202</td>
<td>-0.1446 to 0.3849</td>
<td>0.1448</td>
</tr>
<tr>
<td>Hand mechanical pain threshold (range 8.0 – 420.0 mN)</td>
<td>0.0114</td>
<td>-0.0011 to 0.0240</td>
<td>0.0137</td>
</tr>
<tr>
<td>Hand mechanical pain sensitivity (range 0 – 54.0)</td>
<td>0.0296</td>
<td>-0.0528 to 0.1119</td>
<td>0.0423</td>
</tr>
<tr>
<td>Hand allodynia (range 0 – 25.3)</td>
<td>-0.0950</td>
<td>-0.3895 to 0.1995</td>
<td>-0.0514</td>
</tr>
<tr>
<td>Hand wind-up ratio (range 0.25 – 25.0)</td>
<td>0.0712</td>
<td>-0.2412 to 0.3835</td>
<td>0.0636</td>
</tr>
<tr>
<td>Hand vibration detection threshold (range 2.3 – 8)</td>
<td>0.0187</td>
<td>-0.9595 to 0.9970</td>
<td>-0.1067</td>
</tr>
<tr>
<td>Descending noxious inhibitory controls (DNIC) (range 0.01 – 10.0)</td>
<td>-0.1109</td>
<td>-1.1920 to 0.9702</td>
<td>-0.1130</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other variables in this table, plus age and sex
### 7.4.4. Manchester pain count final model

The final regression model included all variables which were statistically significantly associated with Manchester pain count when fully adjusted, namely sleep quality, number of medications, number of OA sites, IPQ sub-scales consequences, timeline and identity, CDT at the foot, TSL at the foot, tender point count and MPT at the hand, together with the variable signifying whether pain status had changed between baseline and sub-study measurement. In this final model, sleep quality, the presence of osteoarthritis (OA) at 3 sites compared to none, IPQ timeline, CDT at the foot, TSL at the foot and tender point count remained significantly associated with the number of pain sites (see Table 7.7).

#### Table 7.7 Final regression model (imputed, survey weighted) against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>0.3699</td>
<td>0.1648 to 0.5750</td>
</tr>
<tr>
<td>Number of medications (range 0 – 17)</td>
<td>0.0248</td>
<td>-0.1626 to 0.2121</td>
</tr>
<tr>
<td>Number of OA sites (0 is reference) 1 2 3</td>
<td>0.2051 3.4110 8.0449</td>
<td>-1.4029 to 1.8130 -0.3810 to 7.2031 2.3187 to 13.7710</td>
</tr>
<tr>
<td>IPQ consequences (range 0 – 10)</td>
<td>0.2234</td>
<td>-0.0693 to 0.5161</td>
</tr>
<tr>
<td>IPQ timeline (range 0 – 10)</td>
<td>0.2500</td>
<td>0.0582 to 0.4418</td>
</tr>
<tr>
<td>IPQ identity (range 0 – 10)</td>
<td>0.1761</td>
<td>-0.1016 to 0.4537</td>
</tr>
<tr>
<td>Foot cool detection threshold (range -0.6 to -32°C)</td>
<td>-0.0968</td>
<td>-0.1831 to -0.0105</td>
</tr>
<tr>
<td>Foot thermal sensory limen (range 1.3 – 50°C)</td>
<td>-0.0788</td>
<td>-0.1475 to -0.0101</td>
</tr>
<tr>
<td>Tender point count (range 0 – 18)</td>
<td>0.3115</td>
<td>0.1375 to 0.4856</td>
</tr>
<tr>
<td>Hand mechanical pain threshold (range 8.0 – 420.0 mN)</td>
<td>0.0070</td>
<td>-0.0001 to 0.0141</td>
</tr>
</tbody>
</table>

PSQI = Pittsburgh Sleep Quality Index  
IPQ = Illness Perception Questionnaire  
OA = Osteoarthritis
In trying to ascertain how well a model fits the observed data, the $R^2$ measure expresses the proportion of the variance in an outcome which is explained by the predictor variables in the model. $R^2$ can be calculated on imputed (but not sample weighted) data in Stata using the command “mibeta”.

Table 7.8 showed the $R^2$ values for each individual variable regressed against Manchester pain count and for the whole model (excluding the variable for change of pain status).

**Table 7.8 – $R^2$ values for variables in regression model (imputed) against Manchester pain count and for whole model**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality (PSQI)</td>
<td>0.2221</td>
</tr>
<tr>
<td>Number of medications</td>
<td>0.0820</td>
</tr>
<tr>
<td>Number of OA sites</td>
<td>0.1196</td>
</tr>
<tr>
<td>IPQ consequences</td>
<td>0.1732</td>
</tr>
<tr>
<td>IPQ timeline</td>
<td>0.1706</td>
</tr>
<tr>
<td>IPQ identity</td>
<td>0.1535</td>
</tr>
<tr>
<td>Foot cool detection threshold</td>
<td>0.0019</td>
</tr>
<tr>
<td>Foot thermal sensory limen</td>
<td>0.0080</td>
</tr>
<tr>
<td>Tender point count</td>
<td>0.2109</td>
</tr>
<tr>
<td>Hand mechanical pain threshold</td>
<td>0.0133</td>
</tr>
<tr>
<td>Whole model</td>
<td><strong>0.4594</strong></td>
</tr>
</tbody>
</table>

PSQI = Pittsburgh Sleep Quality Index  
OA = osteoarthritis  
IPQ = Illness Perception Questionnaire

A parsimonious model containing only those variables still statistically significant in the final model (see Table 7.7), namely tender point count, CDT and TSL at the foot, number of OA sites, brief IPQ timeline and sleep quality, was found to have an $R^2$ of 0.4334. As tender point count is known to be a marker of distress (see section
6.7.2) as well as indicating low pressure pain threshold, HAD anxiety and HAD depression, which are measures of psychological distress, were included in the regression analysis, plus the variable for change of pain status between baseline and the sub-study. The results are shown in Table 7.9. It can be seen that only one of the six variables in the parsimonious model, namely TSL at the foot, was no longer still statistically significant in this model.

Table 7.9 – Parsimonious regression model (imputed, survey weighted) plus anxiety and depression against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>0.4358</td>
<td>0.2346 to 0.6370</td>
</tr>
<tr>
<td>IPQ timeline (range 0 – 10)</td>
<td>0.3365</td>
<td>0.1657 to 0.5073</td>
</tr>
<tr>
<td>Tender point count (range 0 – 18)</td>
<td>0.3170</td>
<td>0.1413 to 0.4926</td>
</tr>
<tr>
<td>Foot cool detection threshold (range -0.6 to -32°C)</td>
<td>-0.1003</td>
<td>-0.1958 to -0.0047</td>
</tr>
<tr>
<td>Foot thermal sensory limen (range 1.3 – 50°C)</td>
<td>-0.0637</td>
<td>-0.1339 to 0.0065</td>
</tr>
<tr>
<td>Number of OA sites (0 is reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.0730</td>
<td>-1.6373 to 1.7832</td>
</tr>
<tr>
<td>2</td>
<td>3.4614</td>
<td>-0.4110 to 7.3337</td>
</tr>
<tr>
<td>3</td>
<td>8.4585</td>
<td>2.6574 to 14.2596</td>
</tr>
<tr>
<td>HAD anxiety (range 0 – 21)</td>
<td>0.1461</td>
<td>-0.0525 to 0.3446</td>
</tr>
<tr>
<td>HAD depression (range 0 – 21)</td>
<td>-0.0348</td>
<td>-0.2445 to 0.1750</td>
</tr>
</tbody>
</table>

PSQI = Pittsburgh Sleep Quality Index  
IPQ = Illness Perception Questionnaire  
OA = osteoarthritis  
HAD = Hospital Anxiety and Depression scale

7.5 Principal components analysis

Principal components analysis (PCA) (see Appendix VII) can be used to reduce the complexity of a large number of correlated variables by loading them onto a smaller
number of uncorrelated factors called components. PCA was carried out using the Stata command “pca” on all the QST variables (except tender point count), namely warm, cool, mechanical and vibration detection thresholds, heat, cold and mechanical pain thresholds, thermal sensory limen, paradoxical heat sensation, sensory response function, allodynia and wind-up ratio for both the hand and foot, and DNIC. The analysis in this section was performed on unimputed data, as Stata 11 cannot carry out PCA on imputed data.

Tender point count was the only QST variable to be significantly related to Manchester pain count whether fully adjusted or not (see Table 7.6), so it was decided to run the PCA excluding tender point count and include that in the model independently. This also allowed PCA to be run separately for QST variables measured at the hand and foot, as it would not necessarily be expected that the variables would be associated with each other in the same way when measured at the hand and the foot.

Table 7.10 shows the coefficients for each of the QST variables, for each of the 4 principal components for the hand above the parallel analysis cut-off shown in Figure 7.1.
In Table 7.10, the highest value coefficient (ignoring signs) for each variable has been highlighted, to show which component each variable is principally loaded onto. Component 1 contains the highest coefficients for thermal detection variables, so may be labelled “Hand thermal detection”. Component 2 contains the highest coefficients for variables requiring participant ratings of mechanical stimuli, so may be labelled “Hand mechanical rating”. Component 3 contains the highest coefficients for thermal and mechanical pain thresholds, so may be labelled “Hand pain thresholds”. Component 4 contains the highest coefficients for mechanical and vibration detection thresholds, wind-up ratio and DNIC, so may be labelled “Hand mechanical detection and central processing”. It should be noted that some of the variables have a high coefficient in the “unexplained” category, e.g. DNIC, which shows that a large proportion of its variance is not explained by these components.
Table 7.10 – Coefficients of QST variables for each of four principal components (hand)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Component 1</th>
<th>Component 2</th>
<th>Component 3</th>
<th>Component 4</th>
<th>Unexplained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand cool detection threshold</td>
<td>-0.5572</td>
<td>0.0507</td>
<td>0.0005</td>
<td>0.0610</td>
<td>0.2194</td>
</tr>
<tr>
<td>(range 0.3 – 31.9°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand warm detection threshold</td>
<td>0.5726</td>
<td>0.0288</td>
<td>0.0368</td>
<td>0.0172</td>
<td>0.1382</td>
</tr>
<tr>
<td>(range 0.2 – 18.0°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand thermal sensory limen</td>
<td>0.5286</td>
<td>0.0538</td>
<td>0.0050</td>
<td>0.0161</td>
<td>0.2597</td>
</tr>
<tr>
<td>(range 0.8 – 22.2°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand cold pain threshold</td>
<td>0.0518</td>
<td>-0.0556</td>
<td><strong>-0.6453</strong></td>
<td>0.0385</td>
<td>0.2671</td>
</tr>
<tr>
<td>(range 0 – 27.3°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand heat pain threshold</td>
<td>0.1230</td>
<td>-0.0679</td>
<td><strong>0.6133</strong></td>
<td>0.0596</td>
<td>0.2661</td>
</tr>
<tr>
<td>(range 33.0 – 50.0°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand mechanical detection threshold</td>
<td>0.1092</td>
<td>-0.0291</td>
<td>0.0783</td>
<td><strong>0.5879</strong></td>
<td>0.4733</td>
</tr>
<tr>
<td>(range 0.25 – 78.8 mN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand mechanical pain threshold</td>
<td>-0.0784</td>
<td>-0.2204</td>
<td><strong>0.2899</strong></td>
<td>0.1899</td>
<td>0.6751</td>
</tr>
<tr>
<td>(range 8.0 – 420.0 mN)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand mechanical pain sensitivity</td>
<td>0.0134</td>
<td><strong>0.6459</strong></td>
<td>-0.0524</td>
<td>0.0155</td>
<td>0.1871</td>
</tr>
<tr>
<td>(range 0 – 54.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand allodynia (range 0 – 25.3)</td>
<td>0.0054</td>
<td><strong>0.6388</strong></td>
<td>0.0582</td>
<td>0.1088</td>
<td>0.2368</td>
</tr>
<tr>
<td>Hand wind-up ratio (range 0.25 – 25.0)</td>
<td>0.1484</td>
<td>-0.2475</td>
<td>-0.3258</td>
<td><strong>0.3284</strong></td>
<td>0.4890</td>
</tr>
<tr>
<td>Hand vibration detection threshold</td>
<td>0.1009</td>
<td>-0.1477</td>
<td>0.0340</td>
<td><strong>-0.6660</strong></td>
<td>0.4168</td>
</tr>
<tr>
<td>(range 2.3 – 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Descending noxious inhibitory controls (DNIC)</td>
<td>-0.1185</td>
<td>-0.1681</td>
<td>0.0498</td>
<td><strong>0.2132</strong></td>
<td>0.8519</td>
</tr>
<tr>
<td>(range 0.01 – 10.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 7.11 shows the coefficients for each of the QST variables, for each of the 3 principal components for the foot above the parallel analysis cut-off shown in Figure 7.2.

**Figure 7.2 – Number of principal components against eigenvalues for QST variables measured at the foot**

![Graph showing eigenvalues for principal components](image)

**PCA = Principal components analysis**

In Table 7.11, the highest coefficient for each variable has been highlighted, to show which component each variable is principally loaded onto. Component 1 contains the highest coefficients for all the thermal variables, as well as vibration detection threshold, so may be labelled “Foot thermal thresholds”. Component 2 contains the highest coefficients for the mechanical variables requiring participant ratings, and wind-up ratio, so may be labelled “Foot mechanical sensitivity and central processing”’. Component 3 contains the highest coefficients for mechanical detection and pain thresholds, so may be labelled “Foot mechanical thresholds”. It should be noted that some of the variables have a high coefficient in the “unexplained” category, e.g. wind-up ratio, which shows that a large proportion of its variance is not explained by these components.
Table 7.11 – coefficients of QST variables for each of four principal components (foot)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Component 1</th>
<th>Component 2</th>
<th>Component 3</th>
<th>Unexplained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foot cool detection threshold (range 0.6 – 32.0°C)</td>
<td>-0.3890</td>
<td>-0.0915</td>
<td>-0.1549</td>
<td>0.4541</td>
</tr>
<tr>
<td>Foot warm detection threshold (range 0.6 - 20°C)</td>
<td>0.4441</td>
<td>0.0586</td>
<td>-0.0075</td>
<td>0.3976</td>
</tr>
<tr>
<td>Foot thermal sensory limen (range 1.3 - 50°C)</td>
<td>0.4720</td>
<td>0.0437</td>
<td>0.0255</td>
<td>0.3229</td>
</tr>
<tr>
<td>Foot cold pain threshold (range 0 – 27.4°C)</td>
<td>-0.3719</td>
<td>0.1375</td>
<td>0.0106</td>
<td>0.6055</td>
</tr>
<tr>
<td>Foot heat pain threshold (range 33.2 – 50.0°C)</td>
<td>0.4647</td>
<td>-0.1153</td>
<td>-0.1641</td>
<td>0.3868</td>
</tr>
<tr>
<td>Foot mechanical detection threshold</td>
<td>0.0061</td>
<td>0.0437</td>
<td>0.7023</td>
<td>0.2654</td>
</tr>
<tr>
<td>Foot mechanical detection threshold (range 0.37 – 512 mN)</td>
<td>-0.0218</td>
<td>-0.0881</td>
<td>0.6629</td>
<td>0.3213</td>
</tr>
<tr>
<td>Foot mechanical pain threshold (range 8.0 – 512 mN)</td>
<td>-0.0443</td>
<td>0.6631</td>
<td>-0.0882</td>
<td>0.1785</td>
</tr>
<tr>
<td>Foot mechanical pain sensitivity (range 0 – 74.4)</td>
<td>0.0463</td>
<td>0.6486</td>
<td>0.0548</td>
<td>0.1918</td>
</tr>
<tr>
<td>Foot allodynia (range 0 – 51.3)</td>
<td>0.0230</td>
<td>-0.2726</td>
<td>-0.0350</td>
<td>0.8666</td>
</tr>
<tr>
<td>Foot wind-up ratio (range 0.9 – 23.3)</td>
<td>-0.2633</td>
<td>-0.0983</td>
<td>-0.0600</td>
<td>0.7473</td>
</tr>
</tbody>
</table>
Table 7.12 – Linear regression (weighted) of principal components against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted for age and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Principal components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Hand thermal detection”</td>
<td>-0.0068</td>
<td>-0.3958 to 0.3822</td>
</tr>
<tr>
<td>“Hand mechanical rating”</td>
<td>0.5746</td>
<td>-0.4807 to 1.6299</td>
</tr>
<tr>
<td>“Hand pain thresholds”</td>
<td>-0.6706</td>
<td>-1.4291 to 0.0880</td>
</tr>
<tr>
<td>“Hand mechanical detection and central processing”</td>
<td>0.0121</td>
<td>-0.6631 to 0.6873</td>
</tr>
<tr>
<td>“Foot thermal thresholds”</td>
<td>-0.4383</td>
<td>-0.9816 to 0.1050</td>
</tr>
<tr>
<td>“Foot mechanical sensitivity and central processing”</td>
<td>-0.4852</td>
<td>-1.4371 to 0.4667</td>
</tr>
<tr>
<td>“Foot mechanical thresholds”</td>
<td>0.5684</td>
<td>-0.1164 to 1.2532</td>
</tr>
</tbody>
</table>
Table 7.12 presents the results from a series of linear regression models (univariately and adjusted for age and sex) quantifying the relationship between each of the seven components and Manchester pain count. It can be seen that none of the components has a statistically significant association with Manchester pain count, with or without adjustment for age and sex. Therefore a final model regressing principal components found to be statistically significant against Manchester pain count could not be constructed.

7.6 Relationships between QST and ACR pain status

The same variables were included in this analysis as for that using Manchester pain count as an outcome (see section 7.4). Tables 7.13 – 7.17 present the results from a series of multiple logistic regression (hereafter generally referred to as “logistic regression”) models quantifying the relationships between each individual predictor variable and the categorical pain status outcome of CWP (ACR definition (Wolfe et al. 1990)), or “some pain” (any pain other than CWP), with “no pain” as the reference category. The data in this section are presented as relative risk ratios with 95% confidence intervals. For a categorical predictor variable, relative risk ratio is the relative risk of a given level of the predictor variable (e.g. "divorced") occurring in a particular outcome category (“some pain” or CWP) compared to it occurring in the referent category (“no pain”). For a continuous predictor variable, the relative risk ratio is the relative risk conferred by a unit increase in the predictor variable (e.g. tender point count) at a given level of the outcome variable (“some pain” or CWP) relative to the referent (“no pain”) category of the outcome variable.

If the 95% confidence intervals for relative risk ratio did not include “1”, it was interpreted that the relationship between the predictor and outcome was not significantly different for the reference category “no pain” and the comparator category “some pain” or CWP $\alpha = 0.05$. The data has been imputed (see section 4.7) and all regressions were sample weighted (see section 4.7). Each regression is also repeated, adjusted for age and sex. The “fully adjusted” column has been adjusted for all the other variables in that table, plus age and sex. All relative risk ratios and confidence intervals were rounded to 4 decimal places or one significant figure, whichever has more digits.
7.6.1 Socio-demographic factors

Table 7.13 gives relative risk ratios for socio-demographic factors logistically regressed against pain category. Compared to participants with “no pain”, those reporting CWP were significantly more likely to be younger and female (rather than male), although these relationships did not persist in the fully adjusted analysis. In addition those reporting “some pain” were significantly more likely to be younger than those with “no pain” only when fully adjusted. The other variables in Table 7.13 (sex, marital status, having children, number of children, age of leaving education and social deprivation) did not show any statistically significant relationships with pain status.

7.6.2 Behavioural, co-morbidity and psychological factors

Table 7.14 gives relative risk ratios for behavioural factors and measures of co-morbidity logistically regressed against pain category. Participants reporting CWP were significantly more likely to have poor sleep quality, have osteoarthritis and take a greater number of medications than those reporting “no pain”. These relationships persisted when adjusted for age and sex, and when fully adjusted. Also, participants reporting “some pain” were significantly more likely to have poor sleep quality and have osteoarthritis than those with “no pain”, when the relationships were unadjusted, when adjusted for age and sex and when fully adjusted, but significantly more likely to take a greater number of medications only when adjusted for age and sex. The other variables (physical activity, alcohol consumption, smoking and having a confidante) did not show any statistically significantly different relationships in the different pain status groups.

