School of Physiotherapy and Exercise Science

Multidimensional Patient Profiles In Chronic Non-Specific Axial Low Back Pain - Subgrouping And Prognosis

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This thesis is presented for the Degree of
Doctor of Philosophy
of
Curtin University

December 2015

Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number: HR112/2012; Royal Perth Hospital Human Research Ethics Committee, Approval Number: EC 2012-148; Sir Charles Gairdner Hospital Human Research Ethics Committee, Approval Number: 2012-197; and Fremantle Hospital Human Research Ethics Committee, Approval Number: AR/13/1.

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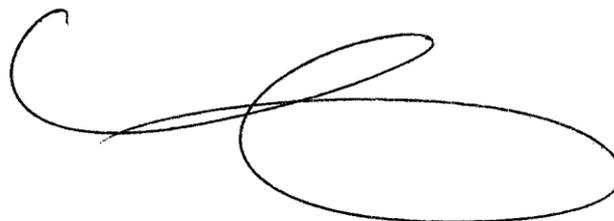
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Abstract

Back pain is the leading cause of disability in the world. The annual prevalence of persistent, chronic low back pain (CLBP) ranges from 15-45%. A wide array of treatments is available, however, outcomes in CLBP are modest at best. These modest outcomes are proposed to be related to a lack of treatment specificity, secondary to presumed sample homogeneity, as well as a lack of consideration of the multidimensional nature of CLBP. To facilitate targeted management of CLBP many classification systems (CS) have been described, however, the majority are uni-dimensional in nature, despite contemporary understanding of CLBP reflecting complex interactions between peripheral and central nociceptive processes, as well as multiple contributing dimensions (demographics, pain characteristics, tissue sensitivity, psychological, social, health, lifestyle and movement). To date, CS have also been derived largely from clinical judgement leaving them open to bias. CS that have utilised non-judgemental or statistical techniques to derive subgroups have been limited by the small number of dimensions investigated.

Therefore, the aims of this thesis are: 1) To examine four individual clinical cases of people with axial CLBP with contrasting multidimensional profiles determined by data from valid and reliable clinical measures, and to consider the complexity of these individual presentations in relation to the limitations of existing CLBP classification systems; 2) To explore statistical subgrouping using standardised clinically-applicable measures from multiple dimensions within a large cohort with axial CLBP; 3) To profile subgroups using data from multiple dimensions associated with CLBP, to facilitate postulation of the clinical implications and pain mechanisms related to the different profiles; and 4) To determine whether multidimensional baseline data, including subgroup membership, are prognostic of outcome at one year follow-up.

Study 1

This study investigated four cases (P1 - P4) with CLBP considering pain characteristics, tissue sensitivity, psychological, social, health, lifestyle, and movement dimensions. Cases were purposefully selected to highlight the

limitations of contemporary CS for CLBP. P1) presented with localised lumbar sensitisation, a directional pain response following spinal movement and elevated pain catastrophising, consistent with dominant peripheral nociception. P2) had a "mixed" profile characterised by localised lumbar hypersensitivity, a directional pain response following spinal movement and elevated fear-avoidance beliefs. This was combined with factors suggestive of centrally-mediated facilitation of nociception such as the presence of functional pain comorbidities and elevated stressful life events in the past year. P3) showed widespread enhanced pain sensitivity possibly reflective of dominant centrally-mediated pain mechanisms, combined with multidirectional pain responses following spinal movement, elevated scores for multiple affective and cognitive factors and multiple comorbidities. P4) had normal pain sensitivity and no increase in pain following movement, but had dominant cognitive and affective factors and comorbidities. The cases are discussed in relation to the limitations of contemporary CLBP CS.

To fulfil the next aim of this research attempts were made to identify subgroups from a range of indicator variables from multiple dimensions (demographics, pain characteristics, tissue sensitivity, psychological, social, health, lifestyle, movement) using Latent Class Analysis. However, it was not possible to obtain a model that converged upon a clear maximum likelihood estimate. Therefore, it was decided to examine the data set by deriving subgroups of people based on three different dimensions: i) tissue sensitivity, ii) psychological questionnaire scores, iii) pain responses following repeated spinal forward and backward bending; and profile these subgroups on the broader multidimensional data.

Study 2

This study used latent class analysis to derive subgroups in an axial CLBP cohort (n=294), based upon results of multimodal sensory testing, and subsequently profiled subgroups on multidimensional data. Bedside (two-point discrimination; brush / vibration / pinprick perception; temporal summation) and laboratory (mechanical detection threshold; pressure / heat / cold pain thresholds; conditioned pain modulation) sensory testing were examined at wrist / lumbar

sites. Data were entered into principal component analysis, and five component scores entered into latent class analysis. Three clusters were derived: Cluster 1 (31.9%) was characterised by average to high temperature and pressure pain sensitivity; Cluster 2 (52.0%) was characterised by average to high pressure pain sensitivity; and Cluster 3 (16.0%) was characterised by low temperature and pressure pain sensitivity. Clusters 1 and 2 had a significantly greater proportion of female participants, and higher depression and sleep disturbance scores than Cluster 3. The proportion of participants undertaking <300 minutes/week of moderate activity was significantly greater in Cluster 1 than Clusters 2 and 3.

Study 3

This study used latent class analysis to derive subgroups in the same cohort based upon data from multiple psychological questionnaires, and subsequently profiled subgroups on multidimensional data. Psychological questionnaire scores entered into latent class analysis included: Depression, Anxiety, Stress scales, Thought Suppression and Behavioural Endurance subscales (Avoidance Endurance questionnaire), Chronic Pain Acceptance questionnaire, Pain Catastrophising scale, Pain Self-Efficacy questionnaire and Fear-Avoidance Beliefs questionnaire. Three clusters were derived: Cluster 1 (23.5%) was characterised by low cognitive and affective questionnaire scores, with the exception of fear-avoidance beliefs; Cluster 2 (58.8%) was characterised by relatively elevated thought suppression, catastrophizing and fear-avoidance beliefs, but lower pain self-efficacy, depression, anxiety and stress; Cluster 3 (17.7%) had the highest scores across cognitive and affective questionnaires. Cluster 1 reported significantly lower pain intensity and bothersomeness than other clusters. Disability, stressful life events and low back region perceptual distortion increased progressively from Cluster 1 to Cluster 3 while mindfulness progressively decreased. Clusters 2 and 3 had more people with increased pain following repeated spinal bending than Cluster 1. Cluster 3 had significantly greater lumbar pressure pain sensitivity, more undiagnosed comorbid symptoms and more widespread pain than other clusters.

Study 4

This study utilised statistical subgroup derivation in the same cohort based upon pain responses (≥2/10, numeric rating scale) following a standardised protocol involving repeated forward and backward spinal bending, and subsequently profiled subgroups on multidimensional data. Four subgroups were derived: 1) no clinically-important increase in pain with bending in either direction (49.0%); 2) increased pain with repeated forward bending only (28.2%); 3) increased pain with repeated backward bending only (9.9%); and 4) increased pain bending in both directions (12.9%). On profiling subgroups 1 and 3 had normal pain sensitivity, but had elevated fear-avoidance beliefs and distorted body perception compared to healthy controls. Subgroup 1 also showed the fastest movement in both directions. Subgroup 2 had elevated disability and pain catastrophising, slower movement speed, and low pain self-efficacy compared to other subgroups. They also demonstrated elevated depression, fear-avoidance beliefs and distorted body perception compared to healthy controls. Subgroup 4 had higher pain intensity, pain catastrophising and lower pain self-efficacy than other subgroups. They also showed elevated lumbar pressure and cold sensitivity, depression, fear-avoidance beliefs and distortion of body perception compared to healthy controls. Clinically-significant amelioration of pain, when moving in the opposite direction to that which was provocative, occurred in 20.5% and 20.7% of participants in subgroups 2 and 3 respectively.

Clinical implications and pain mechanisms for each subgroup are considered in each subgrouping study.

Individual patterns of subgroup membership across all three subgrouping studies were examined. Participants demonstrated 33 out of 36 possible response patterns suggesting presentations in people with CLBP are highly individualised.

Study 5

This study investigated prognostic models for pain intensity, disability, global rating of change and bothersomeness in this cohort at one-year follow-up, utilising multidimensional baseline data, subgroups and broad treatment groupings.

Factors prognostic for higher pain intensity (explaining 23.2% of the variance) included higher baseline pain intensity and punishing spousal interactions, and lower years in education; while participating in exercise as treatment was prognostic of lower pain intensity. Factors prognostic for greater disability (explaining 33.6% of the variance) included higher baseline disability, time taken to complete five forward bends, fear-avoidance beliefs, pain catastrophising, pain self-efficacy, endurance behaviours and punishing spousal interactions; while participating in exercise as treatment was prognostic of lower disability. For a global rating of change rated as much / very much improved participating in exercise as treatment, having some leg pain and higher chronic pain acceptance increased the odds (acceptable discrimination). For CLBP rated as very / extremely bothersome higher baseline pain intensity and forward bend time and receiving spinal injection(s) as treatment increased the odds; while higher age, and years in education and having some leg pain decreased the odds (acceptable discrimination).

To summarise this body of research, Study 1 demonstrated the limitations of existing CLBP CS through examination of the complex multidimensional nature of CLBP in four cases. While subgrouping is hypothesised to facilitate tailored management of CLBP, studies 2, 3 and 4 demonstrated that while subgroups can be statistically-derived based upon pain sensitivity, psychological questionnaires and pain responses following repeated movement, individual patterns of subgroup membership across the three subgrouping studies appear highly variable. These studies highlight that unidimensional classification of people with CLBP is unlikely to capture the complexity of CLBP for an individual, even when multidimensional profiling is utilised. Study 5 demonstrates that even when considering multidimensional baseline data, subgroups and broad treatment groupings in

prognostic models only explain approximately 30% of the variance in outcomes, suggesting consideration of a broader range of potentially prognostic variables may not improve prognosis. This is possibly because prognostic models in CLBP may only determine factors consistently prognostic across the whole sample, rather than those important at the level of the individual. This suggests differing approaches such as consideration of complexity theory or data-rich single case experiments tracking change at multiple time-points may be appropriate to examine multidimensional interactions in people with CLBP.

Highly varied responses across the subgrouping studies highlight the need for a flexible multidimensional framework for assessment of people with CLBP, where relative contributions of multiple interacting dimensions can be considered, as described in the case studies. Factors appearing consistently important to examine across the subgrouping studies are therefore highlighted for consideration in clinical practice. Strengths and limitations of this research, and future research directions are described.

Acknowledgements

I believe the groundwork for this thesis started in 1997 when I first heard Bob Elvey speak in Romford, Essex. He ignited my passion for physiotherapy, but in particular for highly skilled manual therapy, logical thought and pain neurophysiology. It was an honour and a pleasure to study under him on the Master of Manipulative Therapy programme which first brought me to Curtin University in 2000.

At that time I received further inspiration to try to deepen my understanding of pain, and how we as therapists may be able to have some positive effects upon it, from Max Zusman. Again, my knowledge of this field would not be what it is today without Max having imparted some of his vast knowledge during that year and our subsequent correspondence.

It is therefore sad to reflect that between starting this Doctoral degree, and handing in my thesis, both of these people who have shaped my career have passed away. I feel lucky that I was able to see them both "in the flesh" again by returning to Curtin in 2012. I hope, to some small extent, that this work does justice to their memories.

Also back in 2000, I met Peter O'Sullivan for the first time. As a fantastic teacher on the Master's programme, I was determined to stay in touch. I felt privileged when, in London in 2010, he suggested that he might have a project that I might be interested in. The wheels were henceforth set in motion for my return to Perth.

I have found the PhD process really interesting, great fun (most of the time) and highly challenging (quite a lot of the time). I have no doubt that in the future I will look back upon these years with great fondness. For all of this I would like to thank my four supervisors. Thank you to Peter for dreaming up the project in the first place (even if we ended up doing a totally different one to the one we actually set out to do!), for inviting me to be involved with it, for guiding me through from start to finish, and even for finding me clinical work to help pay the bills. Darren Beales has been a friend since the Master's programme back in 2000. When Peter asked if I would like him as part of my supervisory team I had no hesitation. I admired his clarity of thought and direction back then, and have been glad to try to absorb

some of these attributes over the course of this degree. Thanks to Darren for being a sounding board, and a halfway house between a "mate" and a supervisor. Without Anne Smith this project would have been impossible. The statistics involved in this project have been, for me, mind-blowingly complex. Thanks to Anne for her patient coaxing along the way. My understanding of things statistical has expanded exponentially over these few years, something that I didn't think was even possible. And finally thank you to Helen Slater for once more fostering my love of pain neurophysiology. I am sure that her approach to this field will influence me into the future. There have been some emotional times during these few years, and I thank her especially for her understanding. I would like to thank all four supervisors for having different ways of thinking about this project, and different ways of writing. I hope that I may have taken the best bits from each of you.

Also at Curtin I would like to thank Guy Anza, Rob Waller and Paul Davey for getting hold of, fixing, and teaching me to use all of the equipment and software that became involved along the way. You saved me a lot of sweat and tears.

Thanks also to Curtin for awarding me an Australian Postgraduate Award and Curtin Postgraduate Scholarship, allowing me to concentrate on this research full time. Thanks also to the Musculoskeletal Association of Chartered Physiotherapists for awarding me their Doctoral Award and Educational Bursary, and to the Chartered Society of Physiotherapy Charitable Trust for further funding.

Thank you also to everybody with low back pain that took part in this research. I hope that it was worth it.

I want to thank my mum and dad, for encouraging and financially assisting me to come to Curtin back in 2000, and then not being too surprised, or put out, when over Sunday lunch in Guernsey a few years ago, I said that I was going back. Thanks for supporting me, forever.

A big thank you goes to my great friend Björn. We met at Curtin in 2000, and since then you have been my saviour on numerous occasions. I love the way that you think, both about physiotherapy and about life. I believe that some of your wise

List Of Publications

Journal Publications

Rabey M., Slater H., O'Sullivan P., Beales D., Smith A. (2015) Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: A cluster analysis. *Pain*, 156: 1874-1884. DOI: 10.1097/j.pain.0000000000000244

Rabey M., Beales D., Slater H., O'Sullivan P. (2015) Multidimensional patient profiles in four cases of chronic non-specific axial low back pain: An examination of the limitations of contemporary classification systems. *Manual Therapy*, 20: 138-147. DOI: 10.1016/j.math.2014.07.015

Conference Presentations

Rabey M., O'Sullivan P., Beales D., Slater H., Smith A. (2014) Multidimensional pain profiles in people with axial low back pain: An examination of four differing cases. *Australian Physiotherapy Association (WA Branch) Symposium,* Perth, 17/5/14

Rabey M., O'Sullivan P., Beales D., Slater H., Smith A. (2013) Multidimensional pain profiles in people with axial low back pain: An examination of four differing cases. *Australian Physiotherapy Association Conference 2013,* Melbourne, 17-20/10/13

Poster Presentations

Rabey M., Slater H., O'Sullivan P., Beales D., Smith A. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: A cluster analysis. *World Confederation for Physical Therapy Congress 2015*, Singapore 1-4/5/15

Rabey M., Slater H., O'Sullivan P., Beales D., Smith A. Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: A cluster analysis. *Pain Adelaide 2015*, Adelaide 30/3/15

List of Abbreviations

°C	degrees Centigrade
°C/s	degrees Centigrade per second
AEQ	Avoidance Endurance questionnaire
AIC	Akaike information criterion
AUC	area under the curve
BB	increased pain following backward bending only (movement subgroup)
BES	Behavioural Endurance subscale
BIC	Bayesian information criterion
BMI	body mass index
CI	confidence interval
CLBP	chronic low back pain
cm	centimetres
cm²	centimetres squared
CNS	central nervous system
CPAQ-8	Chronic Pain Acceptance questionnaire (short-form)
CPM	conditioned pain modulation
CPT	cold pain threshold
CS	classification system
CS	conditioning stimulus

DASS	Depression Anxiety Stress scales
FABQ	Fear-Avoidance Beliefs questionnaire
FABQ-PA	Fear-Avoidance Beliefs questionnaire (Physical activity subscale)
FABQ-W	Fear-Avoidance Beliefs questionnaire (Work subscale)
FB	increased pain following forward bending only (movement subgroup)
FB&BB	increased pain following forward and backward bending (movement subgroup)
FreBAQ	Fremantle Back Awareness questionnaire
g	gram
GRC	global rating of change
HPA axis	hypothalamic-pituitary-adrenal axis
HPT	heat pain threshold
Hz	hertz
IPAQ	International Physical Activity Questionnaire
IQR	inter-quartile range
kg	kilograms
kg/m^2	kilograms per metre squared
kPa	kilopascals
kPa/s	kilopascals per second
LBP	low back pain

LCA	latent class analysis
MAAS	Mindful Attention Awareness scale
max	maximum
MCID	minimum clinically important difference
MDT	mechanical detection threshold
min	minutes
min	minimum
mm	millimetres
mN	millinewtons
MPI	(West Haven-Yale) Multidimensional Pain Inventory
MRI	magnetic resonance imaging
n	number of participants
NIP	no increase in pain (movement subgroup)
NRS	numeric rating scale
PC	principal component
PCA	principal component analysis
PCS	Pain Catastrophising scale
PPT	pressure pain threshold
PSEQ	Pain Self-Efficacy questionnaire
PSQI	Pittsburgh Sleep Quality index
QST	quantitative sensory testing

RMDQ   Roland Morris disability questionnaire

ROC   receiver operating characteristic

SD   standard deviation

sec   seconds

StEP   Standardised Evaluation of Pain

TPD   two-point discrimination

TS   temporal summation

TS   test stimulus

TSS   Thought Supression subscale

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Chapter One - Introduction To Thesis

LBP is the world's leading cause of years lived with disability (Vos et al., 2012) and carries a multidimensional burden having psychological, social, occupational, financial and physical effects (Buchbinder et al., 2011). Estimates of the lifetime prevalence of low back pain (LBP) vary from 59% to 84% (Majid and Truumees, 2008, Dunn and Croft, 2004). In approximately 85% of cases of LBP no specific cause can be identified, resulting in a diagnostic label of non-specific LBP (Deyo and Weinstein, 2001, Waddell, 2004). While chronic LBP (CLBP) has often been defined simply as LBP persisting for greater than three months, it may be more appropriate to view it as a persistent, fluctuating condition (Dunn et al., 2006, Axén and Leboeuf-Yde, 2013, Kongsted et al., 2015). The annual prevalence of CLBP is estimated to be 15 - 45% (Manchikanti et al., 2009). Despite increasing healthcare expenditure directed towards its management (Dagenais et al., 2008, Friedly et al., 2010) associated disability, even in developed nations, continues to rise (Martin et al., 2008, Vos et al., 2012).

There is no clear consensus as to how to manage this escalating problem (Waddell, 2004). A wide array of treatments are available, however, outcomes in CLBP are modest at best (Machado et al., 2009, Keller et al., 2007, Bigos et al., 2009, Choi et al., 2010). Only 15% of placebo-controlled trials of treatments for CLBP achieve the minimum clinically important difference (MCID) of two-points on an 11-point numeric rating scale (NRS) for pain intensity, and these outcomes have only been reported in un-replicated smaller-sized trials (Farrar et al., 2001, Machado et al., 2009). When considering level of disability, treatment effect sizes are also small (0.13 - 0.24) (Keller et al., 2007). Overall no one treatment appears obviously superior to any other (Artus et al., 2010).

It has been proposed that a lack of treatment specificity secondary to assumed sample homogeneity (Hush and Marcuzzi, 2012) and an absence of consideration of the complex multidimensional nature of CLBP (Rusu et al., 2012) may underpin such modest outcomes. To attempt to facilitate more targeted management of this disorder (Turk, 2005, Rusu et al., 2012) approximately 40 classification systems (CS)

have been described (Billis et al., 2007, Ford et al., 2007). However limitations exist in present CS. Most are unidimensional in nature, and have been derived based upon clinician judgement rather than statistical derivation. Many early CLBP CS were biomedical, based upon the assumption of pathoanatomical / structural peripheral nociceptive "sources". However, a "source" can only be determined in approximately half of people with CLBP (Laslett et al., 2005), and few specific pathoanatomical findings correlate highly with pain and disability levels (Kjaer et al., 2005, Andrade et al., 2015, Chou et al., 2011). Subsequently CS were developed based upon pain responses to movement (McKenzie and May, 2003, Sahrmann, 2002, O'Sullivan, 2000) as well as psychological and social dimensions known to be prognostic for pain and disability in people with CLBP (Hayden et al., 2010, Hill et al., 2008). However, treatments matched purely to pain responses to movement (Henry et al., 2014, Saner et al., Browder et al., 2007) and psychosocially-derived subgroups (Verra et al., 2015) also appear to deliver only modest positive outcomes.

Contemporary understanding of the multidimensional nature of CLBP reflects the complexity, and potential variability, of differing central and peripheral nociceptive processes and recognition of potential contributions from multiple dimensions associated with CLBP (Rusu et al., 2012, Simons et al., 2014, Hush et al., 2013). These include genetics / epigenetics, demographics and pain characteristics, psychological, social, health / lifestyle and movement (Figure 1). The multidimensional nature of CLBP has also recently been re-framed to include complex and widespread changes in central nervous system (CNS) structure, chemistry and function involved in nociception, regulation of emotion and cognition, and behavioural responses to pain (Borsook, 2012, Wand et al., 2011, Mansour et al., 2014, Hush et al., 2013). These CNS changes may partly help to explain the apparent lack of strong associations between CLBP and pathoanatomical findings, whilst helping explain the greater association between CLBP, disability and psychosocial factors. Demonstration of cortical changes associated with pain persistence and altered motor control, sensorimotor interactions, and behaviours associated with pain (Hodges and Smeets, 2015, Lloyd et al., 2014) have also demanded inclusion of movement-related factors in this re-framing of the disorder.

One CS has attempted to integrate central and peripheral nociceptive processes, pain response to movement, and psychological factors as indicators of a mechanisms-based CS for CLBP (Smart et al., 2011). However, this latter CS did not consider other relevant dimensions (e.g. social, health and lifestyle). Furthermore, this CS has not been evaluated against quantitative sensory testing (QST) which may be considered a "window" through which to examine central and peripheral nociceptive processes underlying different CLBP presentations (Baron et al., 2012).
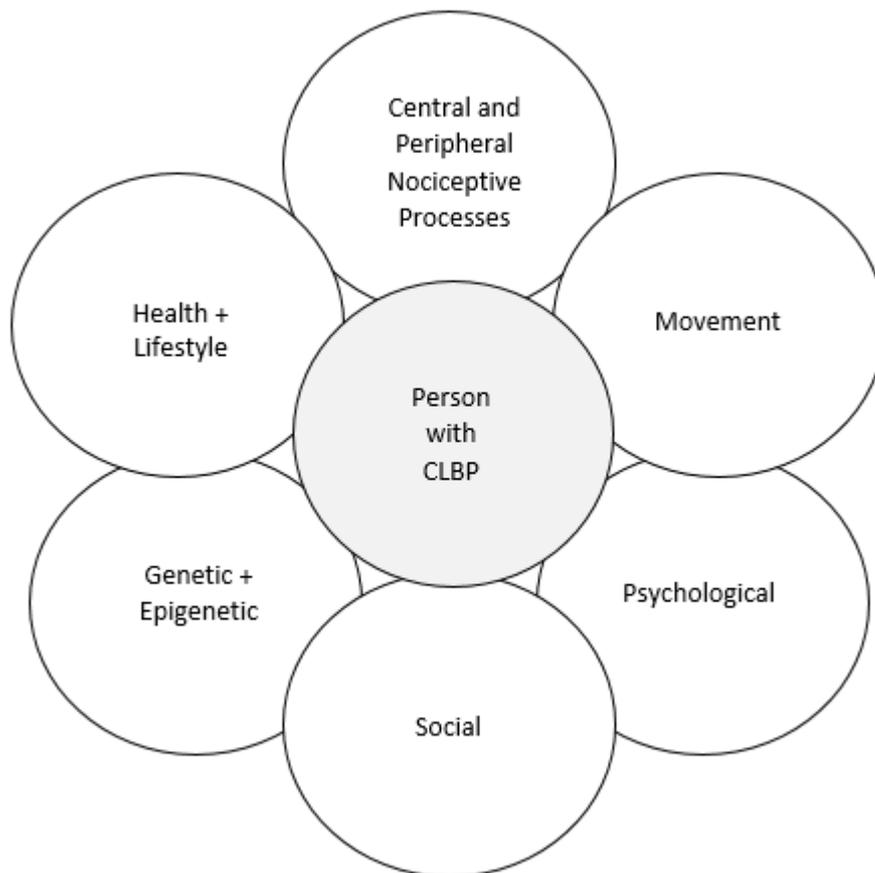
Figure 1. Model of a person with chronic low back pain, considering multiple interacting dimensions.

A lack of consideration of the relative contributions of multiple interacting dimensions that are likely to differ for each individual with CLBP (Hush et al., 2013, Brown, 2009), has been suggested as a limitation of many contemporary CLBP CS (Rusu et al., 2012). In response to these limitations a multidimensional CS has been

proposed (O'Sullivan et al., 2015, O'Sullivan, 2012) that is considered the most all-encompassing CS (Karayannis et al., 2012). This offers a framework for clinicians to consider the relative contributions of multiple dimensions (demographics, pain characteristics, sensory, psychological, social, health, lifestyle, and movement dimensions) involved in an individual's CLBP presentation. Based on this profiling, identification of the modifiable factors associated with the disorder provides the basis for targeted management. One randomised controlled trial has matched treatment to findings from a clinical examination based upon such a multidimensional framework with promising results (Vibe Fersum et al., 2013), although replication studies are required. While a number of aspects of this approach have been validated and found to be reliable (Vibe Fersum et al., 2009, Dankaerts and O'Sullivan, 2011), a potential limitation is that determination of the multidimensional profiles has been undertaken largely based on clinical judgement. Therefore, the relative contribution of each dimension requires objective analysis to reduce this potential bias (Kent et al., 2010). While this CS considers multiple interacting dimensions, it is acknowledged that there may be as yet unknown dimensions, and interactions between dimensions, that are important to consider in people with CLBP.

Ideally, capturing the multiple interacting dimensions and CNS processes underlying the disorder in a person with CLBP would require genetic evaluation and many gold-standard investigations such as polysomnography for sleep assessment or electromagnetic motion analysis and electromyography for motor control assessment (Borsook, 2012). In contrast, using clinically-measurable data would allow for greater clinical translation. Statistical subgrouping using such data would present the most potential for valid subgroups. Such approaches to subgrouping (McCarthy et al., 2012, Viniol et al., 2013, Hill et al., 2008) have been performed previously, but only utilising data from a limited number of dimensions, potentially limiting clinical applicability.

Therefore, to examine the complexity within CLBP in a manner which may be translated into practice, there is a need to employ valid and reliable clinical measurements across multiple relevant dimensions, using statistical derivation of

subgroups. This will facilitate the subsequent multidimensional profiling of such subgroups, and may enable the development of more targeted interventions for this complex disorder.

The aims of subgrouping may be to facilitate targeted treatment for people with CLBP to improve treatment outcomes (Rusu et al., 2012), and to identify subgroups who are at greater risk of poor recovery (Hill et al., 2008, Boersma and Linton, 2005). Therefore, it is important to also determine whether derived subgroups are prognostic of outcome across a range of clinically-important outcomes such as pain intensity, disability, bothersomeness and participant global rating of change. Determining the prognosis associated with membership of any derived subgroups may also facilitate a greater understanding of this complex disorder.

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Chapter Two – Literature Review

2.1   The Problem Of Chronic Low Back Pain

The latest estimate of global point prevalence for low back pain (LBP) is 9.4% (Hoy et al., 2014), with 85% of cases classified as "non-specific", as no specific pathoanatomical cause can be determined (Deyo and Weinstein, 2001, Waddell, 2004). Chronic LBP (CLBP) is often defined as LBP persisting for greater than 3 months, and carries significant individual burden (Buchbinder et al., 2011). As many as 65% of people may report ongoing LBP one year after an acute episode (Itz et al., 2013), and 70% have a recurrent episode within five years (Hestbaek et al., 2003a). This has led CLBP to be viewed as a persistent, recurrent condition with various possible trajectories (Dunn et al., 2006, Axén and Leboeuf-Yde, 2013, Kongsted et al., 2015), from stable, low levels of pain (35%), to permanently high pain and disability with associated poor psychosocial status (21%) (Dunn et al., 2006).

Despite increasing healthcare expenditure directed towards the management of CLBP (Friedly et al., 2010, Manchikanti et al., 2014, Dagenais et al., 2008, Smith et al., 2013) prevalence (Manchikanti et al., 2014, Waxman et al., 2000) and self-reported disability appear to be increasing (Vos et al., 2012, Manchikanti et al., 2014). There is no consensus as to how to best manage this escalating problem (Waddell, 2004). A wide array of treatments is available (including pharmacological, manual, exercise, and psychological therapies), but effect sizes are generally small or moderate at best, especially long term (Machado et al., 2009, Keller et al., 2007, Bigos et al., 2009, Choi et al., 2010), and no specific intervention is superior (Artus et al., 2010).

Possible reasons for poor treatment outcomes in CLBP include a lack of consideration of the complex multidimensional nature of CLBP (Rusu et al., 2012), with many interventions directed predominantly towards one dimension (i.e. movement-based, psychologically-based). Further, many studies assume sample homogeneity rather than considering differing contributions from multiple interacting dimensions across participants (Hush et al., 2013). Potentially, treatment effectiveness would be greater if specific tailored interventions were matched to

specific multidimensional profiles in individuals with CLBP (Rusu et al., 2012, Baron et al., 2012), Woolf and Mannion (1999).

Key Points:

- The majority of LBP is deemed non-specific because a pathoanatomical basis cannot be identified.
- Treatment outcomes for CLBP are moderate at best irrespective of treatment type.
- Consideration of multiple dimensions associated with CLBP may facilitate better management.