Table 7.15 gives relative risk factors for psychological factors logistically regressed against pain status. Participants reporting CWP were significantly more likely to have higher scores on the IPQ sub-scales emotional response and concern than those with “no pain”, and this relationship persisted when adjusted for age and sex, but not when fully adjusted. Participants reporting CWP or “some pain” were more likely that those with “no pain” to have greater anxiety and depression, higher scores on the IPQ sub-scales consequences, timeline and identity, and higher scores on the PCS sub-scales rumination, helplessness and magnification. These relationships persisted when adjusted for age and sex, but only the relationship for IPQ timeline persisted when fully adjusted.
Table 7.13 – Socio-demographic factors (imputed, survey weighted) logistically regressed, some pain, CWP against no pain

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted for age and sex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some pain</td>
<td>CWP</td>
<td>Some pain</td>
<td>CWP</td>
</tr>
<tr>
<td></td>
<td>Relative</td>
<td>95% confidence intervals</td>
<td>Relative</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td></td>
<td>risk ratio</td>
<td></td>
<td>risk ratio</td>
<td></td>
</tr>
<tr>
<td>Socio-demographic factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (34 – 97 years)</td>
<td>0.9789</td>
<td>0.9573 to 1.0010</td>
<td>0.9645</td>
<td>0.9344 to 0.9956</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>1.0717</td>
<td>0.6035 to 1.9032</td>
<td>2.5910</td>
<td>1.1372 to 5.9037</td>
</tr>
<tr>
<td>Marital status (married is reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0.5471</td>
<td>0.1284 to 2.3305</td>
<td>3.0987</td>
<td>0.8234 to 11.6623</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>0.5643</td>
<td>0.1797 to 1.7719</td>
<td>3.1085</td>
<td>0.9094 to 10.6253</td>
</tr>
<tr>
<td>Widowed</td>
<td>1.0595</td>
<td>0.5798 to 2.5082</td>
<td>1.6335</td>
<td>0.5676 to 4.7011</td>
</tr>
<tr>
<td>Having children (no is reference)</td>
<td>0.8945</td>
<td>0.4101 to 1.9508</td>
<td>0.4112</td>
<td>0.1666 to 1.0153</td>
</tr>
<tr>
<td>Age left education (13 – 25 years)</td>
<td>1.0045</td>
<td>0.9075 to 1.1120</td>
<td>0.9417</td>
<td>0.8029 to 1.1045</td>
</tr>
<tr>
<td>Social deprivation (186 – 32241)</td>
<td>1.0000</td>
<td>1.0000 to 1.0000</td>
<td>1.0000</td>
<td>0.9999 to 1.0000</td>
</tr>
</tbody>
</table>
Table 7.13 – Socio-demographic factors (imputed, survey weighted) logistically regressed, some pain, CWP against no pain (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fully adjusted*</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some pain</td>
<td>CWP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative risk</td>
<td>Relative risk</td>
<td>95% confidence</td>
<td>95% confidence</td>
</tr>
<tr>
<td></td>
<td>ratio</td>
<td>ratio</td>
<td>intervals</td>
<td>intervals</td>
</tr>
<tr>
<td>Socio-demographic factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (34 – 97 years)</td>
<td>0.9633</td>
<td>0.9406 to 0.9866</td>
<td>0.9706</td>
<td>0.9410 to 1.0012</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>0.7747</td>
<td>0.4392 to 1.3664</td>
<td>1.5898</td>
<td>0.7033 to 3.5937</td>
</tr>
<tr>
<td>Marital status (married is reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>0.3268</td>
<td>0.0737 to 1.4489</td>
<td>1.3705</td>
<td>0.3036 to 6.1869</td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>0.6838</td>
<td>0.2233 to 2.0942</td>
<td>2.0672</td>
<td>0.6312 to 6.7697</td>
</tr>
<tr>
<td>Widowed</td>
<td>1.8248</td>
<td>0.8301 to 4.0116</td>
<td>1.4902</td>
<td>0.5116 to 4.3412</td>
</tr>
<tr>
<td>Having children (no is reference)</td>
<td>0.6948</td>
<td>0.2795 to 1.7270</td>
<td>0.5090</td>
<td>0.1680 to 1.5422</td>
</tr>
<tr>
<td>Age left education (13 – 25 years)</td>
<td>0.9839</td>
<td>0.8827 to 1.0966</td>
<td>0.9802</td>
<td>0.8427 to 1.1401</td>
</tr>
<tr>
<td>Social deprivation (186 – 32241)</td>
<td>1.0000</td>
<td>1.0000 to 1.0000</td>
<td>1.0000</td>
<td>0.9999 to 1.0000</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other variables in this table
Table 7.14 – Behavioural factors and co-morbidity (imputed, survey weighted) logistically regressed against no pain, some pain, CWP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th></th>
<th></th>
<th>Adjusted for age and sex</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some pain</td>
<td>CWP</td>
<td>Some pain</td>
<td>CWP</td>
<td>Some pain</td>
<td>CWP</td>
<td></td>
</tr>
<tr>
<td><strong>Relative risk ratio</strong></td>
<td><strong>95% confidence intervals</strong></td>
<td><strong>Relative risk ratio</strong></td>
<td><strong>95% confidence intervals</strong></td>
<td><strong>Relative risk ratio</strong></td>
<td><strong>95% confidence intervals</strong></td>
<td><strong>Relative risk ratio</strong></td>
<td><strong>95% confidence intervals</strong></td>
</tr>
<tr>
<td><strong>Behavioural factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity (RAPA aerobic) (sedentary is reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (least)</td>
<td>1.0621</td>
<td>0.2184 to 5.1651</td>
<td>1.0062</td>
<td>0.1619 to 6.2528</td>
<td>1.0295</td>
<td>0.2065 to 5.1326</td>
<td>0.9881</td>
</tr>
<tr>
<td>2</td>
<td>0.4782</td>
<td>0.1155 to 1.9787</td>
<td>1.2443</td>
<td>0.2372 to 6.5271</td>
<td>0.5040</td>
<td>0.1155 to 2.1996</td>
<td>1.2839</td>
</tr>
<tr>
<td>3</td>
<td>0.7007</td>
<td>0.1969 to 2.4942</td>
<td>0.2962</td>
<td>0.0577 to 1.5220</td>
<td>0.7072</td>
<td>0.1895 to 2.6402</td>
<td>0.3338</td>
</tr>
<tr>
<td>4 (most)</td>
<td>0.5684</td>
<td>0.1682 to 1.9210</td>
<td>0.3301</td>
<td>0.0721 to 1.5120</td>
<td>0.5897</td>
<td>0.1663 to 2.0918</td>
<td>0.3723</td>
</tr>
<tr>
<td>Smoking (non-smoker is reference)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>1.1501</td>
<td>0.6430 to 2.0570</td>
<td>0.9267</td>
<td>0.4100 to 2.0944</td>
<td>1.2724</td>
<td>0.6945 to 2.3309</td>
<td>1.1724</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.9735</td>
<td>0.2530 to 3.7460</td>
<td>1.188</td>
<td>0.2209 to 5.6673</td>
<td>0.8243</td>
<td>0.2114 to 3.2145</td>
<td>1.0751</td>
</tr>
<tr>
<td>Alcohol (units of alcohol) (range 0 – 60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9902</td>
<td>0.9593 to 1.0221</td>
<td>0.9455</td>
<td>0.8772 to 1.0192</td>
<td>0.9858</td>
<td>0.9532 to 1.0195</td>
<td>0.9502</td>
<td>0.8769 to 1.0297</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0-21)</td>
<td>1.1334</td>
<td>1.0409 to 1.2340</td>
<td>1.4077</td>
<td>1.2269 to 1.6152</td>
<td>1.1258</td>
<td>1.0338 to 1.2260</td>
<td>1.3867</td>
</tr>
<tr>
<td>Having a confidante</td>
<td>1.1091</td>
<td>0.3693 to 3.3309</td>
<td>4.3895</td>
<td>0.5023 to 38.3564</td>
<td>1.1168</td>
<td>0.3730 to 3.3441</td>
<td>4.2081</td>
</tr>
<tr>
<td>Number of medications (range 0-17)</td>
<td>1.0609</td>
<td>0.9643 to 1.1672</td>
<td>1.2855</td>
<td>1.1546 to 1.4313</td>
<td>1.1307</td>
<td>1.0129 to 1.2623</td>
<td>1.4338</td>
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<tr>
<td>Number of OA sites (0 is reference)</td>
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<tr>
<td>2</td>
<td>3.6509</td>
<td>1.1339 to 11.7545</td>
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<td>1.7403 to 28.2714</td>
<td>4.9301</td>
<td>1.5224 to 15.9649</td>
<td>10.6096</td>
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<tr>
<td>3</td>
<td>0.8135</td>
<td>0.1031 to 6.4201</td>
<td>4.6027</td>
<td>0.6596 to 32.1182</td>
<td>1.2874</td>
<td>0.1648 to 10.0564</td>
<td>11.9079</td>
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Table 7.14 – Behavioural factors and co-morbidity (imputed, survey weighted) logistically regressed against no pain, some pain, CWP (continued)

<table>
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<tr>
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<td>Some pain</td>
<td></td>
<td>CWP</td>
<td></td>
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</tr>
<tr>
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<td>Relative risk</td>
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<td>Relative risk</td>
<td>95% confidence intervals</td>
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<tr>
<td>Physical activity (RAPA aerobic)</td>
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<tr>
<td>(sedentary is reference) 1 (least)</td>
<td>1.3631</td>
<td>0.2511 to 7.3994</td>
<td>2.4499</td>
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<tr>
<td>2</td>
<td>0.4251</td>
<td>0.1042 to 1.7342</td>
<td>1.2474</td>
<td>0.1812 to 8.5892</td>
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<tr>
<td>3</td>
<td>0.8075</td>
<td>0.2249 to 2.8987</td>
<td>0.6805</td>
<td>0.1099 to 4.2131</td>
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<tr>
<td>4 (most)</td>
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<td>0.8813</td>
<td>0.1624 to 4.7814</td>
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<td>Ex-smoker</td>
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<td>0.6334</td>
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<td>Current smoker</td>
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<td>0.1728 to 2.9442</td>
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<td>Alcohol (units of alcohol)</td>
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<td>0.9473 to 1.0200</td>
<td>0.9657</td>
<td>0.8974 to 1.0392</td>
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<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
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<td>1.0202 to 1.2393</td>
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<td>5.7558</td>
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<tr>
<td>Number of medications (range 0 – 17)</td>
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<td>1.1088 to 1.5618</td>
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<td>Number of OA sites (0 is reference)</td>
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<td>4.4536</td>
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<td>3</td>
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<td>8.4788</td>
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</table>

*Fully adjusted = adjusted for the other variables in this table, plus age and sex
RAPA = Rapid Assessment of Physical Activity  PSQI = Pittsburgh Sleep Quality Index  OA = osteoarthritis
Table 7.15 – Psychological factors (imputed, survey weighted) logistically regressed against no pain, some pain, CWP

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Adjusted for age and sex</th>
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</tr>
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<td>CWP</td>
<td>Some pain</td>
<td>CWP</td>
</tr>
<tr>
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<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Psychological factors</td>
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</tr>
<tr>
<td>HAD anxiety (0 – 21)</td>
<td>1.0263</td>
<td>0.9442 to 1.1155</td>
<td>1.2493</td>
<td>1.1283 to 1.3834</td>
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<tr>
<td>HAD depression (0 – 21)</td>
<td>1.0289</td>
<td>0.9512 to 1.1129</td>
<td>1.2125</td>
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<tr>
<td>IPQ consequences (0 – 10)</td>
<td>1.2451</td>
<td>1.0839 to 1.4302</td>
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<tr>
<td>timeline (0 – 10)</td>
<td>1.2379</td>
<td>1.1216 to 1.3663</td>
<td>1.4346</td>
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<tr>
<td>personal control (0 – 10)</td>
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<td>0.9296 to 1.1393</td>
<td>1.0727</td>
<td>0.9534 to 1.2069</td>
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<tr>
<td>treatment control (0 – 10)</td>
<td>1.0070</td>
<td>0.9159 to 1.1072</td>
<td>1.0152</td>
<td>0.9173 to 1.1235</td>
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<tr>
<td>identity (0 – 10)</td>
<td>1.1675</td>
<td>1.0383 to 1.3128</td>
<td>1.4474</td>
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<tr>
<td>understanding (0 – 10)</td>
<td>0.9147</td>
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<td>0.9004</td>
<td>0.7824 to 1.0363</td>
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<td>emotional response(0- 10)</td>
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<td>0.9961 to 1.2378</td>
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<td>concern (0 – 10)</td>
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<td>0.9873 to 1.2356</td>
<td>1.3354</td>
<td>1.1697 to 1.5247</td>
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<tr>
<td>PCS rumination (0 – 14)</td>
<td>1.1293</td>
<td>1.0124 to 1.2598</td>
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<td>1.1860 to 1.5367</td>
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<tr>
<td>magnification (0 – 12)</td>
<td>1.2345</td>
<td>1.0127 to 1.5048</td>
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<td>1.3521 to 2.0689</td>
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<td>helplessness (0 – 24)</td>
<td>1.1426</td>
<td>1.0147 to 1.2866</td>
<td>1.3096</td>
<td>1.1490 to 1.4927</td>
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</table>
Table 7.15 – Psychological factors (imputed, survey weighted) logistically regressed against no pain, some pain, CWP (continued)

<table>
<thead>
<tr>
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<td>Some pain</td>
<td></td>
<td>CWP</td>
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</tr>
<tr>
<td></td>
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<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
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<tr>
<td><strong>Psychological factors</strong></td>
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<tr>
<td>HAD anxiety (0 – 21)</td>
<td>0.9145</td>
<td>0.8029 to 1.0417</td>
<td>1.0039</td>
<td>0.8575 to 1.1754</td>
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<td>HAD depression (0– 21)</td>
<td>0.9712</td>
<td>0.8585 to 1.0986</td>
<td>0.9882</td>
<td>0.8536 to 1.1442</td>
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<tr>
<td>IPQ consequences (0 – 10)</td>
<td>1.1461</td>
<td>0.8935 to 1.4700</td>
<td>1.2303</td>
<td>0.8575 to 1.1754</td>
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<tr>
<td>timeline (0 – 10)</td>
<td>1.2077</td>
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<td>1.3487</td>
<td>1.1608 to 1.5670</td>
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<td>personal control (0 – 10)</td>
<td>1.0142</td>
<td>0.8878 to 1.1586</td>
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<td>0.8400 to 1.1919</td>
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<td>treatment control (0 – 10)</td>
<td>1.0220</td>
<td>0.9064 to 1.1524</td>
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<td>0.9161 to 1.2060</td>
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<td>identity (0 – 10)</td>
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<tr>
<td>understanding (0 -10)</td>
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<td>emotional response(0-10)</td>
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<td>concern (0 – 10)</td>
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<td>PCS rumination (0 – 14)</td>
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<td>magnification (0 – 12)</td>
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<td>1.3070</td>
<td>0.9060 to 1.8855</td>
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<tr>
<td>helplessness (0 – 24)</td>
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<td>1.0190</td>
<td>0.8016 to 1.2953</td>
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</table>

*Fully adjusted = adjusted for the other variables in this table, plus age and sex
HAD = Hospital Anxiety and Depression scale       IPQ = Illness Perception Scale       PCS = Pain Catastrophising Scale
7.6.3 Thermal and mechanical QST

Table 7.16 gives relative risk factors for thermal QST factors logistically regressed against pain status. Compared to those with “no pain”, participants with CWP were significantly more likely to have a lower CDT at the foot (i.e. reduced sensitivity), but only when the model was fully adjusted. None of the other variables (warm detection threshold, thermal sensory limen, heat pain threshold and cold pain threshold at hand and foot, and cool detection threshold at the hand) showed any significant relationships with pain status.

Table 7.17 gives relative risk factors for mechanical QST factors logistically regressed against pain status. Compared to those with “no pain”, participants with CWP were significantly more likely to have a higher tender point count and a higher mechanical pain threshold at the hand. These relationships persisted when adjusted for age and sex and when fully adjusted. In addition, those with “some pain” were significantly more likely than participants with “no pain” to have a higher tender point count, but only when adjusted for age and sex or fully adjusted.
Table 7.16 – Thermal QST factors (imputed, survey weighted) logistically regressed against no pain, some pain, CWP

<table>
<thead>
<tr>
<th>Variable</th>
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<td>Some pain</td>
<td>CWP</td>
<td>Some pain</td>
<td>CWP</td>
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</tr>
<tr>
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<td>Relative</td>
<td>95% confidence intervals</td>
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<td>Thermal QST factors</td>
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</tr>
<tr>
<td>Foot cool detection threshold (range 0.6 – 32.0°C)</td>
<td>0.9966</td>
<td>0.9638 to 1.0306</td>
<td>0.9955</td>
<td>0.9498 to 1.0434</td>
<td>0.9771</td>
<td>0.9428 to 1.0127</td>
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<td>Foot warm detection threshold (range 0.6 - 20°C)</td>
<td>0.9682</td>
<td>0.9133 to 1.0264</td>
<td>0.9208</td>
<td>0.8407 to 1.0085</td>
<td>0.9940</td>
<td>0.9323 to 1.0598</td>
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<td>Foot thermal sensory limen (range 1.3 - 50°C)</td>
<td>1.0021</td>
<td>0.9765 to 1.0284</td>
<td>0.9564</td>
<td>0.9143 to 1.0004</td>
<td>1.0185</td>
<td>0.9870 to 1.0510</td>
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<td>Foot cold pain threshold (range 0 – 27.4°C)</td>
<td>1.0022</td>
<td>0.9710 to 1.0344</td>
<td>1.0257</td>
<td>0.9820 to 1.0713</td>
<td>0.9945</td>
<td>0.9617 to 1.0284</td>
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<td>Foot heat pain threshold (range 33.2 – 50.0°C)</td>
<td>0.9861</td>
<td>0.9015 to 1.0785</td>
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<td>0.8102 to 1.0092</td>
<td>1.0132</td>
<td>0.9210 to 1.1147</td>
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<td>Hand cool detection threshold (range 0.3 – 31.9°C)</td>
<td>1.0081</td>
<td>0.8803 to 1.1544</td>
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<td>0.8617 to 1.0634</td>
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<td>0.8451 to 1.1421</td>
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<td>Hand warm detection threshold (range 0.2 – 18.0°C)</td>
<td>1.0494</td>
<td>0.9207 to 1.1961</td>
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<td>0.8977 to 1.2617</td>
<td>1.1012</td>
<td>0.9454 to 1.2827</td>
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<td>Hand thermal sensory limen (range 0.8 – 22.2°C)</td>
<td>1.0056</td>
<td>0.9312 to 1.0860</td>
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<td>0.9109 to 1.0966</td>
<td>1.0214</td>
<td>0.9340 to 1.1170</td>
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<td>Hand cold pain threshold (range 0 – 27.3°C)</td>
<td>0.9945</td>
<td>0.9622 to 1.0280</td>
<td>1.0166</td>
<td>0.9717 to 1.0636</td>
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<td>0.9589 to 1.0279</td>
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<td>Hand heat pain threshold (range 33.0 – 50.0°C)</td>
<td>0.9905</td>
<td>0.9299 to 1.0552</td>
<td>0.9364</td>
<td>0.8539 to 1.0269</td>
<td>0.9937</td>
<td>0.9258 to 1.0665</td>
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Table 7.16 – Thermal QST factors (imputed, survey weighted) logistically regressed against no pain, some pain, CWP (continued)