2.2   CLBP As A Multidimensional Pain Disorder

Contemporary understanding of CLBP reflects the complexity, and potential variability, of interactions between differing nociceptive processes, plus potential influences of associated dimensions (Rusu et al., 2012, Simons et al., 2014, Hush et al., 2013, O'Sullivan et al., 2015) such as genetics / epigenetics, demographics, pain characteristics, psychological, social, health, lifestyle and movement (Chapter 1, Figure 1). This multidimensionality aligns with the definition of pain as, "An unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage." (IASP Taxonomy Working Group, 2011)(Paragraph 2) The relative dominance of these dimensions likely varies across individual presentations (O'Sullivan et al., 2015, Simons et al., 2014, Brown, 2009), and can contribute to negative feedback loops, potentially perpetuating the disorder (Moseley and Flor, 2012, Borsook, 2012, Simons et al., 2014).

It is unlikely that the development of CLBP occurs in a linear fashion, and more likely reflects a complex, dynamic, emergent process (Chi et al., 2012, Simons et al., 2014, Griffiths and Byrne, 1998). Consistent with an emergent process involving multiple interacting dimensions which may explain such presentations in people with CLBP, allostasis is the physiological process of adaptation to real or perceived physical and psychological stressors (e.g. daily hassles, stressful life events; negative cognitions

or affect, poor sleep quality, comorbidities, endurance behaviours, pain). Allostasis is designed to maintain the body in a state of physiological homeostasis (McEwen and Gianaros, 2010) and involves non-linear interactions between neuroendocrine, inflammatory / immune, and autonomic responses to excessive or repetitive stressors (Kozlowska, 2013, Gatchel et al., 2007, McEwen and Kalia, 2010, McEwen and Gianaros, 2010). Key systems involved in allostasis are the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS) (Gatchel et al., 2007). Allostatic load is the cumulative, long-term "wear and tear" (McEwen and Gianaros, 2010) (p.191) on the brain and body as a consequence of an individual maintaining allostasis. Ongoing stressors may have a negative impact upon regions of the brain, (hippocampus, amygdala, pre-frontal cortex) involved in appraisal of stressors and the effector organs of systems involved in maintaining allostasis. In turn this may increase negative behaviours and cognitions such as an increased startle response, sleep disturbance, anxiety or depression; and lead to epigenetic alterations which may facilitate nociceptive processing (Sibille et al., 2012, Ganzel et al., 2010, McEwen and Gianaros, 2010, McEwen and Gianaros, 2011).

High allostatic load may facilitate HPA axis dysfunction which is suggested to contribute to the onset or maintenance of chronic pain predominantly via altered cortical structure and function, impaired tissue repair, and immune suppression (Gatchel et al., 2007). A number of small (n=20-72) studies of people with CLBP have shown evidence for both hypercortisolism (Alaranta et al., 1983, Sudhaus et al., 2009, Sudhaus et al., 2012) and hypocortisolism (Griep et al., 1998, Garofalo et al., 2007, Muhtz et al., 2013). Hypercortisolism is commonly suggested to relate to prolonged activation of the HPA axis (Gatchel et al., 2007). Mechanisms causing hypocortisolism are speculative (Heim et al., 2000, Fries et al., 2005), but hypocortisolism may follow hypercortisolism (Fries et al., 2005), with persistent stress exposure leading to downregulation of the HPA axis (McBeth and Power, 2012). Conflicting evidence regarding HPA axis dysfunction in people with CLBP may therefore relate to the stage of the disorder. Larger, longitudinal studies are required to elucidate these relationships further.

The HPA axis and SNS interact and stimulate each other (Chrousos, 2009) at both peripheral and central levels. SNS activation is associated with altered stress responses and elevated fear resulting in increased arousal, heart and respiratory rates, skeletal muscle tone and metabolism (Kozlowska, 2013, Chrousos, 2009). SNS activation may cause up-regulation and sensitisation of receptors involved in nociception (Light and Vierck, 2009). Complex interactions at both peripheral and central levels also occur between the HPA axis, SNS and immune system, potentially leading to pro-inflammatory effects (Chrousos, 2009, Kozlowska, 2013) which may increase peripheral and central sensitisation (Costigan and Woolf, 2000, Woolf, 2010), key processes in musculoskeletal pain disorders including CLBP.

While interactions between multiple dimensions associated with CLBP and neuroendocrine, inflammatory / immune and autonomic responses may help explain pain persistence, they may not fully explain the complex behaviors associated with CLBP. Numerous other hypothetical models, incorporating the effects of multiple interacting dimensions upon pain-related neurophysiology and behaviours, have been described to attempt to explain the complexity of CLBP presentations (Moseley and Vlaeyen, 2015, Simons et al., 2014, Vlaeyen and Linton, 2012, Zusman, 2008). Presently all models require ongoing examination.

Key Points:

- CLBP is a complex, multidimensional pain disorder.
- Multiple dimensions may interact differently in different individuals resulting in diverse CLBP experiences.
- Multiple interacting dimensions may create feedback loops facilitating ongoing pain and disability.
- Sustained allostatic load may be a factor in the emergence or persistence of CLBP.

2.3   The Evolution Of The Biopsychosocial Model Of Chronic Low Back Pain

Such complexities have not always been considered in the management of people with CLBP. Historically, diagnoses for people with CLBP have been biomedically-

based, assuming structural pathologies were the peripheral nociceptive "source". While examination for specific structural diagnoses in people with low back disorders, such as fractures or radiculopathy, is considered a key part of diagnostic triage (Waddell, 2004), the majority of LBP is considered non-specific because no structural cause can be reliably identified (Deyo and Weinstein, 2001, Waddell, 2004). Systematic reviews suggest "abnormal" findings are common on imaging in asymptomatic individuals (Brinjikji et al., 2015, Jensen et al., 2008). Few specific pathoanatomical findings correlate highly with pain and disability levels (Kjaer et al., 2005, Andrade et al., 2015, Chou et al., 2011), and few pathoanatomical findings predict future symptoms (Jarvik et al., 2005).

Subsequently classification systems (CS) for CLBP have been developed based upon examination and treatment of aberrant movement patterns (Sahrmann, 2002, O'Sullivan, 2000, McKenzie and May, 2003). These CS still assume a peripheral nociceptive sources of symptoms. However, it has been suggested that such uni-dimensional approaches offer limited guidance for treatment as they do not consider the potential contribution of numerous other dimensions to pain persistence (O'Sullivan, 2005).

With greater understanding of CLBP the biomedically-driven, pathoanatomical view of CLBP evolved to a broader bio-psycho-social conceptualisation (Waddell, 2004), with negative psychological and social factors being consistently prognostic of greater disability (Hayden et al., 2010). However, continued reconceptualization has led to consideration of further dimensions associated with CLBP, such as health and lifestyle dimensions. In combination with a greater understanding of peripheral and central nociceptive processes, this has formed the contemporary view that CLBP is a complex multidimensional disorder (Rusu et al., 2012, Simons et al., 2014, Hush et al., 2013). However, translation of this concept into research, education and clinical practice has been described as limited (Pincus et al., 2013, Foster and Delitto, 2011).

2.4   Clinical Examination Of Chronic Low Back Pain As A Multidimensional Pain Disorder

Given the multidimensional nature of CLBP (Simons et al., 2014, Hush et al., 2013, Rusu et al., 2012) a thorough examination of the disorder should include genetic screening, plus consideration of clinically-measurable dimensions such as pain sensitivity and psychological factors (Borsook and Kalso, 2013). However, genetic screening and many gold-standard investigations are not readily available and are far beyond the scope of daily clinical practice (Borsook, 2012). To facilitate translation into clinical practice, measures examining multiple dimensions must be readily applied clinically, taking into account time-constraints, availability and expense of necessary equipment and practitioner training. For example, the gold standard for examination of sleep would be polysomnography, which requires participant attendance at a sleep study centre overnight. Wearing an accelerometer over the course of one or more nights is also a commonly utilised research method for assessing sleep levels (Van De Water et al., 2011b). However, these options are difficult to incorporate into a clinical assessment, whereas subjective sleep questionnaires such as the Pittsburgh Sleep Quality Index (Buysse et al., 1989), are easily applicable. To facilitate translation into practice this thesis therefore focuses specifically on clinically-applicable measures (Table 1) from each of the dimensions associated with CLBP as shown in Figure 1. These have been identified in cross-sectional studies, as being associated with, or prognostic of, greater pain or disability in CLBP, predictive of poor treatment outcomes or otherwise having a strong biological rationale for consideration (Kamper et al., 2010). Each of these dimensions and the factors associated with them will be discussed in turn.

Table 1

Dimensions associated with chronic low back pain for which clinically applicable measures are available.

Tissue sensitivity dimension	Demographic / pain characteristic dimension	Psychological dimension
Touch	Gender	Depression
Pressure	Age	Anxiety
Brushing	Pain intensity	Stress
Heat	Disability	Bothersomeness
Cold	Pain distribution	Fear-avoidance beliefs
Vibration	Symptom duration	Pain catastrophising
Two-point discrimination	Pain descriptors	Mindfulness
Temporal summation	Aggravating factors	Endurance behaviours
Pinprick		Pain self-efficacy
Conditioned pain modulation		Acceptance
Body perception		Perceived risk of pain persistence
Social dimension	**Movement dimension**	**Health / lifestyle dimensions**
Occupational factors	Movement patterns	General health
Stressful life events	Speed of movement	Comorbidities
Education	Behaviours associated with pain	Widespread pain
Social support		Sleep
Compensation status	Pain responses following repeated movement	Physical activity levels
		Smoking
		Body mass index

2.4.1 Psychological dimension.

Many negative psychological factors are consistent prognostic indictors for pain and disability in people with CLBP (Hayden et al., 2010). Negative psychological factors include both cognitive factors such as kinesiophobia, pain catastrophising, low pain self-efficacy, or maladaptive coping strategies; and affective factors such as depressed mood, anxiety or stress (Campbell et al., 2013a, Pincus and McCracken, 2013, Ramond et al., 2011). Rather than acting as independent prognostic indicators (Foster et al., 2010), psychological factors cluster in people with CLBP, leading to calls to consider them as broader constructs (e.g. pain-related distress) (Foster et al., 2010, Campbell et al., 2013a). The literature does not consistently indicate which

factors may be most important to examine in people with CLBP. Psychological factors associated with CLBP in the literature will be considered. However, other factors, to date not considered in specific relation to CLBP, may be important for future consideration.

As well as influencing allostatic load, and HPA axis function, psychological factors may influence persistent pain and disability through numerous other mechanisms. These mechanisms include: increasing peripheral nociceptive input secondary to greater lumbar muscle activation and subsequent tissue stress (Geisser et al., 2004, Thomas and France, 2007, Hodges and Smeets, 2015, Marras et al., 2000, Lewis et al., 2012, Hasenbring and Verbunt, 2010); through "hyperalgesic priming": latent hyper-responsiveness of nociceptors to cytokines, which may be initiated by immune activation in association with stressful events (Reichling and Levine, 2009); via common genetic and epigenetics influences (Pinheiro et al., 2014), via common changes in cortical activation and subsequent descending pain modulation (Zusman, 2002, Boakye et al., 2015) and through associated negative behaviours such as poorer sleep quality (Åkerstedt, 2006, Boakye et al., 2015) and lower physical activity levels (Utschig et al., 2013, Smith and Blumenthal, 2013).

Cognitive factors.

Fear-avoidance beliefs.

There is a vast body of literature relating to fear-avoidance. The original fear-avoidance model (Vlaeyen et al., 1995), which has recently been modified (Vlaeyen and Linton, 2012, Asmundson et al., 2012, Crombez et al., 2012, Pincus et al., 2010), hypothesised that some people with CLBP perceive pain as threatening / a sign of tissue damage or re-injury, resulting in activity avoidance and perpetuating disability. Systematic and narrative reviews support that greater fear-avoidance beliefs are prognostic of greater disability (Leeuw et al., 2007, Wertli et al., 2014b) particularly in sub-acute LBP. Meta-analysis reveals that fear-avoidance beliefs mediate the relationship between pain and disability (Lee et al., 2015), broadly in line with the fear-avoidance model.

Pain catastrophising.

Pain catastrophising, an exaggerated negative cognitive response to painful stimuli (perceiving such stimuli as having elevated threat value) (Sullivan et al., 1995) is highly integrated into the fear-avoidance model (Vlaeyen and Linton, 2012). A recent systematic review revealed that pain catastrophising is independently prognostic of greater pain and disability in people with CLBP, possibly in a dose-response manner (Wertli et al., 2014a). A narrative review has also suggested that pain catastrophising may interact with numerous affective factors including anxiety and depression (Quartana et al., 2009). In cross-sectional studies of CLBP cohorts, pain catastrophising has also been positively associated with communicative and protective pain behaviours (Thibault et al., 2008), punishing interactions with significant others (Boothby et al., 2004) and poor sleep quality (van de Water et al., 2011a, Ashworth et al., 2009).

Endurance behaviours.

An alternate coping strategy than avoidance is known as endurance behaviour, where people persist with tasks despite ongoing pain, supress thoughts relating to pain and may demonstrate low mood (distress endurance) or not (eustress endurance). In two small cross-sectional studies (n=52, n=49) endurance behaviours have been associated with higher pain intensity, disability and activity levels, and lower health-related quality of life in people with CLBP (Plaas et al., 2014, Scholich et al., 2012). These behaviours are also prognostic for elevated pain and disability in people with sub-acute LBP (Hasenbring et al., 2012). Why people may develop endurance behaviours is unclear (Van Damme and Kindermans, 2015), but is likely to be affected by interacting cognitive, emotional, and social factors (McCracken and Samuel, 2007).

Chronic pain acceptance.

Chronic pain acceptance involves being in ongoing pain without trying to avoid or control it. Studies examining this (McCracken et al., 2004a, McCracken et al., 2004b) have included samples with diffuse musculoskeletal pain disorders, rather than people with CLBP specifically. Cross-sectional studies have consistently shown

higher acceptance is associated with lower disability (McCracken and Eccleston, 2006, Wright et al., 2011, McCracken and Eccleston, 2005, Vowles et al., 2008a, Esteve et al., 2007, Vowles et al., 2008b, McCracken and Samuel, 2007). A large study (n=641) by Vowles et al. (2008b) utilised cluster analysis of scores from the Chronic Pain Acceptance questionnaire to derive three subgroups. This questionnaire has two subscales: i) activity engagement (engaging in everyday activities with pain present), ii) pain willingness (not engaging in behaviour to limit contact with pain). One subgroup (n=146) scored highly on both subscales indicating high levels of pain acceptance. Another had low scores on both subscales (n=239). The third subgroup scored highly for activity engagement but low for pain willingness (n=286). Similar subgroups were derived using comparable methodology in two other mixed chronic pain cohorts (Costa and Pinto-Gouveia, 2011, Bernini et al., 2014), lending validity to these subgroups (Kent et al., 2010). The combined results of these studies suggest those with lower pain acceptance may have more pain, disability, depression, anxiety, stress, healthcare usage, and lower activity levels and mindfulness (Vowles et al., 2008b, Costa and Pinto-Gouveia, 2011, Bernini et al., 2014). One moderately-sized (n=118) prognostic study has shown that pain acceptance explains a significant amount of the variance in depression, disability, pain-related anxiety, analgesic usage and work status at four-month follow up (McCracken and Eccleston, 2005). The relationship between low chronic pain acceptance and greater disability appears linked to the individual adopting behaviours that limit pain (McCracken et al., 2004a, McCracken et al., 2004b).