<table>
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<tr>
<th>Variable</th>
<th>Fully adjusted*</th>
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<th>CWP</th>
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<td>95% confidence intervals</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
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<td>Thermal QST factors</td>
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<tr>
<td>Foot cool detection threshold</td>
<td>0.9937</td>
<td>0.9458 to 1.0440</td>
<td>0.92831</td>
<td>0.8661 to 0.9950</td>
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<td>(range 0.6 – 32.0°C)</td>
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<tr>
<td>Foot warm detection threshold</td>
<td>0.9486</td>
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<td>(range 0.6 - 20°C)</td>
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<td>Foot thermal sensory limen</td>
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<td>(range 1.3 - 50°C)</td>
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<tr>
<td>Foot cold pain threshold</td>
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<td>0.9669 to 1.0429</td>
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<td>(range 0 – 27.4°C)</td>
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<tr>
<td>Foot heat pain threshold</td>
<td>1.0104</td>
<td>0.8858 to 1.1524</td>
<td>0.97507</td>
<td>0.8223 to 1.1563</td>
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<tr>
<td>(range 33.2 – 50.0°C)</td>
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<tr>
<td>Hand cool detection threshold</td>
<td>1.0947</td>
<td>0.8551 to 1.4015</td>
<td>0.9789</td>
<td>0.8214 to 1.1666</td>
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<tr>
<td>(range 0.3 – 31.9°C)</td>
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<tr>
<td>Hand warm detection threshold</td>
<td>1.2814</td>
<td>0.9847 to 1.6675</td>
<td>1.2427</td>
<td>0.8926 to 1.7302</td>
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<td>(range 0.2 – 18.0°C)</td>
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<tr>
<td>Hand thermal sensory limen</td>
<td>0.9620</td>
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<td>0.9483</td>
<td>0.8413 to 1.0689</td>
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<tr>
<td>(range 0.8 – 22.2°C)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand cold pain threshold</td>
<td>0.9729</td>
<td>0.9299 to 1.0178</td>
<td>0.9678</td>
<td>0.9130 to 1.0258</td>
<td></td>
</tr>
<tr>
<td>(range 0 – 27.3°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand heat pain threshold</td>
<td>0.9553</td>
<td>0.8722 to 1.0463</td>
<td>0.9289</td>
<td>0.8211 to 1.0507</td>
<td></td>
</tr>
<tr>
<td>(range 33.0 – 50.0°C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other variables in this table, plus age and sex
<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted for age and sex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some pain</td>
<td>CWP</td>
<td>Some pain</td>
<td>CWP</td>
</tr>
<tr>
<td></td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Tender point count (range 0–18)</td>
<td>1.0752</td>
<td>0.9978 to 1.1587</td>
<td>1.3025</td>
<td>1.1942 to 1.4207</td>
</tr>
<tr>
<td></td>
<td>1.0954</td>
<td>1.0117 to 1.1861</td>
<td>1.3199</td>
<td>1.2004 to 1.4512</td>
</tr>
<tr>
<td>Foot mechanical detection threshold (range 0.37 – 512 mN)</td>
<td>0.9983</td>
<td>0.9927 to 1.0040</td>
<td>1.0023</td>
<td>0.9960 to 1.0086</td>
</tr>
<tr>
<td></td>
<td>0.9991</td>
<td>0.9929 to 1.0052</td>
<td>1.0011</td>
<td>0.9972 to 1.0050</td>
</tr>
<tr>
<td>Foot mechanical pain threshold (range 8.0 – 512 mN)</td>
<td>0.9981</td>
<td>0.9951 to 1.0011</td>
<td>1.0003</td>
<td>0.9967 to 1.0039</td>
</tr>
<tr>
<td></td>
<td>0.9983</td>
<td>0.9952 to 1.0014</td>
<td>1.0011</td>
<td>0.9972 to 1.0050</td>
</tr>
<tr>
<td>Foot mechanical pain sensitivity (range 0 – 74.4)</td>
<td>1.0008</td>
<td>0.9818 to 1.0202</td>
<td>0.9866</td>
<td>0.9562 to 1.0179</td>
</tr>
<tr>
<td></td>
<td>1.0044</td>
<td>0.9851 to 1.0240</td>
<td>0.9926</td>
<td>0.9613 to 1.0249</td>
</tr>
<tr>
<td>Foot allodynia (range 0 – 51.3)</td>
<td>0.9866</td>
<td>0.9519 to 1.0225</td>
<td>0.9151</td>
<td>0.8066 to 1.0382</td>
</tr>
<tr>
<td></td>
<td>0.9997</td>
<td>0.9625 to 1.0383</td>
<td>0.9413</td>
<td>0.8317 to 1.0654</td>
</tr>
<tr>
<td>Foot wind-up ratio (range 0.9 – 23.3)</td>
<td>0.9845</td>
<td>0.9003 to 1.0765</td>
<td>0.9752</td>
<td>0.8638 to 1.1009</td>
</tr>
<tr>
<td></td>
<td>0.9775</td>
<td>0.8896 to 1.0741</td>
<td>0.9469</td>
<td>0.8349 to 1.0739</td>
</tr>
<tr>
<td>Foot vibration detection threshold (range 0 – 8)</td>
<td>1.0741</td>
<td>0.9486 to 1.2162</td>
<td>1.0630</td>
<td>0.8852 to 1.2765</td>
</tr>
<tr>
<td></td>
<td>1.0121</td>
<td>0.8830 to 1.1602</td>
<td>0.9175</td>
<td>0.7323 to 1.1496</td>
</tr>
<tr>
<td>Hand mechanical detection threshold (range 0.25 – 78.8 mN)</td>
<td>0.9932</td>
<td>0.9406 to 1.0486</td>
<td>1.0228</td>
<td>0.9505 to 1.1006</td>
</tr>
<tr>
<td></td>
<td>1.0025</td>
<td>0.9365 to 1.0730</td>
<td>1.0383</td>
<td>0.9630 to 1.1195</td>
</tr>
<tr>
<td>Hand mechanical pain threshold (range 8.0 – 420.0 mN)</td>
<td>1.0011</td>
<td>0.9980 to 1.0043</td>
<td>1.0047</td>
<td>1.0003 to 1.0090</td>
</tr>
<tr>
<td></td>
<td>1.0009</td>
<td>0.9975 to 1.0044</td>
<td>1.0058</td>
<td>1.0012 to 1.0105</td>
</tr>
<tr>
<td>Hand mechanical pain sensitivity (range 0 – 54.0)</td>
<td>1.0138</td>
<td>0.9866 to 1.0417</td>
<td>0.9973</td>
<td>0.9607 to 1.0353</td>
</tr>
<tr>
<td></td>
<td>1.0205</td>
<td>0.9929 to 1.0488</td>
<td>1.0064</td>
<td>0.9689 to 1.0454</td>
</tr>
<tr>
<td>Hand allodynia (range 0 – 25.3)</td>
<td>1.0052</td>
<td>0.9171 to 1.1017</td>
<td>0.9623</td>
<td>0.8254 to 1.1219</td>
</tr>
<tr>
<td></td>
<td>1.0237</td>
<td>0.9289 to 1.1282</td>
<td>0.9964</td>
<td>0.8559 to 1.1599</td>
</tr>
<tr>
<td>Hand wind-up ratio (range 0.25 – 25.0)</td>
<td>1.0108</td>
<td>0.9234 to 1.1064</td>
<td>0.9801</td>
<td>0.8585 to 1.1190</td>
</tr>
<tr>
<td></td>
<td>1.0129</td>
<td>0.9270 to 1.1067</td>
<td>0.9746</td>
<td>0.8491 to 1.1186</td>
</tr>
<tr>
<td>Hand vibration detection threshold (range 2.3 – 8)</td>
<td>0.9454</td>
<td>0.7416 to 1.2052</td>
<td>1.4249</td>
<td>0.9107 to 2.2295</td>
</tr>
<tr>
<td></td>
<td>0.8864</td>
<td>0.6881 to 1.1418</td>
<td>1.3329</td>
<td>0.8465 to 2.0988</td>
</tr>
<tr>
<td>Descending noxious inhibitory controls (DNIC) (range 0.01 – 10.0)</td>
<td>1.0548</td>
<td>0.7717 to 1.4419</td>
<td>0.9642</td>
<td>0.6231 to 1.4920</td>
</tr>
<tr>
<td></td>
<td>1.0433</td>
<td>0.7615 to 1.4294</td>
<td>0.9526</td>
<td>0.6049 to 1.5002</td>
</tr>
</tbody>
</table>
Table 7.17 – Mechanical QST factors (imputed, survey weighted) logistically regressed against no pain, some pain, CWP (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Some pain</th>
<th>CWP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fully adjusted*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Mechanical QST factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender point count (range 0-18)</td>
<td>1.0995</td>
<td>1.0096 to 1.1975</td>
</tr>
<tr>
<td>Foot mechanical detection threshold (range 0.37 – 512 mN)</td>
<td>1.0012</td>
<td>0.9934 to 1.0091</td>
</tr>
<tr>
<td>Foot mechanical pain threshold (range 8.0 – 512 mN)</td>
<td>0.9959</td>
<td>0.9918 to 1.0000</td>
</tr>
<tr>
<td>Foot mechanical pain sensitivity (range 0 – 74.4)</td>
<td>0.9792</td>
<td>0.9476 to 1.0119</td>
</tr>
<tr>
<td>Foot allodynia (range 0 – 51.3)</td>
<td>0.9661</td>
<td>0.9037 to 1.0329</td>
</tr>
<tr>
<td>Foot wind-up ratio (range 0.9 – 23.3)</td>
<td>0.9440</td>
<td>0.8528 to 1.0450</td>
</tr>
<tr>
<td>Foot vibration detection threshold (range 0 – 8)</td>
<td>1.0744</td>
<td>0.9009 to 1.2813</td>
</tr>
<tr>
<td>Hand mechanical detection threshold (range 0.25 –78.8 mN)</td>
<td>1.0062</td>
<td>0.9543 to 1.0609</td>
</tr>
<tr>
<td>Hand mechanical pain threshold (range 8.0 – 420.0 mN)</td>
<td>1.0037</td>
<td>0.9991 to 1.0083</td>
</tr>
<tr>
<td>Hand mechanical pain sensitivity (range 0 – 54.0)</td>
<td>1.0510</td>
<td>0.9990 to 1.1057</td>
</tr>
<tr>
<td>Hand allodynia (range 0 – 25.3)</td>
<td>1.0349</td>
<td>0.8958 to 1.1956</td>
</tr>
<tr>
<td>Hand wind-up ratio (range 0.25 – 25.0)</td>
<td>1.0434</td>
<td>0.9410 to 1.1570</td>
</tr>
<tr>
<td>Hand vibration detection threshold (range 2.3 – 8)</td>
<td>0.7701</td>
<td>0.5548 to 1.0691</td>
</tr>
<tr>
<td>Descending noxious inhibitory controls (DNIC) (range 0.01 – 10.0)</td>
<td>1.0256</td>
<td>0.7336 to 1.4337</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other variables in this table, plus age and sex
7.6.4. ACR pain status final model

The final regression model included all variables which were significantly differently associated with “no pain” and CWP when fully adjusted, namely sleep quality, number of medications, total number of osteoarthritis (OA) sites, brief IPQ timeline, CDT at the foot, tender point count, MPT at the hand (see Table 7.18). The variables which remained significant in the final model were sleep quality, IPQ timeline and tender point count. It was not possible to calculate $R^2$ for multiple logistic regression on imputed data using Stata, as was done for the linear regression model (see section 7.4.4).

Table 7.18 – Final logistic regression model (imputed, survey weighted) against ACR pain status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Some pain</th>
<th>CWP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk ratio</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>1.0950</td>
<td>0.9985 to 1.2008</td>
</tr>
<tr>
<td>Medications (0 – 17)</td>
<td>1.0021</td>
<td>0.8984 to 1.1177</td>
</tr>
<tr>
<td>OA total (0 is reference) 1</td>
<td>2.5753</td>
<td>0.8298 to 7.9932</td>
</tr>
<tr>
<td>OA total (0 is reference) 2</td>
<td>2.5136</td>
<td>0.6923 to 9.1260</td>
</tr>
<tr>
<td>OA total (0 is reference) 3</td>
<td>0.7730</td>
<td>0.0396 to 15.0988</td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
<td>1.2046</td>
<td>1.0905 to 1.3307</td>
</tr>
<tr>
<td>Foot cool detection threshold (range 0.6 – 32.0°C)</td>
<td>1.0005</td>
<td>0.9548 to 1.0484</td>
</tr>
<tr>
<td>Tender point count (0 – 18)</td>
<td>1.0153</td>
<td>0.9333 to 1.1046</td>
</tr>
<tr>
<td>Mechanical pain threshold (hand) (8.0 – 420.0 mN)</td>
<td>1.0011</td>
<td>0.9974 to 1.0049</td>
</tr>
</tbody>
</table>

PSQI = Pittsburgh Sleep Quality Index
OA = osteoarthritis
IPQ = Illness Perception Questionnaire

A parsimonious model was constructed containing only those variables still statistically significant in the final model (see Table 7.18), namely tender point count, brief IPQ timeline and sleep quality. As tender point count is known to be a marker of distress (see section 6.7.2) as well as indicating low pressure pain threshold, HAD anxiety and HAD depression, which are measures of psychological distress, were included in the logistic regression analysis, plus the variable for
change of pain status between baseline and the sub-study, analogous to the model used for Manchester pain count in section 7.4.4. The results are shown in Table 7.19. It can be seen that all 3 of the variables in the parsimonious model were still statistically significant when adjusted for anxiety and depression.

Table 7.19 – Parsimonious regression model (imputed, survey weighted) plus anxiety and depression against ACR pain status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Some pain</th>
<th>CWP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk</td>
<td>95% confidence</td>
</tr>
<tr>
<td></td>
<td>ratio</td>
<td>interval</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>1.1219</td>
<td>1.0193 to 1.2348</td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
<td>1.2499</td>
<td>1.1227 to 1.3914</td>
</tr>
<tr>
<td>Tender point count (0 – 18)</td>
<td>1.0391</td>
<td>0.9556 to 1.1300</td>
</tr>
<tr>
<td>HAD anxiety (0 – 21)</td>
<td>0.9592</td>
<td>0.8598 to 1.0701</td>
</tr>
<tr>
<td>HAD depression (0 – 21)</td>
<td>0.9498</td>
<td>0.8558 to 1.0541</td>
</tr>
</tbody>
</table>

PSQI = Pittsburgh Sleep Quality Index  
IPQ = Illness Perception Questionnaire  
HAD = Hospital Anxiety and Depression scale

7.7 Discussion

7.7.1 Change in pain status

The relevance of a change in a participant’s pain status was that the data collected in the baseline questionnaire would be associated with the baseline pain status, whereas the data collected at the sub-study would be associated with the pain status on that day. Existing evidence is that the number of pain sites is relatively stable over time; a population based study which divided the body into 10 sites and collected data at 2 time points 14 years apart found that 46.2% of participants reported the same number of pain sites, or one more or one fewer, at follow-up compared to baseline (Kamaleri et al. 2009a). Participants in the present study who took part in the sub-study had an interval of between approximately one month and approximately 8 months between completing the baseline and sub-study questionnaires. Given this short interval and the relative coarseness of the
gradation ("no pain", "1-2 painful areas", "3+ painful areas" or CWP) it is quite surprising that only 53.1% of participants had the same pain status. The questionnaires did state “pains during the past month” (see Appendices I and IV), so it was not simply that a participant had an atypical day when completing the pain assessment. For this reason a pain status change variable was generated and included in both final models (see sections 7.4.4 and 7.6.4), coded 0 if pain status remained the same and 1 if it changed.

In the study mentioned above, only 5.4% of those reporting any pain at baseline had no pain at follow-up (Kamaleri et al. 2009a). In the present study, 21.2% of participants reporting any pain at baseline had no pain at the time of the sub-study. Once again this is a higher proportion than would have been anticipated.

**7.7.2 Manchester pain count as outcome**

The association between the variables regressed against Manchester pain count in this Chapter, and pain, has been shown in previous studies (see sections 2.3 and 2.8.5). The variables which were found to be significantly associated with Manchester pain count after being adjusted for a group of other, related variables plus age and sex were sleep quality, number of medications, number of OA sites, IPQ sub-scales consequences, timeline and identity, tender point count, CDT at the foot, TSL at the foot and MPT at the hand. Sleep quality, number of OA sites, brief IPQ timeline, CDT at the foot, TSL at the foot and tender point count remained significant in the final model.

Sleep quality has been found to be associated with pain in previous studies (see section 2.3.4) in that poorer sleep quality has been related to the presence of clinical pain, and also to low pressure pain thresholds. The Pittsburgh Sleep Quality Index (PSQI) is scored between 0 and 21, with 0 indicating no sleep problems and 21 severe problems. The \( \beta \) coefficients listed in Table 7.3 were all positive, indicating that a higher PSQI score was associated with pain in more body areas (pain “widespreadness”). These results fit with previous evidence.

“Number of medications” has been used as an indication of general health, in that a person taking a large number of medications is likely to have more co-morbidities than someone taking few medications (Perkins et al. 2004). A greater number of co-morbidities have been found to be associated with the likelihood of reporting pain (see section 2.3.11). The \( \beta \) coefficients in Table 7.3 were positive, indicating that a
greater number of medications was associated with pain “widespreadness” as would be expected. Another measure of co-morbidity used in the present study was the presence of osteoarthritis (OA) in the hands, knees and hips, calculated as a total score ranging from 0 – 5 (see section 4.3.3). No participant had OA in more than 3 areas. The β coefficients for the association with Manchester pain count given in Table 7.3 show a definite trend, with the lowest value for 1 area of OA and the highest for 3 as compared to none. OA at 2 and 3 sites was statistically significantly associated with Manchester pain count when fully adjusted, and 3 OA sites was still significantly associated with Manchester pain count in the final model. OA is associated with clinical pain, especially in older people (see section 2.3.11), and as the median age of sub-study participants was 68 years, this is in agreement with previous studies.

The sub-scales of the brief IPQ are each related to a particular construct, based upon the work of Leventhal (see section 2.3.2). The consequences sub-scale relates to how much pain affects the person’s life, with 0 indicating no effect and 10 severe effects. The timeline sub-scale relates to the length of time the person believes the pain will last, with 0 indicating a short time and 10 forever. The identity sub-scale relates to the extent to which other symptoms are experienced as a result of pain, with 0 indicating no symptoms and 10 many severe symptoms. If a participant did not have pain at the time of completing the questionnaire, they were instructed to think about the last time they had pain (see Appendix I). It might be thought that this was particularly likely to affect the response to the timeline sub-scale, as a participant was unlikely to think the pain would last forever if it had already gone away. However, of the 96 participants with “no pain” at the time of the sub-study, 11 of them (11.5%) scored a maximum score (10) on the IPQ timeline sub-scale, and 82 of them (85.4%) scored other than zero, showing that this is not necessarily the case, indicating that negative pain beliefs are not conditional upon having pain at the time. Scoring highly on any of these three IPQ sub-scales was significantly associated with reporting increasing numbers of pain sites (Table 7.4), showing that more negative beliefs about pain were associated with an increased “widespreadness” of pain. Although negative pain beliefs, such as catastrophising and locus of control, have been found to be associated with the presence of pain (see section 2.3.2), there are no published studies using the IPQ having pain as the illness condition.

Of the QST measures in the present study, tender point count, CDT at the foot, TSL at the foot and MPT at the hand were the only ones found to be significantly
associated with Manchester pain count when fully adjusted. A higher tender point count, a lower CDT compared to baseline (i.e. a larger temperature difference from baseline), a smaller TSL and a higher MPT were all associated with greater pain “widespreadness” (see Table 7.6).

High tender point count has been found to be associated with the presence of pain (Aggarwal, Macfarlane, and McBeth 2012; Croft, Schollum, and Silman 1994) and with vulnerability to the development of CWP (Gupta et al. 2007a), so this finding in the present study confirms previous findings. Tender point count has also been associated with distress (see section 6.7.2), but the fact that tender point count was still statistically significant in a regression including measures of anxiety and depression (see Table 7.9) shows that in this case it is more likely to be a measure of reduced pressure pain threshold. Therefore these data demonstrate that increasing “widespreadness” of musculoskeletal pain is significantly associated with a widespread reduction in pressure pain threshold, indicating a generalised hypersensitivity to pressure pain.

The previous evidence available on people with musculoskeletal pain is that their thermal detection thresholds do not differ significantly from those of pain-free controls (see section 2.8.5). However, in the present study, both CDT at the foot and TSL at the foot varied with number of pain sites. Changes to detection thresholds are associated with peripheral nerve damage, e.g. diabetic neuropathy, which is also associated with the occurrence of pain (Spallone et al. 2011). While such changes could explain the association between reduced sensitivity to CDT and increasing number of painful areas, it would not explain the association between a smaller TSL (which indicates increased sensitivity) and increasing number of painful areas. Also, if peripheral nerve damage was present, it would be expected to affect other QST variables measured at the foot. CDT at the foot was 0.16°C lower (i.e. further from baseline), and TSL at the foot was 0.14°C larger, for each additional painful area, both of which are very small changes (see Table 6.1).

The limited evidence available on people with musculoskeletal pain (see section 2.8.5) indicates that a lower not higher MPT would be expected in people with more pain. The reason for the opposite being observed in the present study is unclear. It may be that changes in peripheral sensory mechanisms leading to hypoalgesia are involved; however, if this was the case, similar differences would be expected in other QST variables. It should be noted that an increase in MPT at the hand of 0.01
mN per additional body area reported as having pain is extremely small, although statistically significant (see Table 6.1).

The final model contained those variables found to be statistically significant when fully adjusted (sleep quality, number of medications, IPQ sub-scales consequences, timeline, and identity, tender point count, CDT at the foot, TSL at the foot and mechanical pain threshold at the hand). This model explained about 46% of the variance in the Manchester pain count. Comparison with other studies is difficult as $R^2$ is rarely reported in the literature, but a study of pain and disability post-fracture of the radius which considered education level, involvement in legal action and previous injury found they accounted for 25% of the variance in outcome (MacDermid et al. 2002). The parsimonious model containing only those 6 variables found to be statistically significant in the final model (sleep quality, number of OA sites, IPQ timeline, CDT at the foot, TSL at the foot and tender point count) explained about 43.3% of the variance in Manchester pain count.

### 7.7.3 ACR pain status as an outcome

Multiple logistic regression is used for an outcome variable which has more than 2 categories, but these can be ordinal or nominal. Although ordered logistic regression could have been used in these analyses, as the categories are in order of increasing number of painful body areas, the use of logistic regression allowed the comparison of variables between “no pain” and CWP, which allowed the study’s hypotheses to be tested (see section 3.2). It also allowed comparison between “some pain” and “no pain”, which meant that trends could be observed with increasing numbers of painful body areas.

The variables which were found to have significant associations with reporting CWP compared to “no pain” when fully adjusted were sleep quality, number of medications, OA total, brief IPQ timeline, tender point count, CDT at the foot and MPT at the hand. It should be noted that with the exception of TSL at the foot and the brief IPQ sub-scales consequences and identity, these are the same variables included in the final regression model with Manchester pain count as the outcome. These variables have already been discussed and compared to existing literature in section 7.7.4. One possible reason that different variables were found to be statistically significantly associated with the two different pain outcomes is that
Manchester pain count purely measures “widespreadness” of pain and does not take chronicity into account, as CWP does.

Relative risk ratios for “some pain” relative to “no pain” can be compared to CWP relative to “no pain” to look for trends. For example, the relative risk ratio for sleep quality between having “no pain” and “some pain” was smaller than the relative risk ratio between “no pain” and CWP. This was true for the unadjusted model, when adjusted for age and sex and when fully adjusted. As the relative risk ratios were all greater than one, this showed a gradient of effect of higher PSQI score (i.e. poorer sleep quality) from “no pain” to “some pain” and CWP, which provided evidence of a dose-response relationship between sleep quality and pain. The same gradient of effect was visible for number of medications, number of OA sites (especially for 3 OA sites), and the other variables found to be statistically significant when fully adjusted.

7.7.4 Advantages and limitations of this analysis

An advantage of the linear regression and multiple logistic regression models used in the present analyses is that they can be carried out on imputed and sample weighted data in Stata. The use of imputation allowed the data for all sub-study participants to be used in the analysis, as only full data sets can be used in regression analyses (called complete case analysis). In non-imputed data this meant that even one missing data point would cause a participant to be dropped from the analysis, resulting in a lower number of participants included in individual analyses, which would reduce the power to detect true relationships (type II error). There is also evidence that multiple imputation reduces the bias inherent in complete case analysis (see Appendix IX). The use of sample weighting in the present analysis models allowed the data collected at sub-study to be applied to the whole PAALS cohort. Regression also allows multivariate analysis, which allows potential confounders to be included in the model, and reduces the number of tests of significance, so eliminating the need to correct for multiple testing. Potential confounding by age, sex and other factors can be adjusted for in the models.

The present study is cross-sectional in design, so it is not possible to determine whether any observed differences in the QST variables preceded the onset of CWP or any change in the number of body areas with pain.
An attempt was made to construct a stepwise model from the variables included in this results chapter, i.e. adding variables one at a time until the maximum amount of variance in the outcome was explained. However, this was not possible due to collinearity between variables, namely that variables were being perfectly predicted by the variables already in the model, so the analysis could not continue. To overcome this problem “fully adjusted” models (Tables 7.2 – 7.6 and 7.10 – 7.14) were used.

One possible method of reducing the total number of variables in a model and avoiding collinearity is to use principal components analysis (see Appendix VII). This was carried out on the QST variables only, and 7 components which met the inclusion criteria were identified. However, none of these were statistically significantly associated with Manchester pain count, so their use was not pursued.

### 7.8 Conclusion

More participants changed in a measure of pain “widespreadness” between baseline and the sub-study than would have been anticipated in such a short period of time (1 – 8 months). This is relevant because some variables were measured in the main questionnaire, so are related to baseline pain status, and some were measured at sub-study and are therefore related to pain measured at that time point. This issue was accommodated in the final model by having a binary variable for change in pain status.

Principal component analysis was carried out on the QST data (excluding tender point count) and successfully found 7 components. However, none of them were statistically significantly associated with Manchester pain count, so they were not used to construct a model. This is unsurprising as the only QST variables significantly associated with Manchester pain count were MPT at the hand, CDT at the foot and TSL at the foot.

Far fewer QST variables were statistically significantly associated with pain than would have been expected from previously published data. Tender point count, cold detection threshold at the foot, thermal sensory limen at the foot and mechanical pain threshold at the hand were significantly associated with Manchester pain count, and there was a significant difference in the association of tender point count, cold detection threshold at the foot, and mechanical pain threshold measured at the hand with “no pain” and CWP. Referring back to the
objectives stated in section 7.1 hypotheses i) to v) were not supported. A difference in two of the detection thresholds (CDT at the foot and TSL at the foot) with pain were found, contrary to hypothesis iii. Hypothesis i stated there would be a decrease in pain thresholds, and even though there was a significant relationship between MPT and pain, it was in the opposite direction to that proposed. Only hypothesis vi) “There will be an increase in the number of tender point sites with a) and increasing number of Manchester pain sites and b) CWP”, was supported. The other QST variables were not significantly related to pain even when unadjusted.

Tender point count was significantly associated with both pain outcomes. As tender point count is an indicator of general distress (Croft, Schollum, and Silman 1994) as well as pressure pain threshold, a further linear regression analysis was performed which included factors which were statistically significant in the final model, plus HAD anxiety and HAD depression, which are measures of psychological distress. Tender point count remained significantly associated with Manchester pain count in this model, showing that in this case it appears to indicate pressure pain threshold, and that widespread mechanical hypersensitivity is associated with CWP. Referred hyperalgesia, i.e. increased sensitivity to painful stimuli in areas of the body not experiencing pain, can be a sign of central sensitisation (Graven-Nielsen and Arendt-Nielsen 2002).

The QST data from the present study has already been compared to the literature in section 6.7.1. The differences may be largely due to the fact that published data were collected from screened, “healthy” volunteers or from patients whereas the PAALS cohort is a population-based cohort.

In the final linear regression model, ten predictor variables accounted for 46% of the variance in Manchester pain count. Although $R^2$ values are not often published, this appears to be quite a large proportion.
8 Results – Age and sex as moderators of the relationship between QST and pain

8.1 Overview

The analyses in this chapter tested hypotheses 2 and 3, which addressed the moderating effects of age and sex respectively on the relationships between QST variables and pain. The data was imputed to compensate for missing data at baseline and sub-study, and sampling weights were applied to allow the whole study cohort to be represented in analyses using data from sub-study participants.

Three QST predictor variables, tender point count, cool detection threshold (CDT) at the foot, and thermal sensory limen (TSL) at the foot, were found to be significantly associated with Manchester pain count in the final model in Chapter 7. Two QST predictor variables, tender point count and CDT at the foot, were found to be significantly associated with ACR pain status in the final model in Chapter 7. The use of an interaction term allowed the effect of a moderator on the association between each predictor variable and outcome variable to be ascertained. The relevant QST variables were each included in new models as an interaction term with age, and in separate models as an interaction term with sex. The predictor and moderator variables were also included separately in each model. These analyses were repeated, adjusted for the other factors found to be statistically significant in Chapter 7. This process was carried out with Manchester pain count and ACR pain status as outcomes.

It was found that the relationships between Manchester pain count and tender point count, CDT at the foot and TSL at the foot, and between ACR pain status and both CDT at the foot and tender point count, were not moderated by age or sex.

8.2 Objectives

The present study was designed primarily to investigate the association between QST variables and the presence of pain, and the effects of moderating factors (age and sex) on this relationship, as shown in the hypothesised pathway in Figure 3.1. The study hypotheses were developed from this pathway. This Results chapter presents data which tests hypotheses 2 and 3 (see section 3.2), namely:

2) The relationship between QST results and chronic pain will be moderated by age so that detection thresholds will increase, pain thresholds will increase,
subjective pain ratings will increase, WUR will increase and DNIC will decrease with increasing age, and that this will be more pronounced at the foot than the hand.

3) The relationship between QST results and chronic pain will be moderated by sex so that pain thresholds will be lower, pain ratings higher, WUR higher and DNIC lower for women than men. Detection thresholds will be unaffected by sex.

These hypotheses were only tested on those QST variables which were found to be significantly associated with pain in the final models in Chapter 7, because it is more likely that a detectable moderating effect would be discernable for these than for the other QST variables. For a binary moderating variable to significantly moderate the relationship between a predictor variable and an outcome variable which was not in itself statistically significant, the relationship for one of the categories would have to be very slight, e.g. a positive relationship for females and no relationship for males, or the relationships for the categories would need to vary in opposite directions, e.g. a positive relationship for females and negative for males. There is no a priori reason to expect this to be the case for the relationships involving any of the QST variables.

8.3 Moderation of QST variables by age

Moderation was modelled by creating an interaction term between CDT at the foot, TSL at the foot or tender point count, and age group. Age was divided into two groups: 65 years or under, and over 65 years (see section 4.7 for more detail). The analyses were carried out on imputed, survey-weighted data (see Appendices IX and VI respectively). Separate analyses were carried out for the CDT, TSL and tender point count interaction terms, against Manchester pain count, and for the CDT and tender point count interaction terms against ACR pain status. Each analysis also contained the separate predictor and moderator variables which made up the interaction term, because this was essential to allow correct interpretation of the statistics (see Appendix X). Linear regression was used for the continuous outcome variable, and data were presented as β coefficients with 95% confidence intervals (C.I.). If the 95% C.I did not include “0”, the result was considered to be statistically significant. Multiple logistic regression was used for the categorical pain status outcome variable “no pain”, “some pain” or CWP, and data are presented as
relative risk ratios with 95% confidence intervals. In the multiple logistic regression models, if the 95% C.I. did not include “1”, the result was considered to be statistically significant. The analyses were repeated adjusted for the variables found to be statistically significantly related to the relevant outcome pain variable in the Chapter 7 final models (see Tables 7.7 and 7.18), namely number of OA sites, IPQ timeline and sleep quality for the linear regression, and IPQ timeline and sleep quality for the logistic regression, plus sex. All coefficients were rounded to four decimal places or one significant figure, whichever had more digits.

Results
In a univariate model, i.e. containing only the outcome, interaction term, moderator and predictor variables, the relationship between CDT at the foot and Manchester pain count was not significantly moderated by age. This persisted in the fully adjusted model (see Table 8.1). Similarly, the relationships between TSL and the foot (see Table 8.2) and Manchester pain count, and tender point count (see Table 8.3) and Manchester pain count were not statistically significantly moderated by age, in either the univariate or fully adjusted models.

Age did not moderate the relative risk ratios of CDT at the foot between the categories “no pain” and “some pain” or CWP. This was the case for the univariate and fully adjusted models (see Table 8.4). Similarly, age did not moderate the relative risk ratio of tender point count (see Table 8.5) between the pain categories, when unadjusted or fully adjusted.
Table 8.1 – Foot CDT moderated by age (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Cool detection threshold x age group</td>
<td>0.1382</td>
<td>-0.2506 to 0.5269</td>
</tr>
<tr>
<td>Cool detection threshold (foot) (range 0.6 – 32.0°C)</td>
<td>-0.1923</td>
<td>-0.5576 to 0.1731</td>
</tr>
<tr>
<td>Age group (younger is reference)</td>
<td>-0.6823</td>
<td>-3.1355 to 1.7710</td>
</tr>
<tr>
<td>Osteoarthritis total (0 is reference)</td>
<td></td>
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<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
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<tr>
<td>IPQ timeline (0 – 10)</td>
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<td>Sex (male is reference)</td>
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</tbody>
</table>

*Fully adjusted = adjusted for the other factors in the model  
IPQ = Illness Perception Questionnaire  
PSQI = Pittsburgh Sleep Quality Index
Table 8.2 – Foot TSL moderated by age (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
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<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
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<tr>
<td>Thermal sensory limen x age group</td>
<td>-0.0246</td>
<td>-0.1931 to 0.1440</td>
<td>0.774</td>
<td>-0.0399</td>
<td>-0.1519 to 0.0721</td>
<td>0.483</td>
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<tr>
<td>Thermal sensory limen (foot) (range 1.3 - 50°C)</td>
<td>-0.0489</td>
<td>-0.1908 to 0.0930</td>
<td>0.498</td>
<td>0.0077</td>
<td>-0.0790 to 0.0944</td>
<td>0.861</td>
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<tr>
<td>Age group (younger is reference)</td>
<td>-0.3006</td>
<td>-3.7652 to 3.1639</td>
<td>0.864</td>
<td>0.1293</td>
<td>-2.4471 to 2.7057</td>
<td>0.921</td>
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<td>Osteoarthritis total (0 is reference)</td>
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<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
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<td>IPQ timeline (0 – 10)</td>
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<td>Sex (male is reference)</td>
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</table>

*Fully adjusted = adjusted for the other factors in the model  
IPQ = Illness Perception Questionnaire  
PSQI = Pittsburgh Sleep Quality Index
Table 8.3 – Tender point count moderated by age (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Tender point count x age group</td>
<td>-0.1995</td>
<td>-0.5240 to 0.1251</td>
</tr>
<tr>
<td>Tender point count (range 0 – 18)</td>
<td>0.7577</td>
<td>0.5445 to 0.9708</td>
</tr>
<tr>
<td>Age group (younger is reference)</td>
<td>-0.1715</td>
<td>-1.6543 to 1.3114</td>
</tr>
<tr>
<td>Osteoarthritis total (0 is reference)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
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<td>2</td>
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<td>-</td>
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<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
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<td>-</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other factors in the model  
IPQ = Illness Perception Questionnaire  
PSQI = Pittsburgh Sleep Quality Index
### Table 8.4 – Foot CDT moderated by age (imputed, survey weighted) logistically regressed, some pain, CWP against no pain

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some pain</td>
<td>CWP</td>
</tr>
<tr>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>p</td>
</tr>
<tr>
<td>Cool detection threshold x age group</td>
<td>1.0419</td>
<td>0.9492 to 1.1437</td>
</tr>
<tr>
<td>Cool detection threshold (foot) (range 0.6 – 32.0°C)</td>
<td>0.9514</td>
<td>0.8733 to 1.0365</td>
</tr>
<tr>
<td>Age group (younger is reference)</td>
<td>0.7044</td>
<td>0.3150 to 1.5750</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other factors in the model  
IPQ = Illness Perception Questionnaire  
PSQI = Pittsburgh Sleep Quality Index
Table 8.5 – Tender point count moderated by age (imputed, survey weighted) logistically regressed, some pain, CWP against no pain

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Some pain</td>
<td>CWP</td>
</tr>
<tr>
<td></td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Tender point count x age group</td>
<td>0.8790</td>
<td>0.7516 to 1.0281</td>
</tr>
<tr>
<td>Tender point count (range 0 – 18)</td>
<td>1.1596</td>
<td>1.0241 to 1.3131</td>
</tr>
<tr>
<td>Age group (younger is reference)</td>
<td>0.8314</td>
<td>0.4002 to 1.7274</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other factors in the model  
IPQ = Illness Perception Questionnaire  
PSQI = Pittsburgh Sleep Quality Index
Moderation was modelled by creating an interaction term between CDT at the foot, TSL at the foot, or tender point count and sex (see section 4.7 for more detail). Separate analyses were carried out for each QST variable interaction term, for each of the outcomes Manchester pain count and ACR pain status. Linear regression was used for the continuous outcome variable, and data were presented as β coefficients with 95% confidence intervals (C.I.). If the 95% C.I did not include “0”, the result was considered to be statistically significant. Multiple logistic regression was used for the categorical pain status outcome variable “no pain”, “some pain” or CWP, and data are presented as relative risk ratios with 95% confidence intervals. In the multiple logistic regression models, if the 95% C.I. did not include “1”, the result was considered to be statistically significant. The analyses were repeated adjusted for the variables found to be statistically. All coefficients were rounded to four decimal places or one significant figure, whichever had more digits.

**Results**

In a univariate model, the relationship between CDT at the foot and Manchester pain count was not significantly moderated by sex. This persisted in the fully adjusted model (see Table 8.6). Similarly, the relationships between TSL at the foot and Manchester pain count (see Table 8.7), and tender point count and Manchester pain count (see Table 8.8) were not statistically significantly moderated by sex, in either the univariate or fully adjusted models.