Mindfulness.

Mindfulness is an, ''awareness that emerges by way of paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment." (Kabat-Zinn, 2002) (p.732) In cross-sectional studies of people with mixed chronic pain diagnoses, greater mindfulness has been associated with higher pain acceptance (Costa and Pinto-Gouveia, 2011, de Boer et al., 2014), self-efficacy (Wright and Schutte, 2014) and lower pain intensity and fear-avoidance beliefs (Schütze et al., 2010). Specifically in people with CLBP (n=87), greater mindfulness was predictive of lower disability, depression, anxiety and

catastrophising after taking part in a multidisciplinary pain management programme. The relationship between mindfulness and disability was mediated by changes in catastrophising (Cassidy et al., 2012).

Pain self-efficacy.

Pain self-efficacy is confidence in one's capacity to undertake activities despite pain (Foster et al., 2010). As well as its association with greater mindfulness (Wright and Schutte, 2014), in cross-sectional studies of CLBP cohorts, greater pain self-efficacy is also associated with lower psychological distress, reduced work absenteeism, reduced protective and communicative pain behaviours, lower pain intensity and disability (Levin et al., 1996, Woby et al., 2007 , Lin, 1998). In a study of people attending primary care for LBP (n=488) greater pain self-efficacy was prognostic of lower pain and disability levels at six-month and five-year follow-up (Campbell et al., 2013b). Two moderately-sized mediation analyses in CLBP cohorts have shown that self-efficacy mediates the relationship between pain and disability (n=184) (Costa et al., 2011), and between fear-avoidance beliefs and pain and disability (n=102) (Woby et al., 2007).

Greater perceived risk of persistent pain.

Greater perceived risk of persistent pain is also prognostic of greater pain, disability and work absenteeism at long-term follow up in people with LBP consulting in a primary care setting (Campbell et al., 2013b, Costa et al., 2007, Gross and Battié, 2005, Henschke et al., 2008). Recently Carstens et al. (2014), using cluster analysis of data regarding recovery expectations at two time-points, derived four subgroups in 281 people with acute LBP. Three subgroups had differing levels of stable expectations for recovery (high, medium, low), while one subgroup had decreasing expectations over the three-months since onset. The subgroup with low recovery expectations (n=55) exhibited high depression, fear-avoidance beliefs and pain catastrophising. Scores for these factors altered in a stepwise manner for the medium (n=67) and high (n=118) scoring subgroups. The subgroup with decreasing expectations over time (n=41) showed increasing depression, fear-avoidance beliefs and pain catastrophising from the first to the second time-point. The authors

propose that negative expectations are associated with heightened levels of distress, leading to poorer outcomes (Carstens et al., 2014).

Affective Factors.

CLBP is also associated with a number of affective or emotional factors.

Depression, anxiety and stress.

Depression and anxiety have been considered to contribute to pain-related distress together with low pain-self efficacy, pain catastrophising and fear-avoidance beliefs (Campbell et al., 2013a). While there may be clear conceptual overlap between depression, anxiety and stress, depression may be uniquely characterised by negative affect, poor self-esteem and decreased motivation, while anxiety is characterised by autonomic arousal and fear, and stress by long-standing tension and irritability (Lovibond and Lovibond, 1995). Depression and anxiety may also reflect mental health disorders commonly comorbid with CLBP (Bair et al., 2008, Pincus and McCracken, 2013).

In a large (n=531) cross sectional study of people with LBP of varying durations, assessed in primary care, pain-related psychological distress was strongly associated with higher pain and disability (Campbell et al., 2013a). A recent systematic review of studies considering all types of chronic musculoskeletal pain, revealed an association between having chronic pain and higher prevalence of symptoms of depression, with approximately one third of participants having clinical depression. The relationship between chronic pain and symptoms of anxiety and stress were less clear (Andersen et al., 2014). However, a recent meta-analysis determined that there was a greater association between chronic pain and anxiety than there was with depression (Burke et al., 2015). The key difference between these two reviews appears to be the inclusion of studies undertaken worldwide (Burke et al., 2015), rather than just in westernised countries (Andersen et al., 2014), suggesting cultural differences may influence these affective factors. Andersen et al. (2014) also suggested there were stronger associations between depression, anxiety and stress and non-specific pain conditions, rather than those with specific diagnoses.

A review of systematic reviews has shown that psychological distress is consistently prognostic of worse outcomes in people with CLBP (Hayden et al., 2009). Specifically depression has been shown to be prognostic of LBP onset (n=131) (Jarvik et al., 2005), and greater pain and disability at one-year follow-up (n=973) (Henschke et al., 2008). Depression and stress have been shown to mediate the relationship between pain and disability in people with sub-acute LBP (n=231) (Hall et al., 2011).

Some clinically / judgementally derived subgroups of people with CLBP suggest that affective factors may not be heterogeneous across all people with CLBP, and interaction with other dimensions such as movement, pain sensitivity and sleep, will combine to influence their presentations (O'Sullivan et al., 2014, Smart et al., 2012). These data suggest differing degrees of psychological factors may be associated with subgroups characterised by complex combinations of underlying pain mechanisms, and will be discussed in detail in following sections.

2.4.2 Social dimension.

Consideration of the social dimension has also become part of the broader multidimensional conceptualisation of CLBP (Waddell, 2004).

Stressful life events.

The majority of research into the associations between life events and LBP has involved retrospective, possibly biased, recall of such events. Such recall may reflect events, perceived as stressful, occurring over a prolonged period (Littman et al., 2006). Early examination of stressful life events, in particular childhood physical or sexual abuse, in a large (n=949) community-based sample showed an association with a higher incidence of LBP (Linton, 1997). Further, in a study of 80 people with LBP of short duration, stressful life events were associated with the onset or exacerbation of symptoms (Craufurd et al., 1990). More recently, a community-based, cross-sectional study (n=396) suggested a possible U-shaped relationship, with those reporting no stressful life events or high levels of such events both having a greater association with CLBP (Seery et al., 2010). The authors suggested that some degree of adversity may facilitate improved coping strategies, reducing

the likelihood of chronic pain. Those at either end of the continuum also displayed elevated disability, poorer employment status, greater healthcare and analgesic usage and greater depression.

Socioeconomic status.

The most common methods for determining socioeconomic status include examining level of education, occupation, income and area of residence (Liberatos et al., 1988). Numerous socioeconomic factors have been considered to have possible associations with CLBP, however the strength of these associations appears variable (Stanaway et al., 2011, Hestbaek et al., 2008, Plouvier et al., 2009, Schneider et al., 2005, Latza et al., 2000). Level of education and occupation appear the most important factors to consider.

Lower years in education has been shown to be prognostic of higher pain intensity and disability, (Costa et al., 2009), while an early systematic review highlighted the association between lower educational level with persistent disability and a greater number of recurrences of LBP (Dionne et al., 2001). Dionne et al. (2001) postulated that educational level may affect pain and disability because a lower socioeconomic status may be associated with greater stress, greater negative health behaviours (e.g. smoking, higher alcohol intake) and more physically demanding occupations (i.e. greater allostatic load (McEwen and Gianaros, 2010, Seeman et al., 2010), or greater peripheral nociceptor sensitisation via higher or sustained tissue stress (Coenen et al., 2014)).

There has been a large body of research that has considered the prognosis associated with a vast array of occupational factors, however the nature of this relationship remains debatable (Hayden et al., 2009). The strongest associations between negative outcomes in CLBP (return to work, disability) and occupational factors are for poor working relationships and heavy work tasks (Hayden et al., 2009). In a cross-sectional study of 2533 people aged >50 years recruited from the general population, low educational status and manual occupations were both associated with greater disability (Lacey et al., 2013). In two large prospective studies, low educational status was significantly associated with the onset of LBP,

but a large proportion of this relationship was explained by undertaking physically or psychologically demanding work roles, or having low job satisfaction (Hagen et al., 2006b, Leclerc et al., 2009). In a review of systematic reviews, compensation claims were also consistently associated with poor return to work rates and disability (Hayden et al., 2009), while cross-sectional studies suggested compensation claims were associated with higher pain intensity, greater anxiety and depression, and poor sleep (Guest and Drummond, 1992, Rainville et al., 1997).

Social support.

In people with chronic musculoskeletal pain, a number of early, small, cross-sectional studies have shown that participant perception of social support (particularly more solicitous or punishing relationships with significant others) is associated with higher pain and disability (Flor et al., 1987, Kerns et al., 1990, Lousberg et al., 1992, Romano et al., 1995). More recent cross-sectional studies of mixed chronic pain sufferers have shown that more solicitous and punishing interactions with significant others are associated with lower pain acceptance (n=228) (McCracken, 2005), while punishing interactions are also associated with greater pain catastrophising (n=62) (Boothby et al., 2004). In particular, the relationship between punishing interactions and pain catastrophising have been suggested to comprise a, "negative cognitive set," (Boothby et al., 2004) (p.505) whereby those with higher levels of pain catastrophising report more punishing interactions with significant others.

2.4.3 Tissue sensitivity dimension.

Tissue sensitivity, in response to both nociceptive and non-nociceptive stimuli, has been reported to be altered in people with CLBP (Scholz et al., 2009, Blumenstiel et al., 2011, Neziri et al., 2012). For thermal and mechanical stimuli, both heightened sensitivity and no increase in sensitivity have been reported (Neziri et al., 2012, Hübscher et al., 2013b, Meeus et al., 2010). Tests of tissue sensitivity do not simply reflect the state of peripheral tissues, but also reflect altered CNS nociceptive and non-nociceptive processing (Cruz-Almeida and Fillingim, 2014), and interactions between the neuroendocrine, inflammatory / immune, and sympathetic nervous

systems (Chrousos, 2009, Kozlowska, 2013, Gatchel et al., 2007, McEwen and Kalia, 2010, McEwen and Gianaros, 2010) which may favour facilitation of nociception and enhanced pain perception (Weissman-Fogel et al., 2008, Nilsen et al., 2012, Zusman, 2002, Costigan and Woolf, 2000, Woolf, 2010). With advances in imaging technologies alterations in spinal cord and brain structure, chemistry and function have been demonstrated in people with CLBP (Borsook, 2012, Wand et al., 2011). However, many areas of the brain are affected, not only those associated with somatosensory processing (Borsook, 2012, Wand et al., 2011). Therefore, if and how these CNS alterations influence tissue sensitivity is currently unclear.

In contrast to brain imaging techniques which are not clinically applicable, psychophysical quantitative sensory testing (QST), is increasingly used in clinical settings (Backonja et al., 2013), and allows determination of clinical somatosensory phenotypes, and postulation of pain-related physiological mechanisms (Baron et al., 2012). Bedside (Scholz et al., 2009) and laboratory QST (Rolke et al., 2006) undertaken at sites local to, and distant from reported symptoms, may allow examination of somatosensory submodalities mediated by different primary afferents (Jensen and Baron, 2003) (Table 2). This QST approach may be indicative of alterations in CNS nociceptive and non-nociceptive processing (Cruz-Almeida and Fillingim, 2014, Yarnitsky et al., 2014, Luomajoki and Moseley, 2011, Baron et al., 2012).

To facilitate translation of this QST approach into clinical practice, quick, clinically applicable, bedside sensory testing have been described (Scholz et al., 2009). However, because of the wide variation in thermal and pressure pain thresholds when tested at lumbar sites (Pfau et al., 2014, Neziri et al., 2011), using standardised laboratory measures (e.g. thermal thresholds tested using a thermode or pressure thresholds using an algometer) may maximise the potential to differentiate sensory profiles, especially in a research context.

Assessment of conditioned pain modulation (CPM) is considered to provide a surrogate measure of a person's capacity for dynamic endogenous pain modulation via activation of descending inhibitory serotonergic and noradrenergic systems (Nir

et al., 2011, Le Bars, 2002, Bouhassira et al., 1992). When combined with examination for temporal summation, CPM may reflect pro- or anti-nociceptive phenotypes (Yarnitsky et al., 2010). CPM can be evaluated experimentally by asking participants to evaluate the intensity of a primary noxious test stimulus in the presence and absence of a secondary noxious conditioning stimulus (Yarnitsky et al., 2010). Four studies have examined CPM in participants with CLBP (O'Neill et al., 2014, Rabey et al., Corrêa et al., 2014, Schliessbach et al., 2014), showing either significantly less inhibition (Corrêa et al., 2014, Schliessbach et al., 2014), or greater facilitation (Rabey et al., O'Neill et al., 2014) of the test stimulus in response to the conditioned stimulus compared to healthy controls.

Table 2

Quantitative sensory testing, test stimuli, fibre types stimulated and postulated mechanisms underlying abnormal positive responses. Adapted from Jensen and Baron (2003) and Treede et al. (2004).

Stimulus	Fibre type	Bedside sensory test	Laboratory quantitative sensory testing	Abnormal positive responses and underlying mechanisms
Static light touch	Aβ	Nylon monofilaments; cotton wool		Static mechanical allodynia; CNS-mediated
Vibration	Aβ	Tuning fork	Vibrameter	
Brushing	Aβ	Brushing		Dynamic mechanical allodynia; CNS-mediated
Punctate / pinprick	Aδ	(Safety) pin, higher calibre nylon monofilament	Calibrated pins	Punctate / pinprick hyperalgesia; peripheral sensitisation or CNS mediated Aδ afferent input; or CNS-mediated Aβ afferent input
Mechanical temporal summation	Aδ / Possibly C	Repetitive stimulation with nylon monofilament	Calibrated pins	Enhanced mechanical temporal summation; peripheral sensitisation or CNS mediated Aδ (Possibly C) afferent input; or CNS-mediated Aβ afferent input
Cold	Aδ	Thermo rollers, acetone / menthol, cold pressor test	Thermo rollers, computer controlled thermode	Cold hyperalgesia; peripheral sensitisation or CNS mediated Aδ or C afferent input
Heat	C	Thermo rollers	Thermo rollers, computer controlled thermode	Heat hyperalgesia; peripheral sensitisation or CNS-mediated Aδ or C afferent input
Blunt pressure	C / Possibly Aδ	Pencil, thumb	Algometer	Mechanical hyperalgesia and allodynia; peripheral sensitisation or CNS-mediated

Note. CNS – central nervous system

A recent meta-analysis (Hübscher et al., 2013a) found low correlations between pain thresholds and pain intensity and disability levels. However, the included studies assumed sample homogeneity, and few studies included dynamic QST (CPM, temporal summation), which may better reflect pain modulation and may be associated with clinical pain morbidity (Yarnitsky et al., 2014).

Many studies have compared QST findings in people with CLBP to healthy control participants, however, such findings appear highly variable. For example, Blumenstiel et al. (2011) showed localised enhanced pain sensitivity in non-clinical participants from the general population, where Giesbrecht and Battie (2005) showed widespread enhanced pain sensitivity in participants from primary care, supporting different QST profiles from different samples (See Table 3 for summaries of such studies). This has led researchers to investigate the existence of subgroups of people with CLBP with different tissue sensitivity profiles. Two studies (Scholz et al., 2009, Coronado et al., 2014) which have performed cluster analysis to derive such subgroups will be discussed in detail in following sections.

Table 3.

Published data from studies undertaking quantitative sensory testing in participants with low back pain compared to healthy control participants.

Reference	Patient Sample	Lumbar QST	QST Tested at Site(s) Remote From Lumbar Region
Lewis et al. (2010)	LBP +/- leg pain; variable chronicity; (n=15)	Higher CPT (i.e. CPT at warmer temperatures).	Higher CPT (deltoid)
Giesbrecht and Battie (2005)	CLBP +/- leg pain; >6 months duration; >4/10 on NRS; recruited from primary care; (n=30)	Lower PPT (i.e. PPT at lower pressures)	Lower PPT (C5 paraspinal muscles, wrist extensor muscles, calf muscle, middle phalanx of second finger)
O'Neill et al. (2011)	LBP >30 days LBP in past year; recruited from general population; (n=57)	Lower PPT	Lower PPT (tibialis anterior, brachioradialis)
Blumenstiel et al. (2011)	LBP >45 days last 3 months; recruited from general population; (n=23)	Lower PPT; Higher VPT (i.e. vibration threshold at greater amplitudes)	-
Puta et al. (2012)	LBP >6 months duration, no spinal disorders or disc pathology on MRI, females; (n=14)	Pinprick hyperalgesia (i.e. greater pain intensity reported on pinprick stimulation)	Pinprick hyperalgesia (dorsal and palmar hand)
Neziri et al. (2012)	LBP >6 months duration; (n=40)	Lower PPT, higher CPT and lower HPT (i.e. HPT at lower temperatures)	Lower PPT (second toe and suprascapular), higher CPT (lateral leg and suprascapular)

Reference	Patient Sample	Lumbar QST	QST Tested at Site(s) Remote From Lumbar Region
Farasyn and Meeusen (2005)	LBP +/- leg pain; >3 weeks / <12 weeks duration; recruited from physiotherapy centre; (n=87)	Lower PPT	PPT equal to control subjects (triceps brachii)
Imamura et al. (2013)	Unilateral CLBP >12 weeks duration; recruited from hospital and general population; (n=20)	Lower PPT	Lower PPT (iliopsoas, L1-S2 dermatomes both legs; except contralateral iliopsoas and S1 dermatome)
Meeus et al. (2010)	CLBP >3 months duration; recruited from hospital and physiotherapists; no specific underlying pathology; (n=21)	PPT equal to control subjects	PPT equal to control subjects (webspace between 1st and 2nd digits of the hand, deltoid, calf)
Hübscher et al. (2013b)	CLBP +/- leg pain; > 3 months duration; recruited from hospital physiotherapy departments and general population; (Acute LBP n=20; CLBP n=30)	Higher CPT. HPT, cold pain tolerance, heat pain tolerance, temporal summation of repeated heat stimuli all equal to controls	Higher CPT, lower cold pain tolerance. HPT, heat pain tolerance, temporal summation of repeated heat stimuli all equal to controls (volar forearm)

Note. Low back pain; CLBP - Chronic low back pain; NRS - Numeric rating scale; CPT - Cold pain threshold; HPT - Heat pain threshold; PPT - Pressure pain threshold; VPT - Vibration perception threshold. Frank radiculopathy, studies with no lumbar test site and studies only employing electrical stimulation excluded.

2.4.4 CLBP characteristics.

Pain intensity and pain-related disability.

Higher baseline pain intensity is consistently prognostic of higher pain intensity, disability and work absenteeism in people with CLBP (Hayden et al., 2009). Similarly, higher baseline pain-related disability levels are consistently prognostic of greater pain, disability and work absenteeism in people with CLBP (Hayden et al., 2009). Any modelling of CLBP should include these variables (Dworkin et al., 2005).

Bothersomeness.

Bothersomeness is considered an overall summary of patient perception of symptoms, including severity, and their physical and psychological impact (Dunn and Croft, 2005). In a cross-sectional study of 935 people with LBP presenting to primary care, the extent to which LBP symptoms bother people has been shown to correlate with pain intensity, disability, depression and anxiety; and is also prognostic of pain, disability, work absenteeism and healthcare usage at six-month follow-up (Dunn and Croft, 2005). Levels of bothersomeness have also been shown to predict clinical outcomes associated with manual therapy interventions (Axen et al., 2011).

Pain duration.

In 619 people with LBP consulting in primary care, greater LBP duration has been associated with higher pain intensity, disability, depression, anxiety, pain catastrophising and a lower likelihood of improvement over a twelve-month follow-up period (Dunn and Croft, 2006).

Dominant axial low back pain.

The referral of pain from the low back into the lower limb is considered an important consideration. "Dominant" radiating leg pain is suggested to reflect radicular pain (Wai et al., 2009). Pain associated with radiculopathy secondary to nerve root compromise reflects specific neuropathic pain (Treede et al., 2008). Though a neuropathic component to axial LBP has been postulated (Forster et al., 2013, Hush and Marcuzzi, 2012), the majority of studies investigating this premise

have examined heterogeneous samples including people with low back-related leg pain (Hush and Marcuzzi, 2012). Forster et al. (2013) specifically included only people with axial LBP, however, they utilised the Pain*DETECT* questionnaire to differentiate those with presumed neuropathic pain from those without. While this questionnaire considers symptoms suggested to be indicative of neuropathic pain (Freynhagen et al., 2006), such symptoms (e.g. allodynia, cold hyperalgesia) may simply reflect altered CNS nociceptive and non-nociceptive processing (Treede et al., 2008, Hush and Marcuzzi, 2012) common in people with CLBP (Table 3) and low-back-related leg pain without frank radiculopathy (Freynhagen et al., 2008, Schäfer et al., 2014, Schäfer, 2009). Differentiation of those with dominant axial LBP may also be important in terms of prognosis, with dominant axial CLBP consistently having better outcomes in terms of pain, disability and quality of life compared to those with low back-related leg pain (Konstantinou et al., 2013). Throughout this thesis the term axial low back pain will be used to refer to self-reported, dominant lumbar region symptoms, rather than dominant leg symptoms (Wai et al., 2009).

Widespread pain.

A number of studies have reported poorer clinical outcomes associated with more widespread pain. A large community-based cross-sectional study (n=3179) suggests more widespread pain is associated with greater disability (Kamaleri et al., 2008b), and in people sick-listed with LBP +/- low back-related leg pain (n=326), widespread tenderness to palpation is associated with higher pain intensity (Jensen et al., 2010b). More widespread pain has also been associated with female sex, smoking, lower activity levels, higher BMI, worse overall health, poor sleep quality (Kamaleri et al., 2008a), greater comorbid symptoms (Jensen et al., 2010a), depression (Andersen et al., 2014), older age, and a history of physically demanding occupations (Coggon et al., 2013). A recent systematic review suggested that female sex, older age, depression and a family history of pain were prognostic of developing chronic widespread pain from chronic localised pain (Larsson et al., 2012). The presence of more widespread pain may suggest specific underlying pain mechanisms that favour generalised heightened sensitivity to nociceptive and, in some cases, to non-nociceptive inputs (Nijs et al., 2010, Baron et al., 2012, Woolf, 2014).

2.4.5 Body perception dimension.

There is growing research to support that CLBP is associated with altered body perception. Altered tactile acuity has been demonstrated in three small CLBP studies (n=16, n=38, n=90), using two-point discrimination testing (TPD) (Luomajoki and Moseley, 2011, Moseley, 2008) and graphaesthesia (Wand et al., 2010). Tactile acuity is processed in the primary somatosensory (S1) cortex (Duncan and Boynton, 2007, Taylor-Clarke et al., 2004) and considered a clinical assessment of the acuity of the body schema (Pleger et al., 2005). In cross-sectional studies TPD has been associated with altered perception of body image (n=59) (Nishigami et al., 2015) and poorer lumbar motor control in people with CLBP (n=45) (Luomajoki and Moseley, 2011).

Examining another perceptual construct relating to CLBP, the Fremantle Back Awareness Questionnaire (FreBAQ) examines an individual's perception of their low back region. In a small (n=51) cross-sectional study FreBAQ scores have been shown to correlate with pain intensity and duration, disability and pain catastrophising (Wand et al., 2014). It has been postulated that altered body perception may influence pain through two mechanisms. Firstly, altered perception may adversely influence movement patterns, possibly leading to peripheral nociception secondary to altering mechanical loading (Hodges and Smeets, 2015, Nijs et al., 2012). Altered perception is also associated with altered cortical function (Pleger et al., 2006, Pleger et al., 2005) possibly influencing pain responses via altered cortical sensorimotor interactions (Hodges and Smeets, 2015, Nijs et al., 2012).

2.4.6 Movement dimension.

In people with CLBP different factors within the movement dimension, e.g. directional pain responses to movement, speed of movement, range of movement and motor control behaviours associated with pain, reflect the complexity of human movement in relation to pain. This involves motor planning, perception and integration of multisensory input (e.g. nociceptive, visual, proprioceptive) (Berniker and Kording, 2011) as well as cognitive and emotional factors (Hodges and Smeets, 2015). Recent demonstration of cortical changes associated with pain persistence

and altered sensorimotor interactions (Hodges and Smeets, 2015) support consideration of movement-related factors in the clinical and biological understanding of CLBP.

Clinicians commonly evaluate pain responses to movement and repeated movements in people with CLBP, particularly forward / backward spinal bending (McKenzie and May, 2003) as exacerbation of pain in response to such movements is common (Sullivan et al., 2009, Reneman et al., 2002, Fujiwara et al., 2010). While patterns for symptom amelioration with repeated movements have been well examined in acute / sub-acute LBP populations (May and Aina, 2012), there is limited knowledge regarding patterns of pain *provocation* following repeated movements in CLBP populations (Hidalgo et al., 2014). Pain responses to repeated movements, have been suggested to reflect pathoanatomical processes (May and Aina, 2012)}, repetition-induced summation of pain due to altered CNS nociceptive processing and / or peripheral nociceptive processes (Sullivan et al., 2009). Pain provocation following repeated spinal bending movements appears to vary in a directional manner (Hidalgo et al., 2014). For some, it is exacerbated by movement in one direction, for others both directions, or not at all (Rabey et al., 2015, Fujiwara et al., 2010, Hidalgo et al., 2014). However, to date these studies have been limited by their non-standardised protocols leaving them vulnerable to interpretation bias.

Some studies have reported a relationship between pain responses to repeated lifting tasks and interacting variables such as baseline pain, disability, anxiety, depression, kinesiophobia, pain catastrophising, general health and protective pain behaviours (Sullivan et al., 2009, Sullivan et al., 2006, Falla et al., 2014). However it is unknown whether factors from other dimensions associated with CLBP (e.g. tissue sensitivity, lifestyle factors) may also be associated with differing pain responses to repeated movement.

Other factors within the movement dimension may be important to consider in people with CLBP. A recent systematic review identified that people with CLBP generally have reduced range of spinal motion, move more slowly and may have different ratios of lumbar to hip movements during forward bending compared to

healthy controls (Laird et al., 2014). Reductions in range of motion and speed have been postulated to be due to altered, possibly protective, lumbar muscle activity or kinesiophobia (McGregor et al., 1997, Geisser et al., 2004, Thomas and France, 2007). In cross-sectional studies greater levels of protective and communicative behaviours have been associated with greater pain catastrophising (Thibault et al., 2008), lower pain self-efficacy (Levin et al., 1996), and summation of pain with repeated lifting (Sullivan et al., 2009).

2.4.7 Demographics.

Age.

Systematic reviews reveal that the prevalence of disabling LBP, and its associated burden, increases with increasing age (Dionne et al., 2006, Hoy et al., 2014). Increasing age is also considered as potentially prognostic of poor outcome (greater pain, disability and work absenteeism) in people with LBP (Hayden et al., 2009, Verkerk et al., 2012). However, recent secondary analysis of data from seven randomised controlled trials for the treatment of LBP (pharmacological, manual therapy, exercise) suggests that older age does not modify treatment outcomes (Ferreira et al., 2014). While pain sensitivity may reduce in people of older age, pain tolerance also reduces possibly due to reduced endogenous pain modulation (Cole et al., 2010, Gibson, 2006). Differences in pain perception in older people may also relate to the increasing proportion of females within older age ranges (Ruda, 1993) (see below) and increasing levels of depression associated with older age (Atkas and Cavlak, 2011). With increasing age, people tend to report increasing disability due to a broad range of health complaints (Australian Bureau of Statistics, 2010).

Sex.

A critical review of the literature concerning the interactions between sex and pain suggests that females have a greater prevalence of LBP (Mogil, 2012), and are more likely to have disabling LBP (Fillingim et al., 2009). The prevalence of widespread pain complaints is also greater in females (Fillingim et al., 2009). Pain thresholds and tolerance appears consistently lower in females (Mogil, 2012). These sex differences are possibly mediated through numerous genetic, epigenetic, nervous system,

hormonal and environmental interactions (Mogil, 2012, Bartley and Fillingim, 2013) possibly influencing greater central sensitisation (Woolf, 2014) in females (Racine et al., 2012).

2.4.8 Health and lifestyle dimensions.

Broader aspects of an individual's health may significantly influence the presentation and management of people with CLBP (Chou R, 2010, Hayden et al., 2009, Hartvigsen et al., 2013). This dimension considers other health conditions and behaviours (e.g. smoking, physical activity) that may have specific influences upon CLBP, but may also interact in an individual's presentation by increasing their allostatic load (McEwen and Gianaros, 2010, Dominick et al., 2012).

Body mass index.

In a very large (n=63968) community-based sample the prevalence of CLBP has been shown to increase with increasing body mass index (BMI) (Heuch et al., 2010). There is an association between greater CLBP and disability and BMI ($>24kg/m^2$) (Shiri et al., 2009, Urquhart et al., 2011). However, in systematic reviews BMI does not appear to be consistently prognostic of pain, disability or work absenteeism (Hayden et al., 2009). Possible mechanisms underlying the association between BMI and CLBP will be discussed in the following section.

Physical activity levels.

Systematic reviews examining time spent on sedentary activities or physical activities show conflicting evidence for an association with CLBP (Chen et al., 2009, Sitthipornvorakul et al., 2011), while there appears to be a weak relationship between lower physical activity and greater disability in people with LBP (Lin et al., 2011). These inconsistencies may be explained by two large, community-based studies (n=3364, n=5999) which have shown that pain and disability in CLBP appear to have a non-linear "U-shaped" association with the level of physical activity undertaken, suggesting people with high levels of either sedentary behaviour or physical activity have greater pain and disability compared to people in the middle of the continuum (Auvinen et al., 2008, Heneweer et al., 2009).

In a cross-sectional study both greater BMI and lower activity levels have been associated with more widespread pain (Kamaleri et al., 2008a). Lower physical activity and high BMI are associated with higher systemic, circulating inflammatory markers (Lavie et al., 2011, Lavoie et al., 2010, Tilg and Moschen, 2006, Pischon et al., 2003, Paley and Johnson, 2015). While pro-inflammatory biomarkers may influence pain sensitivity, studies of pain sensitivity in obese people offer varied results (Okifuji and Hare, 2015). Conversely higher activity levels have been related to higher pressure (Andrzejewski et al., 2010) and thermal pain thresholds and lower unpleasantness ratings for noxious thermal stimuli (Ellingson et al., 2012). However, there is no clear association between LBP and systemic inflammation (Beastall et al., 2008, Gebhardt et al., 2006). BMI has also been positively associated with adrenocorticotropic hormone release, suggesting that increasing BMI may also influence HPA axis function (Veldhuis et al., 2009). Obesity is also postulated to influence CLBP through alteration of biomechanics and subsequent physical tissue overload due to abnormal distribution of adipose tissue (Paley and Johnson, 2015).