Sex did not moderate the relative risk ratios of CDT at the foot between the categories “no pain” and “some pain” or CWP. This was the case for the univariate and fully adjusted models (see Table 8.9). Similarly, sex did not moderate the relative risk ratio of tender point count (see Table 8.10) between the pain categories, when unadjusted or fully adjusted.
Table 8.6 – Foot CDT moderated by sex (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta coefficient</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Cool detection threshold x sex</td>
<td>0.0652</td>
<td>-0.1677 to 0.2981</td>
</tr>
<tr>
<td>Cool detection threshold (foot) (range 0.6 – 32.0°C)</td>
<td>-0.1105</td>
<td>-0.2819 to 0.0609</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>2.6073</td>
<td>0.4937 to 4.7208</td>
</tr>
<tr>
<td>Osteoarthritis total (0 is reference)</td>
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<td>Sleep quality (PSQI) (range 0 – 21)</td>
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<tr>
<td>IPQ timeline (0 – 10)</td>
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<tr>
<td>Age group (younger is reference)</td>
<td></td>
<td></td>
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</tbody>
</table>

*Fully adjusted = adjusted for the other factors in the model  
IPQ = Illness Perception Questionnaire  
PSQI = Pittsburgh Sleep Quality Index
Table 8.7 – Foot TSL moderated by sex (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Thermal sensory limen x sex</td>
<td>-0.0674</td>
<td>-0.2136 to 0.0788</td>
</tr>
<tr>
<td>Thermal sensory limen (foot)</td>
<td>-0.0134</td>
<td>-0.1238 to 0.0970</td>
</tr>
<tr>
<td>(range 1.3 – 50°C)</td>
<td></td>
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<tr>
<td>Sex (male is reference)</td>
<td>2.8320</td>
<td>-0.5120 to 6.1760</td>
</tr>
<tr>
<td>Osteoarthritis total (0 is reference)</td>
<td>-</td>
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<tr>
<td>1</td>
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<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age group (younger is reference)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other factors in the model  
IPQ = Illness Perception Questionnaire  
PSQI = Pittsburgh Sleep Quality Index
Table 8.8 – Tender point count moderated by sex (imputed, survey weighted) regressed against Manchester pain count

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Tender point count x sex</td>
<td>-0.0505</td>
<td>-0.4766 to 0.3756</td>
</tr>
<tr>
<td>Tender point count (range 0 – 18)</td>
<td>0.7188</td>
<td>0.3367 to 1.1008</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>0.0214</td>
<td>1.4841 to 1.5268</td>
</tr>
<tr>
<td>Osteoarthritis total (0 is reference)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age group (younger is reference)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other factors in the model      IPQ = Illness Perception Questionnaire      PSQI = Pittsburgh Sleep Quality Index
Table 8.9 – Foot CDT moderated by sex (imputed, survey weighted) logistically regressed, some pain, CWP against no pain

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th></th>
<th></th>
<th>Interaction terms only</th>
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<th>Interaction terms only</th>
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<th></th>
<th>Interaction terms only</th>
<th></th>
<th></th>
<th>Interaction terms only</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cool detection threshold x sex</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>p</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>p</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>p</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>p</td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cool detection threshold (foot) (range 0.6 – 32.0°C)</td>
<td>1.0680</td>
<td>0.9981 to 1.1429</td>
<td>0.057</td>
<td>1.0722</td>
<td>0.9715 to 1.1835</td>
<td>0.165</td>
<td>1.0759</td>
<td>0.9981 to 1.1597</td>
<td>0.056</td>
<td>1.0762</td>
<td>0.9717 to 1.1919</td>
<td>0.158</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>0.9617</td>
<td>0.9150 to 1.0107</td>
<td>0.123</td>
<td>0.9440</td>
<td>0.8718 to 1.0222</td>
<td>0.155</td>
<td>0.9397</td>
<td>0.8856 to 0.9971</td>
<td>0.040</td>
<td>0.9207</td>
<td>0.8489 to 0.9985</td>
<td>0.046</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>1.7775</td>
<td>0.7910 to 3.9944</td>
<td>0.163</td>
<td>5.4110</td>
<td>1.4892 to 19.6610</td>
<td>0.011</td>
<td>1.7811</td>
<td>0.7361 to 4.3097</td>
<td>0.200</td>
<td>4.6769</td>
<td>1.1672 to 18.7408</td>
<td>0.030</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.0829</td>
<td>0.9906 to 1.1839</td>
<td>0.079</td>
<td>1.3028</td>
<td>1.1260 to 1.5073</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age group (younger is reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.2144</td>
<td>1.1017 to 1.3387</td>
<td>0.000</td>
<td>1.3842</td>
<td>1.2214 to 1.5687</td>
<td>0.000</td>
<td></td>
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</tr>
</tbody>
</table>
| *Fully adjusted = adjusted for the other factors in the model

IPQ = Illness Perception Questionnaire  PSQI = Pittsburgh Sleep Quality Index
Table 8.10 – Tender point count moderated by sex (imputed, survey weighted) logistically regressed, some pain, CWP against no pain

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interaction terms only</th>
<th>Fully adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Some pain</td>
<td>CWP</td>
</tr>
<tr>
<td></td>
<td>Relative risk ratio</td>
<td>95% confidence intervals</td>
</tr>
<tr>
<td>Tender point count x sex</td>
<td>1.1251</td>
<td>0.9413 to 1.3448</td>
</tr>
<tr>
<td>Tender point count (range 0 – 18)</td>
<td>0.9853</td>
<td>0.8454 to 1.1483</td>
</tr>
<tr>
<td>Sex (male is reference)</td>
<td>0.7136</td>
<td>0.3400 to 1.4977</td>
</tr>
<tr>
<td>Sleep quality (PSQI) (range 0 – 21)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IPQ timeline (0 – 10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age group (younger is reference)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Fully adjusted = adjusted for the other factors in the model  IPQ = Illness Perception Questionnaire  PSQI = Pittsburgh Sleep Quality Index
8.5 Discussion

In the context used here, moderation refers to a difference in the relationship between the predictor and outcome variables at different values of the moderating variable (Kraemer et al. 2001). Appendix X gives more detail as to how moderation is dealt with in statistical analysis. The moderators used in the present study were age and sex, with each divided into two groups.

8.5.1 Moderation by age

The relationships between CDT at the foot and Manchester pain count, and TSL at the foot and Manchester pain count, were not moderated by age group. It had already been noted that the older age group had a higher CDT (expressed as a positive number, i.e. further from baseline) at the foot and the hand than the younger group (see Table 6.2), and the older age group also had a larger TSL at both the hand and the foot than the younger group, and all these reached statistical significance after the correction for multiple testing. Both CDT and TSL at the foot were statistically significantly associated with Manchester pain count only when fully adjusted, not when unadjusted or adjusted only for age and sex (see Table 7.5), which implied that a combination of factors strengthened these relationships. There was no significant difference in the foot CDT x age interaction term, between “no pain” and either “some pain” or CWP. CDT at the foot was significantly different for participants with CWP compared to “no pain”, only when fully adjusted for factors including age (see Table 7.17), which indicated that the inclusion of a combination of factors in the model strengthened the relationship. Published studies on the effect of age on thermal detection thresholds indicate that these generally increase with increasing age (see section 2.9.2), but the literature on thermal detection thresholds in people with musculoskeletal pain indicates that these are comparable to values from pain-free controls (see section 2.8.5). As pain prevalence and occurrence of CWP increase with age (see section 2.4.1) a moderating effect of age might have been considered possible from this evidence.

The relationship between tender point count and Manchester pain count was not moderated by age. The older age group had a slightly higher tender point count than the younger age group, but this did not reach statistical significance (see Table 6.2). Tender point count was significantly associated with Manchester pain count even when adjusted for factors including age, which implied that age did not significantly affect the relationship, but this may also reflect the strength of the
association (see Table 7.6). There were also no significant differences in the tender point x age interaction term between “no pain” and either “some pain” or CWP. Published studies do not show differences in tender point count with age (see section 2.9.2), but they do show an association between tender point count and pain (Croft et al. 1996), and as pain prevalence and occurrence of CWP increase with age (see section 2.4.1) a moderating effect of age might have been expected.

There is not a single cut-off age for what constitutes “older” (Gagliese and Melzack 2005). The reason for the choice of cut-off at 65 years in the present study has already been discussed (see section 6.7.3), but even the younger group were “old” by some standards. The median age of the younger group was 58.5 years (range 34-65 years), while the median of the older group was 78 years (range 66-97 years). Some population-based studies have defined “older” as over 50 years (Croft, Jordan, and Jinks 2005; Mottram et al. 2008; Shi et al. 2010), or over 55 years (Keenan et al. 2006). QST studies measuring DNIC had “older” groups with mean ages of 68.1 years (Lariviere et al. 2007), 65.2 years (Riley, III et al. 2010) and 63.1 years (Edwards, Fillingim, and Ness 2003). A study measuring heat pain threshold and tolerance had an “older” group with a mean age of 62.2 years (Edwards and Fillingim 2001). It is possible that moderation by age would have been found if different age groups had been used, or if there had been more, younger people in the sub-study group.

No study has previously considered the moderating effect of age on the relationship between QST variables and pain, so these findings add to the body of knowledge on differences in pain with ageing.

8.5.2 Moderation by sex

The relationships between CDT at the foot and Manchester pain count, and between TSL at the foot and Manchester pain count, were not moderated by sex. Neither of these variables were significantly different between females and males, after correction for multiple testing (see Table 6.3), although TSL at the foot was non-significantly smaller in females than males. It has already been commented that both CDT and TSL at the foot were statistically significantly associated with Manchester pain count only when fully adjusted, not when unadjusted or adjusted only for age and sex (see Table 7.5). There was no significant difference in the foot CDT x sex interaction term between “no pain” and either “some pain” or CWP. CDT at the foot was significantly different for participants with CWP compared to “no
pain", only when fully adjusted (see Table 7.16), which indicated that the inclusion of other factors strengthened the relationship.

The relationship between tender point count and Manchester pain count was not moderated by sex. Even though it has already been reported that tender point count was significantly higher for females than males (see Table 6.3), the relationship between tender point count and Manchester pain count was not attenuated when adjusted for age and sex (see Table 7.6), showing that these factors did not significantly alter that relationship. There were no significant differences in the tender point count x sex interaction term between “no pain” and either “some pain” or CWP. Published studies do show that females have a higher tender point count than males (see section 2.9.1), but as females also have a higher pain prevalence than males (see section 2.5.2), this could cancel out any moderating effect of sex.

No study has previously considered the moderating effect of sex on the relationship between QST variables and pain. A review found that the differences in QST results between males and females were equivocal (Racine et al. 2012a), but in the present study, females were found to be significantly more sensitive than males on several measures (see section 6.5). Differences in pain prevalence between the sexes are almost universally observed (see section 2.5.2), and this was also true in the present study, but the differences in Manchester pain count and presence of CWP compared to “no pain” for males and females were only statistically significant in an unadjusted model (see sections 7.4.1 and 7.6.1). So from published studies it is not clear whether a moderating effect of sex would have been expected or not. The findings from the present study add to the body of knowledge on differences in pain between the sexes.

8.6 Conclusion

No significant moderating effects of age or sex were found between CDT at the foot, TSL at the foot or tender point count and Manchester pain count, or between either CDT at the foot or tender point count and ACR pain status. There is no existing literature on moderation of these relationships.
9.0 Conclusion

Chronic pain is a major health care problem, with 40 to 50% of adults experiencing it at any given time. It is also under-reported to health care professionals, often under-treated, and in older adults the pain also becomes increasingly disabling. Much of the burden of pain is unexplained by disease processes. An alternative explanation is a susceptibility to pain due to a pain processing abnormality in the central nervous system, which would make itself apparent through quantitative sensory testing (QST).

Developed countries are undergoing a demographic shift with respect to the ageing of populations. Pain is part of the morbidity burden which is expected to increase as the population ages. However, the change in pain prevalence with age does not correspond simply with increasing age. Some types of pain show a mid-life peak in prevalence and subsequent decline which may reflect a qualitative difference between pain in younger and older adults. Prior to undertaking the present study there was limited published QST data collected from older people, making it difficult to determine any pattern of age-related differences or to associate them to differences in pain experience changes with ageing.

Women almost always experience more pain than men, and yet reported differences in QST data between the sexes are inconsistent.

The present study

To address these gaps in our understanding, the present study surveyed a community-based cohort with over 2300 participants aged 34 – 101 years returning a completed questionnaire. A sub-group of 290 participants were selected on the basis of their pain status, and underwent a physical assessment including QST.

Analyses of the relationships between the QST variables and pain found that three of them, cool detection threshold (CDT) measured at the foot, thermal sensory limen (TSL) measured at the foot, and tender point count, were significantly associated with pain in a final, fully adjusted model. However, further analysis found no moderating effects of age or sex on these relationships. The other factors which were significant in every model tested were sleep quality and IPQ timeline, which measured beliefs about the duration of pain.
Implications of the findings

CDT at the foot and TSL at the foot were found to be significantly associated with the pain outcome variables. However, these are both thermal detection threshold measurements, and previous studies have shown that thermal detection thresholds do not vary with pain. There is no obvious mechanism which would explain these findings in the absence of relationships between any of the other QST variables (other than tender point count) and pain. This may be interpreted in 3 ways: 1) the result is a false positive, 2) there is an unknown mechanism at work, and 3) unmeasured confounding. These shall be discussed in turn.

A false positive may explain the finding, as hypothesis testing is based upon probability and there is always a possibility that an association may be found where none exists (type II error). There is also the possibility that a true association may be missed (type I error), for example a possible association between other QST variables and pain. These have been mitigated in the present study in two ways. First, the power calculation indicated a power of 99.9% for the sample size to detect differences in QST variables between pain groups, should they exist. Second, Bonferroni correction and multivariate models were employed to minimise the risk of type II error intrinsic in multiple testing.

Alternatively, an unknown mechanism may underlie the observed relationship. The median age of the sub-study participants was 68 years, so the mechanism could be related to the fact that they were older than most subjects from previous QST studies. One possibility is difference in beliefs or attitudes at different ages. A population-based study on participants aged 17 – 91 years investigated how pain attitudes differed with age, and found that Stoic-Reticence (“no good complaining”), Cautious-Reluctance (“avoid labelling an experience as painful until certain”) and Cautious-Self-doubt (“avoid decision when unsure”) with respect to pain reporting were higher in older than younger participants (Yong et al. 2001). It might be that these traits apply differentially to pain reporting using a manikin, and responding to experimental pain in the presence of a tester. Whilst it is recognised that physiological changes associated with ageing can affect sensation, it is highly unlikely that these would affect the relationship between these particular sensory stimuli and pain without influencing the relationships involving the other QST variables.

The effect of unmeasured confounding could be significant. There are always unknown confounders in any epidemiological study. However, there are also known
risk factors for pain which have not been included in the models, for example stoicism (Yong et al. 2001) (see above), traumatic life events (Jones et al. 2009), accidents (Jones et al. 2011), family history of CWP (Kindler et al. 2010), and income (Hagen et al. 2002), to name but a few. These may or may not confound the relationships between QST variables and pain.

Tender point count was found to be associated with both outcome pain variables, in the same direction as has been found in previous studies, i.e. more pain being associated with higher tender point count. Unlike the other QST variables, tender point count has previously been measured in population-based studies (Croft, Schollum, and Silman 1994; Eggermont, Shmerling, and Leveille 2010), as well as in either “healthy” volunteers or patient groups. So as well as confirming an established finding, the data on tender point count confirms that the participants in the present study do not appear atypical.

The absence of moderating effect of sex on the relationships between QST predictor variables and pain outcome variables was somewhat surprising, as the differences in QST between the sexes have been found to be small and equivocal (Racine et al. 2012a) whereas higher pain prevalence in females compared to males is almost universally acknowledged. The absence of moderating effect of age on those same relationships is less unexpected, as the differences found in pain prevalence with age do vary somewhat between studies (although there is a general increase in pain with increasing age), and the evidence for differences in QST with age is somewhat sparse.

Sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI), was the predictor variable which explained more variance in the Manchester pain count than any other, over 22%. Sleep quality was significantly associated with Manchester pain count when unadjusted and for all levels of adjustment, and there were significant differences between “no pain” and both “some pain” and CWP, when unadjusted and for all levels of adjustment. It was statistically significant in the final models for both pain outcomes. Although the associations between sleep quality and pain have been previously documented, this finding is still noteworthy, not least because of the size of the relationship.

Relating QST results to pain sensitivity mechanisms

Both central and peripheral sensitisation are possible mechanisms to increase susceptibility of an individual to pain. Peripheral sensitisation occurs when the
responsiveness of nociceptors is increased locally due to an injury or inflammation. As well as tender point count being associated with increasingly widespread pain in the existing literature, an association has also been found between pain in a particular body segment and a tender point in that same segment (Croft et al. 1996), so it is possible that the relationship between tender point count and pain found in the present study may be due at least in part to peripheral sensitisation. This would not necessarily affect the other QST measures, as there were no tender point measurements at the hand or foot, and also a tender point reflects sensitivity in the deep tissues rather than the skin. However, the fact that much musculoskeletal pain is not related to known injury or disease mechanisms, and that in widespread pain each painful site would need to be peripherally sensitised individually, would make peripheral sensitisation unlikely to be a significant contributor to widespread pain.

Peripheral sensitisation would not be expected to alter sensory detection thresholds such as cool detection threshold or thermal sensory limen. In the present study mechanical pain threshold at the hand was lower in those with no pain than those with chronic widespread pain, which is the reverse of what would be expected if periperal sensitisation was present in participants with pain but not in those without pain.

The presence of central sensitisation would be expected to affect pain perception rather than detection thresholds, and in particular to influence levels of temporal summation (wind-up) and descending noxious inhibitory controls (DNIC). In the present study, DNIC and wind-up were not significantly different for participants with different pain status, but two of the detection thresholds were different. Mechanical pain threshold differed between the pain status groups in the opposite direction to that which would be expected if central sensitisation was present in those with the most widespread pain. Tender point count was higher for those with more widespread pain, but this finding in isolation is poor evidence for central sensitisation.

**Strengths of the present study**

The PAALS study (of which the present study was a part) was the first study to apply QST to a population-based sample of participants. This means that they were more representative of the general population than participants in previous QST studies, which used either healthy participants, with “healthy” having various
definitions but always including absence of pain, or clinical populations. Even the participants in the present study who did not report having pain were not “healthy” in that sense, as very few exclusion criteria were applied so they were likely to have a similar level of co-morbidity to the general population.

The number of participants on whom QST was carried out was large in the context of published studies, and although not the largest number overall, the largest number on whom such a comprehensive battery of tests had been carried out. A large sample size increases the power of a study to detect significant relationships, if they exist. The PAALS study was also unusual in having so many older participants, the median age of those undergoing QST being 68 years and the range 34 – 97 years. This included 42 people aged 85 or older, who can be described as “oldest old” (Dini and Goldring 2008), which demonstrates that it is possible to recruit people of this age into a study, and successfully carry out the same, full battery of tests as were done on the younger participants.

The results of QST vary depending upon the test method used, and the differences seen between groups, e.g. with or without pain, males and females, depends upon the type of stimulus used. By using the test protocol developed by the German Research Network on Neuropathic Pain, the present study has produced data which can be compared to data from other studies, and which covers the sensory modalities which are considered to be important in the field of pain research.

Missing data is always an issue in observational studies. The present study used a method of imputation which is recognised as giving reliable results, to overcome the potential bias of using complete cases only. Only a fraction of the whole study cohort underwent the QST battery, so this data was “missing by design” for most participants. The use of sample weighting allowed the QST results to be applied to the whole cohort.

Weaknesses of present study

A major limitation of the present study is that it was cross-sectional in design, meaning that the temporal relationships between putative risk factors and outcomes could not be investigated. The PAALS study, of which the present study was a part, will be collecting follow-up data one year after previous contact with each participant, which will allow some of these relationships to be studied. The number of participants in the sub-study was limited by the resources available. Although the number of participants on whom QST was carried out was large compared to other
studies, it was small enough to limit the number of variable categories which could be used, e.g. age groups, and still have sufficient numbers of participants in each group to have adequate power in the analyses.

Missing data are common in epidemiological studies, and only 41% of the sub-study participants in the present study had complete data. Although the use of imputation is generally thought to reduce bias compared to using complete cases only, reducing the level of missing data would be preferable.

Reflections on the present study

If the present study was repeated within similar resource constraints, by including a greater number of younger (under 40 years) participants in the sub-study, data from groups of participants with more widely differing ages could be compared.

Moderation by age of the relationship between QST variables and pain may exist, but may only become apparent when comparing adults at the extremes of the age range.

If a measure of stoicism had been included in the questionnaire and included in the multivariate models as a confounder, this might have uncovered an age moderation effect. The existing literature has shown that stoicism is differently associated with pain severity reporting in older and younger people (Yong 2006), but the effect of stoicism on QST data is unknown.

Future work

Chronological age may not be the most appropriate measure of ageing when looking at pain. The physiological, psychological, and social changes associated with increasing age do not all proceed at the same rate, and they change faster in some individuals than in others. One definition of frailty is the increasing accumulation of largely unrelated health conditions. It has been found to increase the risk of older people having moderate to severe pain (Shega et al. 2012). Frailty may be a more appropriate measure than chronological age as a moderator of the relationship between QST variables and pain.

Age and sex may interact as moderators between QST variables and pain. For example, age could be a strong moderator of some of the relationships in women but not in men. Differences between men and women due to hormonal or social
role distinctions may not persist during the many changes associated with ageing. The data collected for the present study could be used to investigate this. Further work on data collected by the PAALS study may help to clarify the relationships identified in the present study. The mediation of the relationship between QST variables and pain by pain cognitions, psychological state, physical activity and sleep quality indicated in Figure 3.1 (hypothesised model) was not tested in the present study. It is possible for mediation to occur even where the relationship between the predictor and outcome variable is not statistically significant (Hayes 2009). It is also possible that QST factors not significant in final regression models might still show moderation by age or sex, so this needs to be investigated. The follow-up data being collected by the PAALS study can be used to see whether changes in pain are predicted by QST variables. The whole study would need to be repeated in another population to confirm the findings.

The ultimate purpose of data collected by the present study and similar studies must be to advance knowledge in the field of human health, in order to allow better interventions for the treatment of pain to be developed. Generalised, mechanical hyperalgesia (as measured by tender point count), beliefs about the duration of pain, and poor sleep quality should now both be the subject of intervention studies to develop new treatments for pain. Generalised mechanical hyperalgesia is characteristic of fibromyalgia, and recommendations for the treatment of fibromyalgia include a combination of exercise, cognitive behavioural therapy or other psychological therapy, and analgesic drugs (Carville et al. 2008). These could be trialled on other musculoskeletal pain conditions. Novel treatments for insomnia, such as internet-delivered cognitive behavioural therapy (Espie et al. 2012), could be included in pain research. Motivational interviewing has been shown to be effective in altering health beliefs in other health conditions (Cunningham et al. 2012), and could be used in pain studies.
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The British Pain Society and The Royal College of General Practitioners (2004), *A practical guide to the provision of Chronic Pain Services for adults in Primary Care*.