General health.

Systematic reviews reveal that poor self-report general health is consistently prognostic of disabling CLBP and work absenteeism (Chou R, 2010, Hayden et al., 2009). A large, cross-sectional study of community-dwellers (n=3325) revealed that it is also associated with more widespread pain (Kamaleri et al., 2008b).

Increasing allostatic load, due to broader health problems including other non-painful (e.g. cardiac or bowel) disorders is associated with greater chronic pain prevalence (Dominick et al., 2012, Helme and Gibson, 1999). Non-specific health complaints such as irritable bowel syndrome and chronic fatigue syndrome commonly associated with CLBP, may have common underlying mechanisms relating to altered HPA axis, SNS and immune function (Nater et al., 2011).

Comorbidities.

A number of diagnosed medical conditions (some of which are other musculoskeletal pain disorders) (Beales et al., 2012, Dominick et al., 2012), undiagnosed symptoms (Tschudi-Madsen et al., 2011, Hagen et al., 2006a), or

functional pain disorders (Mayer and Bushnell, 2009) are associated with CLBP (Table 4).

It is important to consider the presence of comorbidities in patients with CLBP as they may affect treatment options, worsen outcomes and increase healthcare expenditure (Giamberardino and Jensen, 2012, Nimgade et al., 2010, Ruetsch et al., 2013, Hartvigsen et al., 2013). Whether the comorbidities affecting a particular individual share common mechanisms with CLBP (Nater et al., 2011) or not, it is likely that their existence will increase allostatic loading (McEwen and Gianaros, 2010).

Table 4
Comorbidities associated with low back pain.

Diagnosed musculoskeletal pain disorders	Other diagnosed comorbidities	Non – musculoskeletal symptoms	Functional pain states
Osteoarthritis Rheumatoid arthritis Osteoporosis	Incontinence Respiratory problems Diabetes Eating disorders Hay fever / allergy Heart disease Hearing impairment Visual impairment Eczema Cancer Blood pressure problems Thyroid problems Neurological disorders Ulcer or stomach disease Anaemia or other blood disease Depression Anxiety disorder	Flushes / heat sensations Constipation Palpitations Chest pain Breathing difficulties Stomach discomfort Diarrhoea Tiredness Dizziness	Irritable Bowel Syndrome Temporomandibular Disorder Fibromyalgia Pelvic Pain Chronic Fatigue Syndrome Migraine or severe headache

Note. Taken from: Beales et al. (2012), Hagen et al. (2006a), Hestbaek et al. (2003b), Smith et al. (2009), Tschudi-Madsen et al. (2011).

Sleep quality.

Poor sleep quality is associated with greater pain, disability, catastrophising, depression and anxiety, and widespread pain (Nalajala et al., 2013, van de Water et al., 2011a, Kamaleri et al., 2009, Kamaleri et al., 2008a). Experimental data suggest thermal, pinprick and pressure pain sensitivity increases when healthy participants are sleep deprived (Kundermann et al., 2004, Schuh-Hofer et al., 2013). Catastrophising and stress increase arousal may disrupt sleep (Nalajala et al., 2013, Åkerstedt, 2006), facilitating tissue hypersensitivity (Lautenbacher, 2012, Quartana et al., 2009). Reduced and fragmented sleep are associated with elevated cortisol and greater SNS activity (Spiegel et al., 1999, Stamatakis and Punjabi, 2010, Kang et al., 2012). A recent critical review suggests that commonalities exist regarding changes to structure and function of brain regions involved in emotional regulation and pain modulation across people with chronic pain, sleep disturbance and depression (Boakye et al., 2015). Disturbed sleep may also be associated with elevated systemic inflammatory markers (Nalajala et al., 2013), which may influence pain sensitivity peripherally. These findings may be consistent with a clinically-derived subgroup (n=19) of people with CLBP who demonstrated elevated pressure and cold pain sensitivity and who showed significantly worse sleep quality compared to people with CLBP and lower pain sensitivity (n=17) and healthy controls (n=19) (O'Sullivan et al., 2014).

Smoking.

A recent meta-analysis has shown that smoking (including being an ex-smoker) is associated with more disabling CLBP, and is prognostic of a higher incidence of LBP (Shiri et al., 2010). There is also a dose-response relationship between current smoking (number of cigarettes per day) and CLBP (Shiri et al., 2010). The authors of this review suggest that because the majority of included studies controlled for confounding variables it is unlikely that the influence of smoking upon LBP is related to sociodemographic factors (e.g. manual work) or poorer mental health status. They postulated smoking may be related to poorer lumbar tissue health and increased pro-inflammatory cytokine release (Shiri et al., 2010).

Key Points:

- Examination of multiple dimensions associated with CLBP should involve clinically-applicable measurements to facilitate translation into practice.

- Psychological factors: Cognitive factors (higher levels of fear-avoidance beliefs, pain catastrophising, endurance behaviours, and perceived risk of persistent pain, and lower levels of chronic pain acceptance, mindfulness, and pain self-efficacy) and affective factors (higher levels of depression, anxiety and stress) may negatively affect pain and disability in people with CLBP.

- Social factors including stressful life events, lower educational level, poor work relationships, physically heavy work, poor social support and punishing interactions with significant others may affect pain and disability in people with CLBP.

- Limited examination of clinical somatosensory phenotypes has been undertaken in people with CLBP to date, with variable results.

- Pain characteristics associated with CLBP include pain intensity, pain-related disability, bothersomeness, pain duration, pain referral and widespread pain.

- Disturbed body perception may affect pain and disability in people with CLBP.

- Changes to movement in people with CLBP are complex, and include altered pain responses to movement, speed of movement, range of movement, control of movement and behaviours associated with pain.

- Sex and older age are associated with higher prevalence of disabling LBP.

- Health and lifestyle factors associated with CLBP include BMI, physical activity, general health, comorbidities, sleep quality and smoking.

2.5   Making Sense Of The Complexity Within CLBP

Clinicians and researchers are continuously faced with the need to try to understand the complex, multidimensional nature of CLBP, particularly to facilitate optimal management for the person living with pain. It is likely that at the level of the individual, the relative contributions of the multiple different dimensions will vary greatly (Rusu et al., 2012, Brown, 2009).

One suggested research priority has been to determine the existence of subgroups within the population of people with CLBP, with differing multidimensional profiles (Costa et al., 2013). These subgroups may then be used to develop targeted management strategies, and facilitate improved treatment outcomes (Rusu et al., 2012, Costa et al., 2013). However, it has also been suggested that CLBP is a constantly evolving, highly individualised experience (Kucyi and Davis, 2015, Brown, 2009, Griffiths and Byrne, 1998), and that to improve outcomes interventions must be individualised (Borsook and Kalso, 2013), limiting the capacity of subgrouping to target care.

Various approaches have been adopted for determining subgroups with different clinically important characteristics in people with LBP. At the level of the healthcare system, subgroups have been used to triage people with LBP into different management streams based upon factors that have been shown to be prognostic of poor outcome (e.g.Hill et al. (2008)). At the level of the individual, approaches have determined subgroups of people with LBP that will respond differently to specific interventions (treatment effect modifiers) (e.g. Fritz et al. (2007)). Subgroups have also been proposed based upon dimensions hypothesised to drive ongoing pain and disability in CLBP without attempting to predict outcome or prescribe a specific intervention (e.g. Smart et al. (2010), Vibe Fersum et al. (2013)). Irrespective of the approach taken to determine subgroups, for such CS to be valid, they should be based upon valid and reliable measures (Dankaerts et al., 2006), rather than clinician judgement. The selection of variables upon which the CS is based should be based upon review of the relevant literature, and have adequate face validity. CLBP is considered a multidimensional disorder, therefore, the optimal CS should be

multidimensional in nature (Karayannis et al., 2012). Methods for deriving subgroups vary. Each will be described in turn, after which the validation of subgroups will be discussed.

2.5.1   Judgemental subgrouping.

Judgemental LBP CS divide people into different subgroups based upon theoretical models for drivers of the disorder, based upon previously published literature and the experimental observations of (expert) clinician(s). Determination of which subgroup a particular individual belongs to is based upon clinical interpretation of examination findings. Such CS include the majority of movement-based CS (e.g. Sahrmann (2002), O'Sullivan (2000), McKenzie and May (2003)).While making CS clinically recognisable and meaningful, clinician judgement may create bias within the CS by possibly giving inappropriate weighting to differing dimensions (Kent et al., 2010). It may also reduce generalisability (Billis et al., 2007) to clinicians in different settings or with different training, and to varying clinical populations; and may compromise reliability as there is potential for clinician disagreement.

2.5.2   Non-judgemental subgrouping.

Contrastingly, non-judgemental subgrouping does not rely upon an underlying clinical assessment process, but lets data collected from people with CLBP "speak for itself" independent of clinical interpretation and its potential bias. Non-judgemental subgrouping involves statistical methods, broadly defined as the systematic organisation of numerical data. Methods for statistical-derivation of subgroups vary widely in method and complexity, but can be divided into supervised and unsupervised statistical procedures.

Statistical subgrouping – supervised techniques.

Supervised statistical techniques subgroup people according to data at baseline based upon future outcomes. These studies may form subgroups based on factors that are prognostic, or based on factors predictive of outcome of a particular treatment. In both cases, in the area of LBP such subgroups have been predominantly derived using regression analysis.

One example of prognostic supervised statistical subgrouping is the CS described by Hill et al. (2008). This CS utilises valid and reliable self-report questions, which were determined to be prognostic of poor outcome in people with LBP presenting to primary care using regression analysis. Subgroup cut-off scores for risk of poor outcome were determined by examining receiver operating characteristic curves, and levels of sensitivity and specificity.

Subgroups based upon supervised statistical techniques have good face validity, being prognostic or predictive of a certain outcome (e.g. 50% reduction in pain intensity). However, because recovery from LBP is multidimensional, being related to a person's perception of the impact LBP has upon their quality of life, functional capacity, psychological health, and pain intensity (Hush et al., 2009), use of one specific outcome offers a limited reflection of the participant's recovery, and differing subgroups may be derived if a different outcome were chosen (Kent et al., 2010). Subgroups may also differ if different interventions are applied, or different participant populations are examined (e.g. acute versus CLBP).

In LBP the most common utilisation of supervised statistical techniques is where the characteristics of participants with a specific outcome in response to one particular intervention are determined in a specific cohort, to develop a prediction rule guiding treatment selection. Few prediction rules have been adequately validated. Therefore, evidence for the utilisation of clinical prediction rules in the management of people with LBP is limited (Haskins et al., 2015, Patel et al., 2013).

Statistical subgrouping – unsupervised techniques.

Unsupervised statistical techniques derive subgroups using only cross-sectional data. They are termed unsupervised as subgrouping is performed independent of any known subgroups or future outcomes (Kent et al., 2010). Three main types of unsupervised statistical analysis have been used to examine samples of people with LBP: hierarchical cluster analysis, non-hierarchical cluster analysis and latent class analysis (LCA). Both hierarchical and non-hierarchical cluster analysis partition people into non-overlapping groups based on measures of similarity or dissimilarity of their data, most often using distance-based procedures; i.e. individuals are

classified based upon their proximity to other individuals in terms of their multivariate data (e.g. similar questionnaire scores). The aim is to form subgroups where people within the subgroup have similar responses to the variables compared to other members of that subgroup, but have few similarities to the responses of members of other subgroups (maximal within cluster homogeneity, and maximal between cluster heterogeneity) (Hair et al., 2010).

Hierarchical cluster analysis involves the creation of clusters either by agglomerative or divisive methods. For example, in agglomerative hierarchical cluster analysis, the process begins with each person being considered a separate group, then the two people who are most similar are combined into a cluster, with the process continuing until all people belong to the same group, creating a hierarchy of clusters (Hair et al., 2010). To determine the optimum number of clusters, stopping rules using various indices of cluster "distinctiveness" are used. Hierarchical cluster analysis has been used very commonly to derive subgroups in people with CLBP, for example Beneciuk et al. (2012) derived three subgroups with differing levels of fear-avoidance beliefs, while Scholz et al. (2009) derived two subgroups with differing pain characteristics and responses to assessment of temporal summation.

Non-hierarchical clustering methods assign people to clusters where the number of clusters has been pre-specified. Initial cluster centres are set, then each person is assigned to a group based on their proximity to the cluster centres, with an iterative process involving recalculated group centres and reassignment of people continuing until people do not change groups. An example of subgrouping in people with CLBP using non-hierarchical cluster analysis would be the study by Johansson and Lindberg (2000) which derived clusters with differing profiles based upon West Haven-Yale Multidimensional Pain Inventory scores.

Cluster analysis (hierarchical and non-hierarchical) has some limitations. Firstly, it is considered an exploratory technique as no parametric statistical estimation is involved; hence there are no measures of probability that can be used for judging the likely "true" cluster solution. There are a plethora of different methods,

similarity / dissimilarity measures, and methods of choosing the most likely number of groups, each offering a differing cluster solution. Cluster analysis does not accommodate combinations of variables of mixed measurement type, such as counts, nominal or ordinal variables in addition to interval variables; or widely dispersed data (Magidson and Vermunt, 2002). Even when interval data is used, data must be standardised to equalise variance between variables, making interpretation more complex (Hair et al., 2010). Cluster analysis does not provide a facility for uncertainty in group allocation, i.e. some group members may be more representative of the group than others, and does not accommodate missing data (Hair et al., 2010, Magidson and Vermunt, 2002).

Unlike cluster analysis LCA is a probabilistic form of subgrouping which uses maximum likelihood estimation. Using LCA, it is possible to estimate and compare the likelihood of the presence of varying numbers of clusters of people based upon their response patterns for variables used to form the clusters. The relative fit of the observed data between models with differing numbers of clusters can be compared using various fit statistics, most commonly in studies examining people with LBP, the Bayesian information criterion (BIC) statistic (Beales et al., 2012, Tamcan et al., 2010, Barons et al., 2014). A smaller BIC denotes a model fit that has less error, and is more parsimonious, thereby facilitating interpretability (Collins and Lanza, 2010). For each individual it is possible to determine the probability that they belong to a particular cluster, based upon their particular response pattern of variables used to form the clusters. An example of subgrouping using LCA would be the study by Dunn et al. (2006) which derived clusters of people with LBP with differing levels of pain intensity over time to characterise differing courses of the disorder.

LCA has the following advantages over traditional distance-based cluster procedures: i) optimised assignment of individuals to clusters, ii) statistical evaluation of the optimal number of subgroups, iii) utilisation of variables of mixed measurement types without the need for standardisation, iv) provision of classification probabilities for each individual, and v) better accommodation of missing data (Collins and Lanza, 2010, Magidson and Vermunt, 2002). When examining artificial datasets, where cluster membership is known, LCA is

consistently more accurate at identifying clusters than distance-based cluster analysis techniques (Magidson and Vermunt, 2002, Bacher et al., 2004, Kent et al., 2014).