Appendix I – PAALS baseline questionnaire
Participant Questionnaire

Arthritis Research UK Epidemiology Unit
School of Translational Medicine
University of Manchester
Stopford Building
Manchester, M13 9PT
United Kingdom

The information you provide will be used only for research purposes and all your answers will be treated in the strictest confidence.

If you have any questions or queries, please contact:
Rosie Duncan Tel: 0161 275 7314
Email: Rosie.Duncan@manchester.ac.uk
Or
James Anderson Tel: 0161 275 5596
Email: James.Anderson@manchester.ac.uk

What is your date of birth? e.g. 12th August 1945 should be written as 12 08 1945

Day Month Year

Are you?

Male 1 Female 2

Do you have any children?

Yes 1 No 2

If yes, continue with question 4, if no, go to question 5

How many children do you have?


What age did you leave full time education?


During the past 7 days, did you work (for pay and/or as a volunteer)?

If yes, continue with question 8
If no, go to question 10 on page 4

On average how many hours per week do you work (for pay and/or as a volunteer)?

Which of the following categories below best describes the amount of physical activity required on your job and/or volunteer work?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Examples</th>
<th>Please cross one box only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mainly sitting with arm movements</td>
<td>Office worker, watchmaker, assembly line worker, bus driver, etc.</td>
<td></td>
</tr>
<tr>
<td>Sitting and standing with some walking</td>
<td>Cashier, general office worker, light tool and machinery worker</td>
<td></td>
</tr>
<tr>
<td>Walking with some handling of material generally weighing less than 50 pounds/25 kilos</td>
<td>Mailman, walker, construction worker, heavy tool and machinery worker</td>
<td></td>
</tr>
<tr>
<td>Walking and heavy manual work often requiring handling of material weighing more than 50 pounds/25 kilos</td>
<td>Stone mason, farm or general labourer</td>
<td></td>
</tr>
</tbody>
</table>

Are you currently?
- Not working because of ill health/disability
- Working full-time
- Working part-time
- Working full-time in the home
- Not working because of ill health/disability
- Unemployed but seeking work
- Student
- Semi-retired
- Retired

On average, how many of these alcoholic beverages have you drunk each week over the last three months?

- Red wine (glasses per week)
- Beer/bitter/lager/cider (pints each week)
- Spirits (e.g. whisky/gin/vodka (measures per week)
- Sherry or fortified wines (glasses per week)
- White wine (glasses per week)
- Other alcoholic drinks (units per week)

Which of the following statements best describes your smoking history?
- I smoke now
- I don't smoke now but have done in the past
- I have never smoked
The following questions are about aches and pains. Please answer these questions by crossing the box that you think most closely applies to you.

13 During the past month have you had any ache or pain that has lasted for one day or longer?
   Yes ☐  No ☐

If yes, continue with question 14
If no, go to question 22 on page 8

14 Do you have any such ache or pain today?
   Yes ☐  No ☐

15 If you work - did you miss any days in the past month from work because of an ache or pain?
   Yes ☐  No ☐

16 Have you consulted your family doctor in the past 12 months for this ache or pain?
   Yes ☐  No ☐

Please shade any area on the diagrams below where you feel, or have felt, aches and pains during the past month.
Thinking about your pain over the past month, please indicate whether or not you agree with the following statement:

“I ache all over”

Yes [ ] No [ ]

18. In the past month, on average, how intense was your pain, rated on a scale of 0 – 10, where 0 is “no pain” and 10 is “pain as bad as it could be”?

No pain [ ] pain as bad as it could be [ ]

19. In the past month, how much has this pain interfered with your daily activities, rated on a scale of 0-10, where 0 is “no interference” and 10 is “unable to carry out activities”?

No interference [ ] unable to carry out activities [ ]

20. Thinking about this ache or pain, have you been aware of it for more than 3 months?

Yes [ ] No [ ]

21. Thinking about your pain over the past month, please indicate whether or not you agree with the following statement:

“I ache all over”

Yes [ ] No [ ]

22. Please shade on the diagrams below the location of the SINGLE most troublesome pain that you feel. If you do not have any pain please go on to question 27.

23. Thinking about your most troublesome pain, does the pain have one or more of the following characteristics?

- Burning [ ] No [ ]
- Painful cold [ ] No [ ]
- Electric shocks [ ] No [ ]

24. Thinking about your most troublesome pain, is this pain associated with one or more of the following symptoms in the same area?

- Tingling [ ] No [ ]
- Pins and needles [ ] No [ ]
- Numbness [ ] No [ ]
- Itching [ ] No [ ]
Thinking about your most troublesome pain, how long have you been aware of this pain?

- Less than 6 months
- Between 6 months and 12 months
- Between 1 and 3 years
- More than 3 years

Thinking about your most troublesome pain over the past 24 hours, please indicate on the scale below the highest intensity of the pain during the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

Thinking about your most troublesome pain over the past 24 hours, please indicate on the scale below the lowest intensity of the pain during the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

Thinking about your most troublesome pain over the past 24 hours, please indicate on the scale below the average intensity of the pain during the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10

The following questions relate to symptoms in the abdominal area. Please answer them by crossing the box \( \times \) that you think most closely applies to you.

- a) Relieved by going to the toilet (defecation)?
- b) Associated with a change in the number of bowel movements?
- c) Associated with a change in the appearance or consistency of the stool (harder or looser)?

Have you had abdominal ache or pain in the past year which has lasted for 12 weeks or more? (This need not necessarily be 12 continuous weeks)

Yes \( \checkmark \)  No \( \times \)
Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. We are interested in the thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Please answer them by crossing the box that you think most closely applies to you.

**When I’m in pain…**

29. I worry all the time about whether the pain will end

   - Not at all
   - To a slight degree
   - To a moderate degree
   - To a great degree
   - All the time

30. I feel I can’t go on

   - Not at all
   - To a slight degree
   - To a moderate degree
   - To a great degree
   - All the time

31. It’s terrible and I think it’s never going to get any better

   - Not at all
   - To a slight degree
   - To a moderate degree
   - To a great degree
   - All the time

32. It’s awful and I feel that it overwhelms me

   - Not at all
   - To a slight degree
   - To a moderate degree
   - To a great degree
   - All the time

33. I feel I can’t stand it anymore

   - Not at all
   - To a slight degree
   - To a moderate degree
   - To a great degree
   - All the time

34. I become afraid that the pain will get worse

   - Not at all
   - To a slight degree
   - To a moderate degree
   - To a great degree
   - All the time

35. I keep thinking of other painful events

   - Not at all
   - To a slight degree
   - To a moderate degree
   - To a great degree
   - All the time
I can't seem to keep it out of my mind

I keep thinking about how much it hurts

I keep thinking about how badly I want the pain to stop

I anxiously want the pain to go away

I can't seem to keep it out of my mind

To a great degree
To a slight degree
To a moderate degree
All the time
Not at all

To a great degree
To a slight degree
To a moderate degree
All the time
Not at all

To a great degree
To a slight degree
To a moderate degree
All the time
Not at all

To a great degree
To a slight degree
To a moderate degree
All the time
Not at all

There's nothing I can do to reduce the intensity of the pain

I wonder whether something serious may happen

How much does pain affect your life?

How long do you think your pain will continue?

The following questions will ask about your experience of pain. If you do not currently have pain, think about the last time you had pain.

Please answer questions 42 to 49 by circling ONE number from 0 to 10 that best fits with your views.
How much do you think treatment can help your pain?

0 1 2 3 4 5 6 7 8 9 10
absolutely no control extreme amount of control

How much do you experience other symptoms because of your pain?

0 1 2 3 4 5 6 7 8 9 10
not at all extremely helpful

How concerned are you about your pain?

0 1 2 3 4 5 6 7 8 9 10
not at all concerned extremely concerned

How well do you feel you understand your pain?

0 1 2 3 4 5 6 7 8 9 10
don’t understand at all understand very clearly

How much does your pain affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

0 1 2 3 4 5 6 7 8 9 10
not at all affected extremely affected emotionally

Please list the three most important factors that you believe caused your pain. Please list here the order of importance:

1.

2.

3.

This section is concerned with your general feelings and emotions, not just when you are in pain. Please read each item and place a cross [x] in the box opposite the reply which comes closest to how you have been feeling in the past week:

I feel tense or wound up
Not at all Most of the time A lot of the time Time to time, occasionally

I still enjoy the things I used to enjoy
Hardly at all Definitely as much Not quite as much Not at all

I get a sort of frightened feeling as if something awful is about to happen
Very definitely and quite badly Yes, but not too badly A little, but it doesn’t worry me Not at all

I can laugh and see the funny side of things
As much as I always could Not quite as much now Definitely not so much now Not at all
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>55 Worrying thoughts go through my mind</td>
<td>A great deal of the time ( ), A lot of the time ( ), From time to time but not often ( ), Only occasionally ( )</td>
</tr>
<tr>
<td>56 I feel cheerful</td>
<td>Not at all ( ), Not often ( ), Sometimes ( ), Most of the time ( )</td>
</tr>
<tr>
<td>57 I can sit at ease and feel relaxed</td>
<td>Definitely ( ), Usually ( ), Not often ( ), Not at all ( )</td>
</tr>
<tr>
<td>58 I feel as if I am slowed down</td>
<td>Nearly all the time ( ), Very often ( ), Sometimes ( ), Not at all ( )</td>
</tr>
<tr>
<td>59 I get a sort of frightened feeling like “butterflies” in my stomach</td>
<td>Not at all ( ), Occasionally ( ), Quite often ( ), Very often ( )</td>
</tr>
<tr>
<td>60 I have lost interest in my appearance</td>
<td>Definitely ( ), I don’t take so much care as I should ( ), I may not take quite as much care ( ), I take just as much care as ever ( )</td>
</tr>
<tr>
<td>61 I feel restless as if I have to be on the move</td>
<td>Very much indeed ( ), Quite a lot ( ), Not very much ( ), Not at all ( )</td>
</tr>
<tr>
<td>62 I look forward with enjoyment to things</td>
<td>As much as ever I did ( ), Rather less than I used to ( ), Definitely less than I used to ( ), Hardly at all ( )</td>
</tr>
<tr>
<td>63 I get sudden feelings of panic</td>
<td>Very often indeed ( ), Quite often ( ), Not very often ( ), Not at all ( )</td>
</tr>
<tr>
<td>64 I can enjoy a good book or radio or TV programme</td>
<td>Often ( ), Occasionally ( ), Not often ( ), Very seldom ( )</td>
</tr>
</tbody>
</table>
The following questions are related to your sleep. For each question please cross the box that you think most closely applies to you.

Thinking back over the past month on how many days have you:

65 Had trouble falling asleep?

- None
- 1-3 days
- 4-7 days
- 8-14 days
- 15-21 days
- 22-31 days

66 Woken up several times in the night?

- None
- 1-3 days
- 4-7 days
- 8-14 days
- 15-21 days
- 22-31 days

67 Had trouble staying asleep?

- None
- 1-3 days
- 4-7 days
- 8-14 days
- 15-21 days
- 22-31 days

68 Woken up after your usual amount of sleep feeling tired and worn out?

- None
- 1-3 days
- 4-7 days
- 8-14 days
- 15-21 days
- 22-31 days

The following questions are about your current energy levels? Please cross the box that you think most closely applies to you.

69 Do you have any problems with tiredness?

- Less than usual
- No more than usual
- Worse than usual
- Much worse than usual

70 Do you need to rest?

- Less than usual
- No more than usual
- Worse than usual
- Much worse than usual

71 Do you feel sleepy or drowsy?

- Less than usual
- No more than usual
- Worse than usual
- Much worse than usual

72 Do you have problems starting things?

- Less than usual
- No more than usual
- Worse than usual
- Much worse than usual

73 Are you lacking in energy?

- Less than usual
- No more than usual
- Worse than usual
- Much worse than usual
Do you have difficulty concentrating?
- Better than usual
- No more than usual
- Worse than usual
- Much worse than usual

Do you have problems thinking clearly?
- Much worse than usual
- Less than usual
- No more than usual
- Worse than usual

Do you make slips of the tongue when speaking?
- Much worse than usual
- Less than usual
- No more than usual
- Worse than usual

Do you feel weak?
- Much worse than usual
- Less than usual
- No more than usual
- Worse than usual

Do you have less strength in your muscles?
- Much worse than usual
- Better than usual
- No more than usual
- Worse than usual

How is your memory?
- Much worse than usual
- Better than usual
- Same as usual
- Worse than usual

Have you had any problems with your energy levels for 6 months or longer?
- Yes
- No

The following questions ask about the amount and intensity of physical activity you usually do. Please cross the box answering Yes or No to each question.

<table>
<thead>
<tr>
<th>Light activities</th>
<th>Moderate activities</th>
<th>Vigorous activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your heart beats slightly faster than normal but you can still talk and sing. E.g. light housework, light stretching</td>
<td>Your heart beats faster than normal and you can talk but not sing. E.g. brisk walking, gentle swimming</td>
<td>Your heart rate increases a lot and you can’t talk, or your talking is broken up by large gulps. E.g. running, tennis</td>
</tr>
</tbody>
</table>

I rarely or never do any physical activities
- Yes
- No

I do some light and/or moderate physical activities, but not every week
- Yes
- No
<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>83 I do some light physical activity every week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>84 I do moderate physical activity every week but less than 5 days per week or less than 30 minutes on those days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>85 I do vigorous physical activities every week, but less than 3 days per week or less than 20 minutes on those days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>86 I do 30 minutes or more per day of moderate physical activities 5 or more days per week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>87 I do 20 minutes or more per day of vigorous physical activities 3 or more days per week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>88 I do activities to increase muscle strength, such as lifting weights or calisthenics, once a week or more</td>
<td></td>
<td></td>
</tr>
<tr>
<td>89 I do activities to improve flexibility, such as stretching or yoga, once a week or more</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**The following questions are concerned with your ability to carry out everyday activities in the past week? Please cross the box that you think most closely applies to your abilities.**

<table>
<thead>
<tr>
<th>Question</th>
<th>Without any difficulty</th>
<th>With some difficulty</th>
<th>With much difficulty</th>
<th>Unable to do</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 Are you able to dress yourself, including shoelaces and buttons?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91 Are you able to shampoo your hair?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>92 Are you able to stand up from a straight chair?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93 Are you able to get in and out of bed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**94 Are you able to cut your own meat?**

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

**95 Are you able to lift a full cup or glass to your mouth?**

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

**96 Are you able to open a new milk carton?**

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

**97 Are you able to walk outdoors on flat ground?**

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

**98 Are you able to climb up five steps?**

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

**99 Please cross any AIDS or DEVICES that you usually use for any of the activities described in questions 85 to 93:**

- a) Dressing device (button hook, zipper pull etc)
- b) Special or built up chair
- c) Built up or special utensils
- d) Cane
- e) Walker
- f) Crutches
- g) Wheelchair

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

**100 Please cross any categories for which you usually need HELP FROM ANOTHER PERSON:**

- a) Dressing and grooming
- b) Aiding
- c) Eating
- d) Walking

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>101. Are you able to wash and dry your body?</strong></td>
<td>Without any difficulty</td>
</tr>
<tr>
<td><strong>102. Are you able to take a bath?</strong></td>
<td>Without any difficulty</td>
</tr>
<tr>
<td><strong>103. Are you able to get on or off the toilet?</strong></td>
<td>Without any difficulty</td>
</tr>
<tr>
<td><strong>104. Are you able to reach and get down an item weighing approximately 5 pounds from above your head?</strong></td>
<td>Without any difficulty</td>
</tr>
<tr>
<td><strong>105. Are you able to bend down to pick up clothing from the floor?</strong></td>
<td>Without any difficulty</td>
</tr>
<tr>
<td><strong>106. Are you able to open car doors?</strong></td>
<td>Without any difficulty</td>
</tr>
<tr>
<td><strong>107. Are you able to open previously opened jars?</strong></td>
<td>Without any difficulty</td>
</tr>
<tr>
<td><strong>108. Are you able to turn taps on or off?</strong></td>
<td>Without any difficulty</td>
</tr>
</tbody>
</table>
Are you able to run errands and shop?

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

Are you able to get in and out of a car?

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

Are you able to do chores such as vacuuming and garden work?

- Without any difficulty
- With some difficulty
- With much difficulty
- Unable to do

Please cross any AIDS or DEVICES that you usually use for any of the activities described in questions 101 to 111:

a) Raised toilet seat
b) Bath seat
c) Bath bar
d) Long-handled appliances in bathroom
e) Long-handled appliances for reaching
f) Jar opener (for jars previously opened)

To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

- Completely
- Mostly
- Moderately
- A little
- Not at all

How much pain have you had IN THE PAST WEEK? On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number.

Please rate how well you are doing on a scale of 0 to 100 (where zero represents "very well" and 100 represents "very poor" health), please record the number.

Please cross any categories for which you usually need HELP FROM ANOTHER PERSON:

a) Hygiene
b) Reach
c) Gripping and opening things
d) Errands and chores

For the following questions relate to how flexible your joints are, please cross the box that you think most closely applies to you.

117 Can you now (or could you ever) place your hands flat on the floor without bending your knees?

- Yes
- No
- Don't know

118 Do you consider yourself to be double jointed?

- Yes
- No
- Don't know

119 Can you now (or could you ever) bend your thumb to touch your forearm?

- Yes
- No
- Don't know

120 As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?

- Yes
- No
- Don't know

121 As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?

- Yes
- No
- Don't know

For the following questions please cross the box that you think most closely applies to you.

122 Do you have someone with whom you can discuss personal problems or turn to in a time of crisis?

- Yes
- No

If yes, continue with question 123, if no, go to question 125

123 If yes, how much are you able to confide in that person?

- Confide all things
- Confide in most things, but not all
- Confide some things, but not the majority of things
- Confide little or not at all

124 How often do you see that person?

- Every day
- At least once per week
- At least once per month
- Less frequently than once per month

125 If you became ill, for example with bad flu, is there someone you could call on to help you manage?

- Yes
- No
Below are questions relating to your health. For each one please cross the box that applies to you.

126 Have you suffered a fracture (broken bone) since the age of 25 years?

- Yes
- No
- Don't know

127 In the past 12 months:

a) Have you had any falls including a slip or a trip in which you lost your balance and landed on the floor, ground or lower level?

- Yes
- No
- Don't know

b) If yes, has this slip/trip or fall resulted in a fracture?

- Yes
- No
- Don't know

128 Read the list of disorders below. If you have ever suffered from any of the disorders please indicate if you are currently suffering or you have been diagnosed in the past:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Current Diagnosis</th>
<th>Diagnosed in the Past</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Rheumatoid arthritis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Osteoarthritis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Other type of arthritis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d) Osteoporosis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e) Diabetes?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CONSENT FORM

Depending on your response to some of the questions in the questionnaire, we may wish to contact you and invite you to participate in a further part of this study. However we will only do this with your consent.

We are asking for your consent to contact you again. If you agree you may be contacted at a later date via a telephone call with further details. You will be able to decide whether or not you want to take part and are free to change your mind and withdraw your consent at any time. Please read the statements below carefully and indicate whether you will be prepared to be contacted by placing a cross in the box that applies to you and signing your name.

☐ Yes, I give my consent to be contacted with an invitation telephone call. If yes, please provide a current telephone number in the box below:

☐ No, I do not give my consent to be contacted with an invitation telephone call

Signature: ___________________________ Date: ___________________________

Please check carefully to ensure that you have answered all the relevant questions.

Thank you very much for helping us with this health survey!

If you have any questions or queries, please contact:

Rosie Duncan Tel: 0161 275 7314
Email: Rosie.Duncan@manchester.ac.uk

Or

James Anderson Tel: 0161 275 5596
Email: James.Anderson@manchester.ac.uk

Arthritis Research UK Epidemiology Unit
School of Translational Medicine
University of Manchester
Stopford Building
Manchester, M13 9PT
United Kingdom
Appendix II – PAALS clinical assessment sheet
Clinical Assessment Sheet

Patient’s Study ID: 

Researcher’s Name: 

Start time: 

Please fill in the date you completed this form
e.g. 12th August 2010 should be written as 12 08 2010

Day  Month  Year

Height / Bio-Impedance Results Sheet

Ask your participant the following questions to make sure they can undertake the bio-impedance measurement.

Do you have a pacemaker or other internal medical devices?  Yes  No

Are you wearing a hearing aid?  Yes  No

Do you have a mobile phone in your pocket?  Yes  No  N/A

Female participants: is there any possibility that you may be pregnant?  Yes  No

If yes to any of the above questions, do not undertake the Bio-Impedance measurement.