2.5.3   Validation of subgroups.

Once subgroups have been determined their inter- and intra-rater reliability, and validity should be examined (Dankaerts et al., 2006, Kamper et al., 2010). Particularly if subgroups have been derived using statistical analysis, they should be further validated by attempting to replicate the subgroups in a separate sample (Hair et al., 2010).

Subgroups should be profiled across other important variables, ideally from multiple dimensions (e.g. pain intensity, disability, psychological factors, tissue sensitivity) (Kent et al., 2010), and subgroup profiles examined to determine their face validity in terms of whether differences in profiles are consistent with published literature or hypotheses, and whether they are meaningful and clinically recognisable (McCarthy et al., 2004). Meaningfulness of subgroups may be further considered by examining whether they are prognostic of different outcomes over time in longitudinal cohort studies, regardless of any interventions received. This may be important in people with LBP, as those with good prognoses may be appropriately reassured, while modifiable factors within the subgroup profiles of those with poor prognoses may be considered for the development of tailored interventions (Hill et al., 2011, Kamper et al., 2010, Kent et al., 2010).

Randomised controlled trials should then be used to determine whether subgroups are predictive of treatment outcomes (i.e. whether they are treatment effect modifiers) (Kamper et al., 2010). Firstly, a tailored treatment may be compared to a control treatment, where the tailored treatment is hypothesised to be matched to a specific subgroup of participants within the sample. Statistical analysis is used to determine whether there is an interaction between the subgroup and the treatment effect. This study design aims to determine whether the treatment is more effective in the subgroup that it is tailored towards than in the other participants. Alternatively, participants from a number of different subgroups may

receive a number of different treatments, with each individual receiving a treatment matched or unmatched to their subgroup. This study design aims to determine the efficacy of the CS as a whole (Kamper et al., 2010).

The final stage in the validation process may include replication of the prognostic or predictive capabilities of the subgroups, in longitudinal cohort studies or randomised controlled trials in other settings, allowing greater generalisability of the results (Kamper et al., 2010).

2.6   An Overview Of Subgrouping In People With Low Back Pain

The following is an overview of subgrouping of LBP based upon the dimension(s) upon which the subgrouping is based. Multidimensional CS are discussed last. Where relevant, the approach to subgrouping that has been taken will be highlighted. This is not an exhaustive list of documented CS. For such detail readers are referred to Billis et al. (2007), Fairbank et al. (2011) and Ford et al. (2007). As previously discussed pathoanatomically-based CS do not reflect the current multidimensional model of CLBP and will not be considered further. For the same reason, treatment-based subgrouping, where a specific subgroup of people with CLBP are suggested to be most likely to respond to a specific treatment will also not be considered further.

2.6.1   Movement-based subgrouping.

Numerous judgementally-derived CS have evolved based upon pain responses to movement, predominantly forward and backward spinal bending (McKenzie, 1981, Van Dillen et al., 1998, O'Sullivan, 2000). These CS are judgementally-derived and hypothesise abnormal tissue loading to be a reason for ongoing peripherally-mediated nociception in CLBP. The CS developed by McKenzie (McKenzie and May, 2003) advocates structured examination to assess pain responses to lumbar mechanical loading, including repeated movements. Examination determines the presence of a directional preference (a particular direction of repeated movement improves symptoms, and vice versa) and / or a "centralisation" response (spinal loading causes progressive, distal-to-proximal abolition of pain). Patients are

classified as mechanical "responders" or "non-responders" dependent upon whether they exhibit centralisation or a directional preference, or not (McKenzie and May, 2003)(p138). However, this assessment process is based upon clinical judgement, rather than a standardised testing protocol, possibly introducing bias to the assessment. A recent systematic review suggests that the reliability of this examination process is moderate (Karayannis et al., 2012). However, another systematic review suggests that determination of "centralisation" is only possible in 42% of people with CLBP (May and Aina, 2012). This CS acknowledges that in patients with CLBP who do not have a "mechanical" presentation, varied psychosocial or neurophysiological factors may be relevant, however subsequent management strategies are for these factors are not elucidated (McKenzie and May, 2003). Five studies have taken the approach of matched and unmatched treatments directed towards subgroups based upon this CS (Schenk et al., 2003, Browder et al., 2007, Brennan et al., 2006, Long et al., 2004, Delitto et al., 1993). These studies showed significant improvements in pain and / or disability for the matched treatments compared to the unmatched or control treatments. However, all of these studies involved people with acute or sub-acute LBP except the study by Long et al. (2004) which involved people with LBP of varying durations. Further examination of the results of the study by Long et al. (2004) reveals that it is unclear to what degree those in a particular subgroup receiving matched treatment improved compared to those receiving unmatched treatment, and that this study may have been inadequately powered to detect such interactions (Kamper et al., 2010).

Only the study (n=18) by Hidalgo et al. (2014) appears to have determined subgroups of people with sub-acute LBP based upon a pain *provocation*, rather than amelioration, following a standardised repeated movement examination (10 forward and backward spinal bends). However, the reliable determination of each participant's subgroup (flexion pattern 20%, extension pattern 60%) was also based upon spinal palpation which involves a degree of clinical interpretation. The method by which pain responses to movement were measured was not described in this study.

Alternatively, the CS developed by Sahrmann (2002) is based upon the premise that abnormal movement patterns result in "tissue damage" (Sahrmann, 2002) (p4). Presentations are classified in terms of the direction of movement into which the patient is "susceptible" (Sahrmann, 2002)(p4) to such damage. A recent systematic review suggests that the reliability of this examination process is substantial (Karayannis et al., 2012). Treatments are directed towards "normalising" movement to reduce tissue strain. Neurophysiological, psychosocial factors and comorbidities are not considered within this CS (Karayannis et al., 2012), thus the uni-dimensional nature limits the utility of this approach. Two studies have examined this CS in people with CLBP, and have included two treatment groups; one matched to this CS, and another receiving non-specific exercise-based treatment. In one study (n=101) comparisons between the two treatment arms were not reported (Van Dillen et al., 2013), while in the other (n=124) there were no significant differences between matched and control treatments at 6 and 12 month follow up (Henry et al., 2014).

O'Sullivan (2000) described a CS based upon the presence of maladaptive movement patterns in people with CLBP, which were postulated to lead to tissue strain due to suboptimal segmental movement control. However, subsequent evolution of this CS has seen its development into a multidimensional CS (Vibe Fersum et al., 2013, O'Sullivan, 2012, O'Sullivan et al., 2015) to be discussed later in this chapter. Treatment matched solely to the movement component of this CS has shown significant improvements in pain and disability compared to a general postural intervention when participants classified into two of the subgroups (flexion: n=29, active extension: n=20) were included (Sheeran et al., 2013). Overall, movement-based subgroups have been limited by their judgemental derivation and limited multidimensional profiling. Treatments matched to specific subgroups may afford better outcomes than unmatched treatments, but studies using this methodology are lacking in CLBP cohorts.

Overall, there have been no attempts to determine whether different subgroups exist in a large CLBP cohort, based upon differing pain responses following repeated forward and backward spinal bending using valid and reliable, clinically-important,

self-reported changes in pain intensity following a standardised protocol of repeated movements (Dworkin et al., 2005, Sullivan et al., 2009, Salaffi et al., 2004). This may be an important, non-judgemental method for determining whether such different subgroups exist.

2.6.2 Tissue sensitivity subgrouping.

Parallel to development of CS for LBP has been a quest to determine which pain mechanisms underlie certain pain disorders (Woolf and Mannion, 1999). There is little research into pain mechanisms underlying CLBP, possibly because mechanisms are complex phenomena difficult to examine or accurately correlate with clinical presentations (Baron et al., 2012). In particular, to date CS in this category have largely failed to acknowledge the alterations in brain structure, chemistry and function associated with CLBP (Wand et al., 2011).

A recent CS for CLBP +/- low back-related leg pain based on hypothesised pain mechanisms, acknowledges nociceptive aspects of CLBP, and potential neuropathic and CNS contributions to nociception and pain (Smart et al., 2011). (Smart et al., 2010). A Delphi study was used to determine a 38 item checklist to discriminate three subgroups ("nociceptive", "peripheral neuropathic", "central sensitisation"). This included: history of onset, aggravating and easing factors, pain descriptors, temporal patterns and referral patterns, psychosocial factors, movement patterns, responses to provocative orthopaedic tests, peripheral neurological screening and responses to palpation interpreted in terms of normal or abnormal CNS-mediated sensitivity levels. Regression analysis was then utilised to determine the checklist items most closely associated with subgroups which were clinically-derived. Following regression analysis the "nociceptive" subgroup were defined by responses to physical tests or aggravating / easing factors that were deemed proportionate to the presentation. The "peripheral neuropathic" subgroup was described as having a history of nerve injury, positive neural tissue provocation testing (for example, straight leg raise) and dermatomal symptoms. The "central sensitisation" subgroup presented with disproportionate pain responses to movement, widespread hypersensitivity to palpation, and greater disability,

depression and anxiety compared to the other subgroups (Smart et al., 2012). These subgroupings have not been validated neurophysiologically (e.g. QST or nerve conduction studies), and while these subgroup titles suggest underlying mechanisms they are delineated using clinical signs and symptoms that may not necessarily specifically correlate with those pain mechanisms. Furthermore, a certain clinical manifestation may involve multiple interacting mechanisms (Woolf, 2004, Woolf and Mannion, 1999), thus compromising this simplistic CS. There also seems to be a circular approach to deriving this CS. Clinicians were asked to determine the checklist using a Delphi study. Then, using clinical judgement participants were classified into the subgroups, and the best indicators of subgroup membership from the checklist derived using regression analysis. This CS therefore appears to be a combination of judgemental and non-judgemental approaches. Finally, this CS also fails to consider the lifestyle dimension that may influence tissue sensitivity (Andrzejewski et al., 2010, Ellingson et al., 2012, Schuh-Hofer et al., 2013, Kundermann et al., 2004). This CS has not been tested for its reliability in people with LBP and no treatments have been matched to these different subgroups.

QST may provide a "window" through which to explore nociceptive and non-nociceptive processes underlying pain disorders (Baron et al., 2012). Cold and / or pressure pain thresholds have been shown to differ between subgroups with CLBP (O'Sullivan et al., 2014, Tesarz et al., 2015) or low back-related leg pain (Schäfer et al., 2014), however, these subgroups have been clinically derived. The following two studies have derived subgroups in people with CLBP using cluster analysis.

The Standardised Evaluation of Pain (StEP) (Scholz et al., 2009) is a bedside sensory testing protocol (light touch, pinprick, vibration, pressure, brushing, temporal summation, hot / cold) developed to assist postulation of pain mechanisms underlying clinical pain disorders. Using hierarchical cluster analysis of 16 questions regarding symptoms and 23, predominantly sensory bedside tests two subgroups with axial LBP were differentiated: one more likely to complain of paraesthesia / burning pain (n=18), the other more likely to exhibit temporal summation (n=32). The authors suggest caution regarding interpretation of these results because pain descriptors were involved in differentiating these two subgroups, and the evidence

surrounding pain descriptors in the differentiation of pain mechanisms may be considered debatable. Interpretation of this study's outcomes was also limited by the small sample, relatively limited sensory testing and absence of multidimensional profiling of the subgroups.

In a larger mixed cohort (LBP: n=110; neck pain: n=47), Coronado et al. (2014) used hierarchical cluster analysis of pain sensitivity data to derive three subgroups (i: high static pressure and dynamic heat pain sensitivity; ii: high static heat pain sensitivity; iii: low pressure and heat pain sensitivity). While subgroups did not differ across baseline psychological measures, the subgroup with high static pressure and dynamic heat pain sensitivity had significantly lower odds of achieving a clinically important reduction in pain intensity over a two-week intervention. Neither of these QST subgrouping studies have been replicated in separate samples to validate the derived clusters or used to guide matched interventions.

2.6.3 Psychosocial subgrouping.

Subgrouping based on psychosocial factors has increased based on the growing understanding of the influence of the psychosocial dimension on outcomes in people with LBP. The majority of psychosocially-based subgrouping studies have utilised supervised statistical techniques to derive subgroups, initially focussing on data from single psychological questionnaires. For example, using hierarchical cluster analysis Bradley et al. (1978) derived four clusters from the Minnesota Multiphasic Personality Inventory (MMPI) (n=548) which includes subscales to assess personality traits and psychopathology (Greene, 1991). This study was closely replicated by McGill et al. (1983) (n=92) and Rosen et al. (1987) (n=362). Profiling of the derived clusters revealed differences in symptom duration, surgical intervention rates, functional status, compensation status, self-reported distress and rates of previous mental health treatment, adding validity to these clusters. However, in the most comprehensive intervention study based upon clusters derived from MMPI scores (Naliboff et al., 1988) (n=634), there were no significant differences between clusters following an eight week multi-disciplinary intervention.

Subsequently there has been a move away from examining personality traits towards a broader range of psychosocial factors associated with persistent pain. The West Haven-Yale Multidimensional Pain Inventory (WHYMPI) contains nine subscales: pain severity, pain interference, perceived life control, distress, frequency of performing common activities, and support, punishing responses, solicitous responses and distracting responses from significant others (Kerns et al., 1985). Johansson and Lindberg (2000) examined data from the WHYMPI (n=88) in people with LBP of greater than four weeks duration, using non-hierarchical cluster analysis to derive three clusters. Cluster 1 labelled "interpersonally distressed" had low pain and disability, and low social support. Cluster 2 labelled "adaptive copers" had low pain and disability, high social support and a solicitous significant other. Cluster 3 labelled "dysfunctional" had high pain and disability, high social support and a solicitous significant other. Similar clusters have been derived using hierarchical cluster analysis in another CLBP cohort (n=173) (Verra et al., 2011). This study may be considered a replication of the study by Johansson and Lindberg (2000), with the three subgroups having similar proportions and characteristics on the WHYMPI in both studies, thereby increasing the validity of these subgroups. However, pain and disability levels following treatments matched to these subgroups (n=139) did not differ from the results of a standard rehabilitation programme, except in the dysfunctional subgroup where the effect of the matched treatment was moderate (Verra et al., 2015).

There have been many attempts to derive subgroups of people with LBP, predominantly using cluster analysis, based upon specific psychological factors (e.g. fear-avoidance beliefs (Beneciuk et al., 2011)), or combinations of factors (e.g. fear-avoidance beliefs, pain self-efficacy, anxiety, depression and troublesomeness (Barons et al., 2014)) associated with CLBP. However, this unidimensional approach to subgrouping reflects a limited view of CLBP as a disorder. There is some evidence that different psychologically-derived subgroups may have different trajectories for improvement (e.g. persistent mild pain, persistent severe pain, fluctuating pain) in the absence of any intervention (Axen et al., 2011, Dunn et al., 2006, Tamcan et al.,

2010), however, no attempts have been made to target interventions towards these subgroups.

More consistent with a multidimensional approach to CLBP, there have also been a number of attempts to combine the assessment of psychosocial factors with physical examination procedures (e.g. Coste et al. (1992), Klapow et al. (1993)). The only study to validate their subgroups by examining responsiveness to intervention was by Main et al. (1992). This study was still dominated by the psychosocial domain, examining questionnaires (depression, somatic perception) and Waddell's signs, suggested to examine for the presence of "non-organic physical signs" and high levels of illness behaviour (Waddell et al., 1984, Waddell et al., 1980) in 567 participants. Non-hierarchical cluster analysis revealed four clusters labelled: "normal" (no distress or illness behaviour), "at risk" (slightly elevated depressive scores), "distressed depressive" (elevation on all variables, but depression in particular), and "distressed somatic" (elevation on all variables, but somatic awareness in particular). In the predictive component of this study participants receiving conservative intervention (n=87) were followed-up at between one and four years. Those in the two distressed subgroups had a significantly greater risk of higher pain and disability at follow-up than the other two subgroups.