<table>
<thead>
<tr>
<th>Height</th>
<th>cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>kg</td>
</tr>
<tr>
<td>Bio-Impedance measurement</td>
<td>% body fat</td>
</tr>
</tbody>
</table>

Staple the bio-impedance output results in the box below.

Staple results here
**Grip Strength Record Sheet**

Always leave 1 minute between each measurement.

Use non-dominant hand

<table>
<thead>
<tr>
<th>Measurement (kilograms)</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td></td>
</tr>
</tbody>
</table>

**Tender Points Record Sheet**

Apply 1 kg of pressure at a rate of 1 kg/sec until the participant reports the site to be painful or 4 kg of pressure is reached. Record the participant's response below.

CODE:
0 = PRESSURE
1 = DISCOMFORT
2 = DEFINITE PAIN (WITH/OR WITHOUT FLINCH)

Please circle appropriate code

<table>
<thead>
<tr>
<th>RIGHT</th>
<th>LEFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

**NOTES:**
I would like to ask you some questions and carry out a brief examination of the joints in your hands, knees and hips, if that would be ok?

First I would like to ask you some questions about hand symptoms.

1. During the past 30 days, have you had any pain, aching or stiffness in your hands?
   a) Left hand
      Yes ☐, No ☐, Don’t know ☐
   b) Right hand
      Yes ☐, No ☐, Don’t know ☐

If yes, continue with question 2; if no, go to question 3 on page 6.

2. Have you had pain, aching or stiffness most days in the past month?
   a) Left hand
      Yes ☐, No ☐, Don’t know ☐
   b) Right hand
      Yes ☐, No ☐, Don’t know ☐

3. Is there a tissue enlargement of more than two of the 2/3 DIP, 2/3PIP, 1st CMC (both hands)?
   Definite ☐, Possible ☐, No ☐
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Is there a deformity of two or more of the following joints, the 2/3 DIP, 2/3 PIP, 1st CMC (both hands)?</td>
<td>Definite, Possible, No</td>
</tr>
<tr>
<td>5. Are there more than 3 swollen MCP joints?</td>
<td>Definite, Possible, No</td>
</tr>
</tbody>
</table>

Any further comments about the hands add below.

---

```
I would like to ask you some questions about your knees.

6. During the past 30 days have you had any pain, aching or stiffness in or around your knees?
   a) Left knee
      - Yes, No, Don’t know
   b) Right knee
      - Yes, No, Don’t know

If yes to question 6 continue with question 7, if no, go to question 8.

7a. Have you had pain, aching or stiffness on most days in the last month?
    a) Left knee
       - Yes, No, Don’t know
    b) Right knee
       - Yes, No, Don’t know

7b. Do you have stiffness in your knees in the morning?
    a) Left knee
       - Yes, No, Don’t know
    b) Right knee
       - Yes, No, Don’t know

If yes to question 7b continue with question 7c, if no, go to question 8.

7c. Does this stiffness in your knee last less than 30 minutes?
    a) Left knee
       - Yes, No, Don’t know
    b) Right knee
       - Yes, No, Don’t know

If yes to question 7c continue with question 7d, if no, go to question 8.

7d. Does this stiffness in your knee last less than 30 minutes?
    a) Left knee
       - Yes, No, Don’t know
    b) Right knee
       - Yes, No, Don’t know

8. Have you ever had knee replacement surgery, where all or part of the joint was replaced?
   a) Left knee
      - Yes, No, Don’t know
   b) Right knee
      - Yes, No, Don’t know

If yes to both knees in question 8 go to question 14, if no to either or both knees, continue with question 9 on the non-replaced joint(s).
```
Next I would like to ask you some questions about hip symptoms

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>During the past 30 days, have you had any pain, aching or stiffness in your hips?</td>
<td>a) Left hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Right hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15a</td>
<td>Have you had pain, aching or stiffness most days in the past month?</td>
<td>a) Left hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Right hip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15b</td>
<td>Do you have stiffness in your hips in the morning?</td>
<td>a) Left knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Right knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15c</td>
<td>Does this stiffness in your hip last less than 30 minutes?</td>
<td>a) Left knee</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Right knee</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes to question 15a continue with question 15b, if no, go to question 16.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>Have you ever had hip replacement surgery, where all or part of your joint was replaced?</td>
<td>a) Left hip</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Right hip</td>
<td></td>
</tr>
</tbody>
</table>

If yes to both hips in question 16, go to question 20, if no to one or both hips, continue with question 17 on the non-replaced joint(s).
Can I now examine your hips? In order for me to do this I will need you to lie on the examination table.

<table>
<thead>
<tr>
<th>17</th>
<th>Is the flexion of the hips less than 115 degrees?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Left hip</td>
<td>Definite □, Possible □, No □</td>
</tr>
<tr>
<td>b) Right hip</td>
<td>Definite □, Possible □, No □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>18</th>
<th>Is the internal rotation of the hips less than 15 degrees?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Left hip</td>
<td>Definite □, Possible □, No □</td>
</tr>
<tr>
<td>b) Right hip</td>
<td>Definite □, Possible □, No □</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>19</th>
<th>Is there any pain associated with internal hip movements?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Left hip</td>
<td>Definite □, Possible □, No □</td>
</tr>
<tr>
<td>b) Right hip</td>
<td>Definite □, Possible □, No □</td>
</tr>
</tbody>
</table>

Any further comments about the hips add below.

Then ask the following questions.

<table>
<thead>
<tr>
<th>20</th>
<th>Has a doctor told you currently or in the past that you have any of the following forms of arthritis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ankylosing Spondylitis?</td>
<td>□, □, □</td>
</tr>
<tr>
<td>b) Psoriatic Arthritis?</td>
<td>□, □, □</td>
</tr>
<tr>
<td>c) Reiters Syndrome?</td>
<td>□, □, □</td>
</tr>
<tr>
<td>d) Rheumatoid Arthritis?</td>
<td>□, □, □</td>
</tr>
</tbody>
</table>

If yes to rheumatoid arthritis, continue with question 21, if no, this is the end of the joint assessment. Please continue on to the GSF section on page 13.

<table>
<thead>
<tr>
<th>21</th>
<th>Does your doctor currently prescribe any of the following medications for Rheumatoid Arthritis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Methotrexate?</td>
<td>□, □, □</td>
</tr>
<tr>
<td>b) Plaquinil (Hydroxychloroquine)?</td>
<td>□, □, □</td>
</tr>
<tr>
<td>c) Gold Injections/Tablets?</td>
<td>□, □, □</td>
</tr>
<tr>
<td>d) Prednisolone/Steroids?</td>
<td>□, □, □</td>
</tr>
<tr>
<td>e) Sulfasalazine?</td>
<td>□, □, □</td>
</tr>
<tr>
<td>f) A biologic (e.g. adalimumab, etanercept, infliximab)?</td>
<td>□, □, □</td>
</tr>
</tbody>
</table>
### QST HAND Results Sheet

#### Handedness:
Baseline Temperature: C

<table>
<thead>
<tr>
<th>Testing Hand</th>
<th>CDT</th>
<th>WDT</th>
<th>TSL</th>
<th>CPT</th>
<th>HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**USE LEFT HAND. If pain in left hand use right hand. If pain in both hands use left hand.**

#### Thermal Testing

- CDT: von Frey filaments descending from 16mN hair
- WDT: Punctate probes ascending from 8mN probes
- TSL: Not felt
- CPT: Felt
- HPT: Take highest HPT rating for DNIC

#### Mechanical Testing

- MDT: von Frey filaments
- MPT: Punctate probes

#### Codes:
- CW = Cotton Wool
- BR = Brush
- QT = Q-tip

### QST HAND Results Sheet continued

#### Stimulus Response Function

<table>
<thead>
<tr>
<th>128</th>
<th>CW</th>
<th>32</th>
<th>256</th>
<th>BR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CW</td>
<td>256</td>
<td>128</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>32</td>
<td>128</td>
<td>BR</td>
<td>CW</td>
<td>16</td>
</tr>
<tr>
<td>256</td>
<td>8</td>
<td>CW</td>
<td>QT</td>
<td>128</td>
</tr>
<tr>
<td>BR</td>
<td>32</td>
<td>16</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>QT</td>
<td>256</td>
<td>64</td>
<td>CW</td>
</tr>
<tr>
<td>16</td>
<td>BR</td>
<td>512</td>
<td>32</td>
<td>64</td>
</tr>
<tr>
<td>QT</td>
<td>64</td>
<td>8</td>
<td>512</td>
<td>256</td>
</tr>
<tr>
<td>512</td>
<td>16</td>
<td>64</td>
<td>BR</td>
<td>QT</td>
</tr>
<tr>
<td>64</td>
<td>512</td>
<td>QT</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

**Versions:**
- 13
- 14

**Codes:**
- CW = Cotton Wool
- BR = Brush
- QT = Q-tip

**Leave 10 seconds between each of the stimuli.**

**Version 1.2**
Check list for setting up the NeuroScope:
1. Turn on the NeuroScope and the Portapress.
2. Prepare the electrode sites with Nuprep gel (see diagram below).
3. Site the electrodes as shown in the diagram below.
4. Connect ECG leads to electrodes.
5. Attach BP finger cuff. Can the participant feel the cuff pulsing in time with their heart beat? **NEVER** inflate the cuff when it is not attached to your participant’s finger – it will explode!
6. Load up the NeuroScope trace and check that the ECG and BP/HR traces are clear.
7. If they are not see Troubleshooting points in the SOP.

ECG and Blood Pressure Setup

Ensure that the following check list is completed before continuing with the foot QST procedure

<table>
<thead>
<tr>
<th>Thermal Testing</th>
<th>CDT</th>
<th>WDT</th>
<th>TSL</th>
<th>CPT</th>
<th>HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

QST FOOT Results Sheet

Baseline Temperature: C

**USE RIGHT FOOT**, if pain in right foot use left foot. If pain in both feet use right foot.

<table>
<thead>
<tr>
<th>MDT</th>
<th>Not felt</th>
<th>Felt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MPT</th>
<th>Sharp</th>
<th>Blunt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MDT: von Frey filaments descending from 16mN hair
MPT: Punctate probes ascending from 8mN probes
Using 0-100 rating where ‘0’ = no pain and ‘100’ = most intense pain imaginable. Start in top left corner. Please see codes below.

PRESS F1 key the second before administering the 512mN punctate stimulus

Stimulus Response Function

<table>
<thead>
<tr>
<th>8</th>
<th>16</th>
<th>QT</th>
<th>512</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT</td>
<td>BR</td>
<td>64</td>
<td>16</td>
<td>512</td>
</tr>
<tr>
<td>256</td>
<td>512</td>
<td>8</td>
<td>64</td>
<td>QT</td>
</tr>
<tr>
<td>64</td>
<td>32</td>
<td>512</td>
<td>BR</td>
<td>16</td>
</tr>
<tr>
<td>CW</td>
<td>64</td>
<td>256</td>
<td>QT</td>
<td>8</td>
</tr>
<tr>
<td>512</td>
<td>128</td>
<td>16</td>
<td>32</td>
<td>BR</td>
</tr>
<tr>
<td>128</td>
<td>QT</td>
<td>CW</td>
<td>8</td>
<td>256</td>
</tr>
<tr>
<td>16</td>
<td>CW</td>
<td>BR</td>
<td>128</td>
<td>32</td>
</tr>
<tr>
<td>32</td>
<td>8</td>
<td>128</td>
<td>256</td>
<td>CW</td>
</tr>
<tr>
<td>BR</td>
<td>256</td>
<td>32</td>
<td>CW</td>
<td>128</td>
</tr>
</tbody>
</table>

Codes:
- CW = Cotton Wool
- BR = Brush
- QT = Q-tip

Leave 10 seconds between each of the stimuli

Wind-Up Ratio
(using 256mN punctate)

Vibration Detection Threshold

<table>
<thead>
<tr>
<th>Single</th>
<th>Series</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

REMEMBER
Press the F1 key to mark on the ECG trace before each single and press F2 before each series of stimuli on the WUR

Leave 10 seconds between each of the stimuli

PAALS Sub-study Assessment Checklist

At the assessment:

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Stage of Completion: (Completed, Part Completed, Missing, Refused or Not-applicable (n/a))</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioelectrical Impedance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip Strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender Points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joints Examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QST Hand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QST Foot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroscope</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To give to the participant:

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Status: (Not-applicable (n/a), received)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Diary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actiwatch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actiwatch Instructions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Return Envelope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>£10 Payment And/or Travel Expenses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix III – Graphs of QST by age, sex and social deprivation
Foot CPT by age group, kernel density

Hand and foot VDT by age group, kernel density
Hand MDT by social deprivation, kernel density

![Kernel density graph showing hand MDT distribution across social deprivation quartiles.](image-url)
Appendix IV – PAALS sub-study questionnaire
**Participant Questionnaire**

**ID number:**

Please fill in the date you completed this form
e.g. 12th August 2010 should be written as 12 08 2010

Day  Month  Year

If you have any questions or queries, please contact:
Rosie Duncan Tel: 0161 275 7314
Email: Rosie.Duncan@manchester.ac.uk
Or
Alison Littlewood Tel: 0161 275 7314
Email: Alison.J.Littlewood@manchester.ac.uk

---

**Please answer the questions by crossing the box ☐ that you think most closely applies to you.**

1. During the past month have you had any ache or pain that has lasted for one day or longer?
   - Yes ☐   No ☐

2. Do you have any such ache or pain today?
   - Yes ☐   No ☐

3. Thinking about this ache or pain, have you been aware of it for more than 3 months?
   - Yes ☐   No ☐
4. Please shade any area on the diagrams below where you feel, or have felt, aches and pains during the past month.

5. Please shade on the diagrams below the location of the SINGLE most troublesome pain that you feel. If you do not have any pain please go on to question 27.

6. Thinking about your most troublesome pain, does the pain have one or more of the following characteristics?

   - Burning  
   - Painful-cold  
   - Electric Shocks

   [ ] Yes  
   [ ] No

7. Thinking about your most troublesome pain, is this pain associated with one or more of the following symptoms in the same area?

   - Tingling  
   - Pins and Needles  
   - Numbness  
   - Itching

   [ ] Yes  
   [ ] No
Thinking about your most troublesome pain, how long have you been aware of this pain?

- Less than 6 months
- Between 6 months and 12 months
- Between 1 and 3 years
- More than 3 years

Thinking about your most troublesome pain over the past 24 hours, please indicate on the scale below the highest intensity of the pain during the past 24 hours.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no pain</td>
<td>worst pain</td>
<td>imaginable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thinking about your most troublesome pain over the past 24 hours, please indicate on the scale below the lowest intensity of the pain during the past 24 hours.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no pain</td>
<td>worst pain</td>
<td>imaginable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thinking about your most troublesome pain over the past 24 hours, please indicate on the scale below the average intensity of the pain during the past 24 hours.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>no pain</td>
<td>worst pain</td>
<td>imaginable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following questions relate to your usual sleep habits during the past month only. Please record the answer that indicates the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

10. During the past month, what time have you usually gone to bed at night?
   
   Bedtime: ______

11. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
   
   Number of minutes: ______

12. During the past month, what time have you usually got up in the morning?
   
   Getting up time: ______

13. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)
   
   Hours of sleep per night: ______
For each of the remaining questions, please cross the box \( \times \) that is the best response and answer all the questions.

During the past month, how often have you had trouble sleeping because you…

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a. Cannot get to sleep within 30 minutes</td>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Three or more times a week</td>
<td>3</td>
</tr>
<tr>
<td>14b. Wake up in the middle of the night or early morning</td>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Three or more times a week</td>
<td>3</td>
</tr>
<tr>
<td>14c. Have to get up to use the bathroom</td>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Three or more times a week</td>
<td>3</td>
</tr>
<tr>
<td>14d. Cannot breathe comfortably</td>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Three or more times a week</td>
<td>3</td>
</tr>
<tr>
<td>14e. Cough or snore loudly</td>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Three or more times a week</td>
<td>3</td>
</tr>
<tr>
<td>14f. Feel too cold</td>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Three or more times a week</td>
<td>3</td>
</tr>
<tr>
<td>14g. Feel too hot</td>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Three or more times a week</td>
<td>3</td>
</tr>
</tbody>
</table>
### 14h) Had bad dreams

<table>
<thead>
<tr>
<th>Frequency</th>
<th>(\square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td>Three or more times a week</td>
<td>3</td>
</tr>
</tbody>
</table>

### 14i) Have pain

<table>
<thead>
<tr>
<th>Frequency</th>
<th>(\square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td>Three or more times a week</td>
<td>3</td>
</tr>
</tbody>
</table>

a) If any other reason(s), please describe

______________________________

______________________________

b) If any other reason(s), how often during the past month have you had trouble sleeping because of this?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>(\square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td>Three or more times a week</td>
<td>3</td>
</tr>
</tbody>
</table>

### 15) During the past month, how would you rate your sleep quality overall?

<table>
<thead>
<tr>
<th>Rating</th>
<th>(\square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>0</td>
</tr>
<tr>
<td>Fairly good</td>
<td>1</td>
</tr>
<tr>
<td>Fairly bad</td>
<td>2</td>
</tr>
<tr>
<td>Very bad</td>
<td>3</td>
</tr>
</tbody>
</table>

### 16) During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>(\square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td>Three or more times a week</td>
<td>3</td>
</tr>
</tbody>
</table>

### 17) During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>(\square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not during the past month</td>
<td>0</td>
</tr>
<tr>
<td>Less than once a week</td>
<td>1</td>
</tr>
<tr>
<td>Once or twice a week</td>
<td>2</td>
</tr>
<tr>
<td>Three or more times a week</td>
<td>3</td>
</tr>
</tbody>
</table>

### 18) During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

<table>
<thead>
<tr>
<th>Rating</th>
<th>(\square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No problem at all</td>
<td>0</td>
</tr>
<tr>
<td>Only a very slight problem</td>
<td>1</td>
</tr>
<tr>
<td>Somewhat of a problem</td>
<td>2</td>
</tr>
<tr>
<td>A very big problem</td>
<td>3</td>
</tr>
</tbody>
</table>
The following questions relate, in general, to how you are. Here are a number of characteristics that may or may not apply to you. For example, do you agree that you are someone who likes to spend time with others? Please write a number next to each statement to indicate the extent to which you agree or disagree with that statement.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is talkative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tends to find fault with others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does a thorough job</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is depressed, blue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is original, comes up with new ideas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is reserved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is helpful and unselfish with others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can be somewhat careless</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is relaxed, handles stress well</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is full of energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starts quarrels with others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is a reliable worker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can be tense</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is ingenious, a deep thinker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generates a lot of enthusiasm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has a forgiving nature</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tends to be disorganised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worries a lot</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has an active imagination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tends to be quiet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Is generally trusting
Tends to be lazy
Is emotionally stable, not easily upset
Is inventive
Has an assertive personality
Can be cold and aloof
Perseveres until the task is finished
Can be moody
Values aesthetic experiences
Is sometimes shy, inhibited
Is considerate and kind to almost everyone
Does things efficiently
Remains calm in tense situations
Prefers work that is routine
Is outgoing, sociable
Is sometimes rude to others
Makes plans and follows through with them
Gets nervous easily
Likes to reflect, play with ideas
Has few artistic interests
Likes to cooperate with others
Is easily distracted
Is sophisticated in art, music, or literature
Appendix V – Instructions from the German Research Network on Neuropathic Pain protocol
Appendix 1. Verbal instructions for performing quantitative sensory testing.

Test 1. Thermal testing procedures (CDT, WDT, TSL, PHS, CPT, HPT).

“A temperature test of your skin will be performed. First we are testing your ability to detect a change of temperature to ‘cool’ or ‘warm’. A special device that cools or warms your skin will be placed over your... (specify practice area, control and test areas). Secondly another temperature test of your skin will be performed to find the temperature that feels ‘painfully cold or hot’.”

Instructions for testing of cold detection threshold (CDT).

“Please press the stop-button as soon as you feel the slightest change of temperature to ‘cold’. Then the thermode will warm up to starting temperature. This procedure will start in a few seconds and will be repeated a total of 3 times.”

Instructions for testing of warm detection threshold (WDT).

“Please press the stop-button as soon as you feel the slightest change of temperature to ‘warm’. Then the thermode will cool down to starting temperature. This procedure will start in a few seconds and will be repeated a total of 3 times.”

Instructions for testing of thermal sensory limen (TSL).

“Please press the stop-button as soon as you feel the slightest change of temperature to ‘warm’ or ‘cold’, and say as you do so whether the sensation you feel is warm or cold. Then the test continues immediately without prior warming up or cooling down to normal skin temperature. This procedure will be repeated a total of 6 times in a row and start in a few seconds.”

Instructions for testing of paradoxical heat sensations (PHS) during the TSL procedure.

Instruction to the investigator: Some subjects will report a sensation of “warm” or “hot” or “painfully hot” upon cold stimulation during the TSL procedure. These reports have to be marked as “paradoxical heat sensation”.

Instructions for testing of cold pain threshold (CPT).

“The temperature of the skin will decrease to ‘cold’. Eventually a painful component will be added to the sensation of ‘cold’, and it will change in quality from cold to, for example, ‘aching’, ‘stinging’, or ‘burning’. Please press the stop button immediately at the first painful sensation. After pressing the stop-button the thermode will warm up to starting temperature. This procedure will start in a few seconds and will be repeated a total of 3 times.”
Instructions for testing of heat pain threshold (HPT).

“The temperature of the skin will increase to ‘warm’ and a few moments later to ‘hot’. Eventually a painful component will be added to the sensation of ‘hot’, and it will change in quality from ‘hot’ to, for example, ‘burning’ or ‘stinging hot’. Please press the stop-button immediately at the first ‘burning’ or ‘stinging hot’ sensation. Then the thermode will cool down to starting temperature. This procedure will start in a few seconds and will be repeated a total of 3 times.”

Test 2. Testing of the mechanical detection threshold (MDT).

“This is a test of your ability to detect light touch. I will press these hairs to your skin (specify practice area, and control and test areas). Please say ‘Yes’, if you feel the slightest light touch.”

Test 3. Testing of the mechanical pain threshold (MPT).

“This is a test of your ability to detect a sensation of ‘pricking’ or ‘stinging’. Blunt needles that increase in sharpness will be pressed gently against your skin (specify practice area, and control and test areas). At first you may be able to feel them, but not feel that they are ‘pricking’ or ‘stinging’ in any way. However, eventually a component of slight ‘pricking’ or ‘stinging’ will be added to this sensation. Please say “sharp”, immediately as you feel the slightest ‘pricking’ or ‘stinging’ sensation! If you feel the needle touching your skin without any ‘pricking’ or ‘stinging’, please say “blunt”.


“This is a test of your ability to feel different intensities of pain. As in the previous test, blunt needles that increase in sharpness will be pressed gently against your skin. In between you will be touched by gently moving stimuli. Some of these stimuli will be accompanied by a sensation that has a ‘pricking’, ‘burning’ or ‘scraping’ quality, some may not be ‘pricking’, ‘burning’ or ‘scraping’ at all, and some you may not even be able to detect. Please give a number between ‘0’ and ‘100’ for the ‘prickingness’, ‘sharpness’ or ‘strongness of the burning or scraping sensation’ of each stimulus.

‘0’ indicating no pain or any kind of ‘slightly pricking, stinging, burning or scraping sensation’.

‘100’ indicating most intense pain, pricking, stinging, burning or scraping imaginable.”

Test 5. Performing the ‘wind-up’ procedure (WUR).

“This is a test of repeated pinpricks, using the same kind of blunt needle that was used in the last two tests. I will now apply a single pinprick. Please give a number between ‘0’ and ‘100’ for the ‘prickingness’ or ‘sharpness’ of that stimulus.

‘0’ again indicating no pain or any kind of ‘slightly pricking or stinging sensation’.

‘100’ indicating most intense pain, pricking or stinging imaginable.”
Continue, when the subject has rated the single pinprick stimulus:

“I will now apply a series of 10 pinpricks in a row. Please give a number between ‘0’ and ‘100’ for the prickingness or sharpness over that whole series of 10 pinpricks. ‘0’ indicating no pain or any kind of ‘slightly pricking or stinging sensation’. ‘100’ indicating most intense pain imaginable.”

**Test 6. Testing of the vibration detection threshold (VDT).**

“This is a test of your ability to detect vibration. Now I will put this tuning fork, once I have made it vibrate, on your… (specify practice area, control and test areas, and place the tuning fork over a bony part of the referring area). Please tell me if you feel any vibration, and say ‘Now’ immediately that this vibration disappears. This procedure will be repeated a total of 3 times.”

**Test 7. Testing of the pressure pain threshold (PPT).**

“This is a test of your sensitivity to deep pain. Now I will press this pressure meter against your… (specify practice area, and control and test areas), and will gradually increase the pressure. Please say ‘Now’ as soon as the pressure starts to be painful. This procedure will be repeated a total of 3 times.”

(Rolke et al. 2006b)
Appendix VI – Sample weighting of data
Sample weighting of data

The two-phase epidemiological survey is a well-established technique (Dunn et al. 1999). Baseline data are collected from a cohort of participants, and some of these data are used to classify the participants into groups. Participants are sampled from these groups for a more intensive stage of data collection, which would be too resource-intensive to carry out on all the participants. This method of data collection means that only a sub-set of the participants have complete data.

Weighting is a method of applying the data obtained for this sub-set to all the participants. This is not the same as simply copying values obtained from a participant in the sub-set to one or several participants in the larger group, which would lead to a large group of participants having only the same degree of variation within the data as a small group. Summary statistics, e.g. means or prevalence rates, obtained such data would have confidence intervals which were artificially narrow (Dunn et al. 1999). Stata 11 has the facility to handle sample weighted data in the statistically appropriate manner.

Three related features of survey data are important in analysis (StataCorp 2009c).

1) Clustering. This is where sampling units are not the same as the units of analysis. For example, hospitals are sampled, but data is gathered from individual patients. Clustering was not used in the present study.

2) Stratification. A sampling strategy may sample randomly within certain sub-groups (strata) but not in the group as a whole. For example, in the present study participants were selected for the sub-study based on how many painful body areas they reported at baseline, and for weighting purposes they were also stratified by age and sex.

3) Sample weights. These are proportional to the inverse of the probability of that observation being sampled. The sampling weight is an indicator of how many main-group subjects are represented by each sub-group subject.

Participants in the present study were categorised according to age, sex and pain status at baseline. Sample weighting factors were calculated to allow the data from each sub-study participant to be applied to participants in the same stratum in the wider group. These are given in Table 1.
Table 1 - Weighting factors used in the present study

<table>
<thead>
<tr>
<th>Factor combination</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, youngest age group, no pain</td>
<td>7.10</td>
</tr>
<tr>
<td>Male, youngest age group, some pain</td>
<td>5.46</td>
</tr>
<tr>
<td>Male, youngest age group, CWP</td>
<td>10.00</td>
</tr>
<tr>
<td>Male, middle age group, no pain</td>
<td>4.27</td>
</tr>
<tr>
<td>Male, middle age group, some pain</td>
<td>5.00</td>
</tr>
<tr>
<td>Male, middle age group, CWP</td>
<td>4.83</td>
</tr>
<tr>
<td>Male, oldest age group, no pain</td>
<td>12.00</td>
</tr>
<tr>
<td>Male, oldest age group, some pain</td>
<td>7.50</td>
</tr>
<tr>
<td>Male, oldest age group, CWP</td>
<td>18.00</td>
</tr>
<tr>
<td>Female, youngest age group, no pain</td>
<td>6.20</td>
</tr>
<tr>
<td>Female, youngest age group, some pain</td>
<td>5.67</td>
</tr>
<tr>
<td>Female, youngest age group, CWP</td>
<td>11.00</td>
</tr>
<tr>
<td>Female, middle age group, no pain</td>
<td>4.20</td>
</tr>
<tr>
<td>Female, middle age group, some pain</td>
<td>2.57</td>
</tr>
<tr>
<td>Female, middle age group, CWP</td>
<td>2.00</td>
</tr>
<tr>
<td>Female, oldest age group, no pain</td>
<td>9.00</td>
</tr>
<tr>
<td>Female, oldest age group, some pain</td>
<td>7.33</td>
</tr>
<tr>
<td>Female, oldest age group, CWP</td>
<td>7.00</td>
</tr>
</tbody>
</table>
Appendix VII – Principal Components Analysis
Principal components analysis

Principal components analysis (PCA) uses matrix algebra to find lines (eigenvectors) which best describe the relationship between variables. Each eigenvector has an associated eigenvalue which represents the amount of variance in the data along the axis of that eigenvector. There are as many eigenvectors as there are variables, and they are all orthogonal to one another. In a relationship between two variables, the eigenvector with the largest eigenvalue would be a line of best fit through the points, and the other eigenvector would be at 90° to it. Obviously with large numbers of variables it is not so easy to visualise the relationship.

Each data point can be re-expressed in terms of the eigenvectors, giving a new variable (a component) for each eigenvector. If a decision is made not to use all the components, some of the original data will be lost, but this may be expected to be a small proportion if only the components associated with small eigenvalues are dropped. This allows a simplification of data involving large numbers of variables (Smith 2002).

Orthogonal axes may be rotated about their origin and will still remain orthogonal. After rotation, data points will have new co-ordinates, as they have remained stationary but the axes have moved. The varimax method rotates the axes such that for each component, the coefficients of the variables divide into a group which are as high as possible, and a group which are as low as possible. This aids interpretation of the meaning of individual components (Armitage and Berry 1994).

Parallel analysis is a method for determining the number of components to retain from PCA. The program works by creating a random dataset with the same numbers of observations and variables as the original data, and repeating the analysis. When the eigenvalues from the random data are larger than the eigenvalues from the PCA, the components are mostly random noise (UCLA Academic Technology Services 2012).
Appendix VIII – Variables comparison with existing literature
Variables comparison with existing literature

Tables 1, 2 and 3 contain summary data to allow data obtained in the present study to be compared to data in the published literature.

**Table 1 - HAD anxiety and depression**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hinz and Brahler</th>
<th>Present study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.0 (3.6)</td>
<td>4.4 (3.3)</td>
</tr>
<tr>
<td>Depression</td>
<td>4.7 (3.9)</td>
<td>4.8 (4.0)</td>
</tr>
</tbody>
</table>

Comparative data obtained from (Hinz and Brahler 2011), population-based study, participants aged over 18 years, mean (S.D.).

Present study data mean (S.D.).

**Table 2 – Thermal QST variables measured at the hand, “fibromyalgia” or “CWP”**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Desmeules et al “fibromyalgia” (n = 85)</th>
<th>Hurtig et al “fibromyalgia” (n = 29)</th>
<th>Present study “CWP” group (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDT</td>
<td>1.65 (0.88)</td>
<td>1.0 (1.4)</td>
<td>1.4 (1.2 to 2.1)</td>
</tr>
<tr>
<td>WDT</td>
<td>2.59 (1.16)</td>
<td>2.2 (0.3)</td>
<td>1.7 (1.3 to 1.9)</td>
</tr>
<tr>
<td>CPT</td>
<td>17.58 (9.05)</td>
<td>19.7 (6.7)</td>
<td>11.7 (7.7 to 15.0)</td>
</tr>
<tr>
<td>HPT</td>
<td>41.20 (15.61)</td>
<td>41.1 (3.3)</td>
<td>43.0 (40.2 to 45.2)</td>
</tr>
</tbody>
</table>

Comparative data obtained from (Desmeules et al. 2003), FMS patients aged 49 (9.3) years (mean (S.D.)), and (Hurtig et al. 2001), female FMS patients aged 30 – 68 years.

Present study participants were pain-free on the day of testing and aged 34 – 97.

Present study data are median (95% confidence intervals), Desmeules et al and Hurtig et al data are mean (S.D.).
Table 3 - QST variables measured at the hand “no pain”

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rolke et al aged ≥40</th>
<th>Present study “no pain” group (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>CDT</td>
<td>1.35 (0.4 to 4.4)</td>
<td>1.44 (0.5 to 4.2)</td>
</tr>
<tr>
<td>WDT</td>
<td>2.08 (0.7 to 6.1)</td>
<td>2.01 (0.8 to 5.2)</td>
</tr>
<tr>
<td>TSL</td>
<td>3.05 (0.9 to 10.9)</td>
<td>3.22 (1.1 to 9.9)</td>
</tr>
<tr>
<td>PHS</td>
<td>0.02 (0 to 0.3)</td>
<td>0.00 (0 to 0)</td>
</tr>
<tr>
<td>CPT</td>
<td>7.29 (0 to 22.1)</td>
<td>10.43 (0 to 27.0)</td>
</tr>
<tr>
<td>HPT</td>
<td>45.81 (40.1 to 50.0)</td>
<td>44.06 (37.5 to 50.0)</td>
</tr>
<tr>
<td>MDT</td>
<td>0.90 (0.18 to 6.5)</td>
<td>1.17 (0.2 to 6.4)</td>
</tr>
<tr>
<td>MPT</td>
<td>116 (26 to 526)</td>
<td>71 (15 to 332)</td>
</tr>
<tr>
<td>MPS</td>
<td>0.5 (0 to 4.3)</td>
<td>0.63 (0.2 to 4.2)</td>
</tr>
<tr>
<td>ALL</td>
<td>0.00 (0 to 0.01)</td>
<td>0.00 (0 to 0.01)</td>
</tr>
<tr>
<td>WUR</td>
<td>1.97 (0.7 to 5.4)</td>
<td>2.24 (0.7 to 7.1)</td>
</tr>
<tr>
<td>VDT</td>
<td>7.57 (6.6 to 8.0)</td>
<td>7.77 (7.0 to 8.0)</td>
</tr>
</tbody>
</table>

Comparative data obtained from (Rolke et al. 2006a), pain-free healthy volunteers aged 40 – 75, numbers of participants in each group not given.

Present study participants were pain-free on the day of testing and aged 34 – 97.

Present study data are median (95% confidence intervals), Rolke et al data mean (95% C.I).
Appendix IX – Multiple imputation
Multiple imputation

Missing data is relatively common in studies on human subjects, particularly those which use questionnaires (Peyre, Leplege, and Coste 2011). A common way of dealing with this issue is to only include subjects who have complete data in the analysis (complete case analysis or CCA). However, CCA assumes that data are missing completely at random (MCAR), i.e. that the “missingness” makes no difference to the relationships being investigated, and this is usually not the case; this means that the results may be biased, as well as the power of the analysis being reduced because there are fewer observations (Vergouw et al. 2012). There are different categories of missing data. As well as MCAR, where the probability that data are missing does not depend upon observed or unobserved data, missing at random (MAR) data may depend upon the values of observed data, whereas missing not at random (MNAR) data depends upon unobserved data (StataCorp 2009b).

Imputation is a method of replacing missing values with an estimate. Imputation methods which replace the missing value with a single value (e.g. based on the mean response to other items (Hardouin, Conroy, and Sebille 2011)) also assume that missing data are MCAR (Vergouw et al. 2012). Single imputation methods treat the imputed values as if they were actual measured values, and so generates confidence intervals which are artificially narrow and significance tests which are too optimistic (StataCorp 2009b). Multiple imputation is a simulation-based procedure which does not try to replace missing data with “true” values, but deals with it in a way which will allow valid statistical inference (StataCorp 2009b), i.e. the mean and variance of a multiply imputed variable should be close to those of the population (Graham 2009). It replaces the missing values with predicted values from regression of the whole data set, which is repeated in an iterative manner until convergence is achieved. In this case, “convergence” means that two consecutively produced data sets are sufficiently similar to two random draws from the population (Graham 2009). A number of different data sets are constructed in this manner (as implied in the term multiple), and although non-missing values are repeated identically in each data set, missing values are selected from a distribution to allow for a degree of uncertainty in the value being imputed (Vergouw et al. 2012). The multiple data sets are analysed separately, and the parameter estimates combined to give a final set of results (White, Royston, and Wood 2011).

Multiple imputation requires that data are missing at random (MAR) which is a less stringent standard than MCAR (Vergouw et al. 2012). The assumption of data
being MAR is more plausible if more explanatory variables are included in the data set (White, Royston, and Wood 2011). However, even if MAR is violated, analysis using multiply imputed data is still at least as good as using CCA (Graham 2009).

The number of imputations required depends upon the level of “missingness” (Graham, Olchowski, and Gilreath 2007) and also on the data itself and the analysis to be carried out (StataCorp 2009b). Although limited evidence is available, there are recommendations that at least 20 imputations should be carried out (StataCorp 2009b), or at least 40 imputations if there is 50% missing data (Graham 2009). A rule of thumb has been posited based on Monte Carlo error tending to zero, which means that a repeat run of the same set of imputations would give an adequate level of reproducibility. This rule states that the number of imputations should be equal to the number of incomplete cases (White, Royston, and Wood 2011).

Multiple imputation by chained equations is one technique which can be used to generate imputed data sets. First, all missing values are filled with random sampling from observed values. The first variable with missing values is regressed against each of the other variables in turn, but only using cases which have observed values for the first variable. The type of regression depends upon the variable, i.e. linear regression for continuous, logistic for ordinal and multiple logistic for nominal data. The missing values in the first variable are then replaced with simulated draws from that variable’s posterior predictive distribution. The posterior predictive distribution is the distribution of unobserved observations (prediction) conditional on the observed data. This process is then repeated for each variable with missing data in turn. It is repeated for the whole data set until convergence is achieved, and the whole procedure is repeated for each imputed data set which is required (White, Royston, and Wood 2011).

It is recommended that the number of variables should be kept below 100, even with large (n>1000) numbers of subjects, and for smaller sample sizes, the number of variables should be smaller (Graham 2009). The problem of having too many variables can be alleviated by imputing calculated scale measures rather than the individual components which make up the scale. Models containing large numbers of variables, particularly categorical variables, may not achieve convergence (White, Royston, and Wood 2011). Another potential problem of including categorical variables is if a table of the variable against the (categorical) outcome variable has a zero cell. This leads to “perfect prediction” which usually results in the term being
dropped from the model, or very large standard errors (White, Royston, and Wood 2011).

Multiple imputation allows use to be made of data which would be “wasted” if CCA was applied, and is therefore more efficient and more ethical than that alternative (Vergouw et al. 2012).
Appendix X – Moderation in statistical analysis
Moderation in statistical analysis

Moderation refers to a difference in the relationship between the predictor and outcome variables at different values of the moderating variable. In statistical analysis this can be achieved using an interaction term calculated by multiplying together the predictor and moderator variables. If the moderator is a binary variable with its reference category value set at “0” and the other category value at “1”, this makes the result easy to interpret, because the interaction term will also be “0” for the reference category. Both the predictor and moderator terms are also included separately in the model.

In linear regression, the $\beta$ coefficient obtained for the interaction term indicates the additional variation in the outcome variable which is explained by it, when the predictor variable is adjusted for. The linear regression can be represented as

$$ Y = \beta_0 + \beta_p X_p + \beta_i (X_p \times X_m) $$

where

- $Y =$ outcome measure
- $\beta_0 =$ intercept value
- $\beta_p =$ coefficient of predictor variable
- $\beta_i =$ coefficient of interaction term
- $X_p =$ predictor variable
- $X_m =$ moderator variable

Consider as an example the interaction term between tender point count and sex. As $X_m$ takes the value “0” for males and “1” for females, the equation for males is:

$$ Y_{males} = \beta_0 + \beta_p X_p $$

and for females:

$$ Y_{females} = \beta_0 + \beta_p X_p + \beta_i X_p = \beta_0 + (\beta_p + \beta_i)X_p $$

Hence:

$$ Y_{females} = Y_{males} + \beta_i X_p $$

It can be seen that the difference between the two equations is the addition of the coefficient $\beta_i$ for females, which represents the difference in the relationship between $Y$ and $X_p$ for males and females.

The results from multiple logistic regression are given as relative risk ratios in the present study, which are equivalent to $e^\beta$. The relationship between the terms where male is the reference category can be represented as:
$$RRR_{males} = RRR_{females} \times RRR_i = e^{\beta_p + \beta_i}$$

where

- $RRR_{males}$ = relative risk ratio for males
- $RRR_{females}$ = relative risk ratio for females
- $RRR_i$ = relative risk ratio for the interaction term
- $\beta_p$ = $\beta$ coefficient for the predictor variable
- $\beta_i$ = $\beta$ coefficient for the interaction term