Specific questions from the Örebro Musculoskeletal Pain Screening Questionnaire (Linton and Halldén, 1998) concerning pain intensity, disability, fear-avoidance beliefs and depressed mood, have been used to derive clusters. The following three clusters were derived using hierarchical and non-hierarchical cluster analysis: i) low depressed mood and fear-avoidance beliefs, ii) low depressed mood and high fear-avoidance beliefs, iii) high depressed mood +/- high fear-avoidance beliefs (Boersma and Linton, 2005). In a recent study utilising these subgroups (Bergbom et al., 2014), half of the people (n=105) with neck / back pain in each subgroup received matched treatment (graded activity, graded exposure in vivo and cognitive behavioural therapy for each subgroup respectively) and the other half received unmatched treatment. There was no significant between-group differences at nine-month follow-up. One limitation of these approaches may be the lack of targeting

other dimensions associated with CLBP (e.g. movement, pain sensitivity, perceptual disturbances).

Taken together these studies suggest that psychosocial factors alone may be inadequate for the derivation of subgroups which facilitate better treatment outcomes. Psychological measures included across subgrouping studies have been numerous and highly varied, while individual studies have often considered only a limited range of psychological factors. Therefore, it is not clear which psychosocial factors are most important for subgrouping people with CLBP. While the majority of these CS are statistically-derived, reducing bias within the subgrouping, most of these CS require further validation (Kent et al., 2010). Suboptimal outcomes from psychologically-informed interventions directed towards homogeneous samples (Henschke et al., 2010), and interventions tailored towards specific subgroups (Bergbom et al., 2014, Verra et al., 2015) suggest other dimensions are likely to contribute to persistence of symptoms and disability, and hence may be important for the optimal classification and targeted management of this disorder. However, multidimensional profiling of psychologically-derived subgroups has been limited to date.

2.6.4   Multidimensional subgrouping.

Approaches to multidimensional classification of people with CLBP have been varied. The STarT Back approach considers pain referral, comorbid upper quadrant pain, functional impairment and psychological factors to determine three subgroups (Hill et al., 2008). Individual items in this tool were selected using regression analysis of modifiable prognostic indicators from two previous studies, review of prognostic literature for LBP in primary care settings and consensus of an expert panel. Different cut-off scores for the three subgroups (high, intermediate, low) based upon answers to the complete questionnaire were then determined by examining sensitivity, specificity and likelihood ratios (Hill et al., 2008). In a study of 851 people with LBP presenting to primary care, treatments were tested which were matched to these subgroups as follows: the subgroup with the highest-scoring psychological profile received psychologically-informed physiotherapy, the

intermediate subgroup received standard physiotherapy, and the low-scoring subgroup received reassurance. When participants with LBP of unspecified duration, classified using the STarTBack tool, were randomised to either treatment matched to their subgroup or a control treatment (physiotherapeutic intervention as determined by the assessing clinician's judgement), at 12 month follow-up those receiving matched treatment had a significantly greater, but arguably clinically insignificant (Stratford et al., 1996) change in their RMDQ scores (4.3 points v. 3.3 points) Hill et al. (2011). When considering the one-year follow-up disability levels for the different subgroups only the intermediate subgroup demonstrated significantly greater improvements following the matched intervention compared to the control intervention (Hill et al., 2011).

An approach outlined by O'Sullivan (Vibe Fersum et al., 2013, O'Sullivan et al., 2015, O'Sullivan, 2012) has been reported to be the most comprehensive multidimensional CS to date (Karayannis et al., 2012). This CS considers relative contributions of interacting pathoanatomical, neurophysiological, psychological, social, lifestyle, movement and comorbidity dimensions, and acknowledges individual variability in these contributions. This CS has excellent intra-rater reliability (Karayannis et al., 2012), and movement components of this CS have been validated using electromyography and electromagnetic motion analysis (Dankaerts and O'Sullivan, 2011). O'Sullivan et al. (2014) examined healthy control participants and two clinically-derived subgroups with CLBP, one deemed to be "mechanical" (n=17; localised, anatomically defined LBP; mechanical aggravating and easing factors deemed to be proportionate to the presentation, including imaging findings), and the other "non-mechanical" (n=19; widespread / ill-defined, constant, non-remitting LBP with high levels of pain responses to movement). There were between-group differences for pain intensity, disability, cold and pressure pain sensitivity, combined depression, anxiety and stress scores, and sleep disturbance. Participants in the non-mechanical pain group also had a higher STarT Back screening tool risk rating. However, relative contributions and interactions of a broader range of multiple dimensions considered in this CS requires objective analysis, independent of the potential bias of clinical judgment (Kent et al., 2010), in

a larger CLBP cohort. There is evidence, from a randomised controlled trial, suggesting management tailored towards findings from structured examination of multidimensional profiles in people with CLBP may offer moderate to large effects for pain and disability levels compared to manual therapy and exercise (Vibe Fersum et al., 2013). While this trial offers promising results further research is necessary to determine the relative contributions of multiple dimensions in different patient presentations, how these contributions are affected by the different components of the intervention, and whether this approach is generalizable to different treatment settings and populations (Vibe Fersum et al., 2013).

Another multidimensional subgrouping study has utilised unsupervised statistical analysis to derive subgroups. McCarthy et al. (2012) used non-hierarchical cluster analysis of 245 items from multiple dimensions in a sample of 295 people with LBP (+/- leg pain) of unspecified duration. Data was collected from each participant by two independent assessors, using a 245 item standardised clinical assessment (derived from a Delphi study (McCarthy et al., 2006)) containing a body chart, history of the condition, behaviour of symptoms, functional limitations, red flag checklist, psychosocial barriers to recovery, observations, active and passive movements, muscle and neurological assessment. A clinical reasoning section of the assessment asked the examining physiotherapist to consider whether an individual's presentation was dominated by biomedical or psychosocial factors, and whether their dominant pain mechanism was, "nociceptive pain, neurogenic pain, centrally sensitized pain…[or]…affective pain," (McCarthy et al., 2012) (p.94), based upon the CS described by Smart et al. (2010). Two distinct clusters were derived. The smaller cluster (16%) were characterised by painful responses to a greater number of provocative tests (particularly lumbar allodynia), and greater likelihood of clinicians judging that psychosocial factors and central sensitisation dominated their presentations. Their profile was characterised by high self-reported pain intensity, disability, anxiety, depression and fear-avoidance beliefs. However, this study had a number of limitations. Firstly, a number of indicator variables involved clinical reasoning, and 32% of the indicators used had previously only demonstrated

slight agreement (measured by kappa statistics), introducing potential judgemental bias to this subgrouping. To determine the optimal number of clusters within the sample from two, three, four and five cluster solutions cross-validation was undertaken by determining the outcomes of cluster analysis using the results from each assessor separately. However, the two assessors did not have consistently high agreement on all indicators. Therefore differences in the cluster solutions were potentially due to differences in values of the indicator variables. Following cross-validation the two cluster solution was selected as the optimal solution as it was the only solution with adequate correlation between two separate examiners. However, the four and five cluster models demonstrated a better fit to the data in one assessor's case. As previously discussed, the use of cluster analysis does not allow probability-based estimation of the optimal number of clusters. Also the choice of similarity measure can affect results, and no validity check in terms of use of different similarity measures was undertaken. Furthermore the use of such a large number of variables in relation to sample size is questionable. Lastly, health and lifestyle factors, which may facilitate prognostics (Shiri et al., 2010, Chou R, 2010, Hayden et al., 2009) and influence management strategies (Hartvigsen et al., 2013) were not considered, and this subgrouping offers little guidance for matching interventions, particularly to those people in the larger cluster with lower psychological scores.

Key Points:

- CS for CLBP have been developed based upon movement, tissue sensitivity, psychosocial factors.

- Few proposed CS for LBP are multidimensional in nature.

- The degree to which the reliability and validity of CS has been examined varies greatly.

- In the majority of studies treatments matched to specific subgroups have little effect compared to control treatments for the management of CLBP.

- Movement-based subgroups have been limited by their judgemental derivation and limited multidimensional profiling.

- Tissue sensitivity CS have been limited by their judgemental derivation, or examination of a relatively limited range of sensory tests, limited multidimensional profiling and small sample sizes.

- Psychologically-derived subgroups have been limited by inclusion of a limited range of psychological measures and limited multidimensional profiling.

- The multidimensional CS described by O'Sullivan et al. (2015) is comprehensive but requires further objective analysis independent of the potential bias of clinical judgment in a large CLBP cohort.

2.7   Prognostic Studies In Low Back Pain

As previously described, once subgroups of people with CLBP have been determined, steps may be taken to examine their validity. Whether the subgroups are prognostic of outcome in people with CLBP is one such step towards validation (Kamper et al., 2010, Kent et al., 2010). It is also important to determine whether subgroup membership in CLBP is prognostic because the disorder has a high burden (Vos et al., 2012), and tailoring management towards prognostic factors may facilitate improved treatment outcomes (Hill et al., 2011). However, with the majority of CLBP CS not considering multiple interacting dimensions associated with CLBP (Ford et al., 2007, Billis et al., 2007) they are unlikely to reflect the

multidimensional nature of CLBP, and therefore may not explain a large proportion of the variance in outcomes in prognostic models. This is consistent with most prognostic studies for LBP explaining less than 50% of the variance in their chosen outcome measure (Hayden et al., 2010).

Over 200 prognostic factors have been identified in people with LBP, including demographics, pain characteristics, physical examination findings, psychological, socio-environmental, health and work-related factors (Hayden et al., 2010, Hayden, 2007). Reviews of prognostic studies have revealed discrepancies in the variables entered into prognostic models, and conflicting and inconsistent evidence of the prognostic importance of individual factors (Hayden et al., 2010, Verkerk et al., 2012). While the literature as a whole has investigated multiple dimensions in prognostic studies, the dimensions considered in any one study are generally limited. Broader, multidimensional prognostic studies such as those by Campbell et al. (2013b) and Verkerk et al. (2013) have included demographic, pain characteristics, physical, psychological and occupational factors (32 and 23 variables respectively). These studies suggest that as well as examining whether any derived subgroups may be prognostic, prognostic models based upon broad multidimensional data are also required to possibly facilitate improved CLBP management.

Perceived recovery from CLBP is also multidimensional; relating to pain intensity, quality of life, disability and psychological health (Hush et al., 2009). However, few prognostic studies include greater than one outcome measure (Verkerk et al., 2012), and so are unlikely to reflect the multidimensional lived experience of a person with CLBP. Future prognostic studies in people with CLBP should therefore examine multiple outcome measures, possibly in line with the IMMPACT guidelines (Dworkin et al., 2005, Dworkin et al., 2008) for research into chronic pain which suggest measuring pain intensity, physical and emotional functioning, and patient perception of improvement.

Key points:

- Prognostic studies may be important for validating subgroups of people with CLBP, and may guide interventions.
- Prognostic studies should consider variables from multiple dimensions associated with CLBP.
- Prognostic studies should examine multiple outcomes including pain intensity, disability and perceived improvement.

2.8   Summary

There is a vast body of literature describing multiple dimensions that are associated with CLBP, and prognostic of poor outcomes in the disorder. CLBP is an emergent disorder involving complex interactions between peripheral and central nervous systems, immune and endocrine systems and multiple differing dimensions. However, despite contemporary understanding of CLBP as a complex multidimensional disorder, few cross-sectional or prognostic studies have collected data on a broad range of multidimensional data within the same large CLBP cohort. Determination of subgroups of people with CLBP, with differing multidimensional profiles, is suggested to be a research priority. To facilitate translation into practice, subgroups should ideally be statistically-derived from valid and reliable, clinical measures. Many different CS and subgrouping studies have been described. However, the majority of CS for people with LBP are not multidimensional in nature, and have not involved statistical subgroup derivation. Also, rather than focussing on people with axial CLBP many CS and subgrouping studies have included people with low back-related leg pain, possibly complicating their interpretation. Any subsequent profiling of derived subgroups, or prognostic studies involving those subgroups, have also commonly involved only a limited exploration of the multiple dimensions associated with CLBP. When considering the capacity of different subgroups (even those based upon prognostic factors) to influence treatment outcomes, results to date have been modest at best. This may be due to a lack of consideration, by most CS, of the interacting peripheral and central nociceptive

processes and multiple dimensions associated with the disorder, leading to inadequate consideration of possible pain mechanisms underlying specific presentations, and subsequent inadequate tailoring of interventions.

Overall, review of the literature suggests that an ideal approach to subgrouping in people with CLBP would consist of collecting a broad range of multidimensional data with underlying theoretical or empirical support for its relevance to CLBP, using valid and reliable measures, in a large and widely representative CLBP cohort. Subsequently statistical methods, particularly LCA, should be used to determine the existence and number of subgroups within the dataset (Kent et al., 2010). Validation of derived subgroups may then take place on numerous levels including examination of multidimensional profiles, and determination of whether derived subgroups are prognostic of outcome.

2.9   Aims

Therefore the aims of this thesis are as follows:

1) To examine four individual clinical cases of people with axial CLBP with contrasting multidimensional profiles determined by data from valid and reliable clinical measures, and to consider the complexity of these individual presentations in relation to the limitations of existing CLBP CS.
2) To use statistical subgrouping techniques using standardised clinically-applicable measures from multiple dimensions to explore the existence of subgroups within a large cohort with axial CLBP.
3) To profile different subgroups on data from multiple dimensions associated with CLBP, to facilitate postulation of the clinical implications and pain mechanisms related to those different profiles.
4) To determine whether multidimensional baseline data, including subgroup membership, are prognostic of outcome at one year follow-up.

2.10   Significance Of This Research

No studies to date have collected a broad range of clinically-measurable multidimensional data in a large cohort of people with axial CLBP in order to

determine the existence of statistically-derived subgroups. This body of research will be the most extensive exploration of patient profiling in a CLBP cohort, drawing together factors utilised independently in previous studies, and adding previously unconsidered factors. The research will concentrate upon axial CLBP, where previous studies have included low back-related leg pain. This research will facilitate examination of subgrouping and multidimensional profiles allowing postulation regarding their clinical implications and underlying pain mechanisms in people with axial CLBP. The prognostic component of this study will be the broadest prognostic study in CLBP to date, examining which variables and / or subgroups across all dimensions relevant to CLBP are prognostic for different aspects of improvement. Overall this research will increase understanding regarding the complexity of CLBP and postulation of the underlying pain mechanisms. In future this may facilitate opportunities for more targeted interventions in clinical practice which may lead to improved treatment outcomes.

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Chapter Three – Study One

Multidimensional Pain Profiles In Four Cases Of Chronic Non-Specific Axial Low Back Pain: An Examination Of The Limitations Of Contemporary Classification Systems.

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Original article

Multidimensional pain profiles in four cases of chronic non-specific axial low back pain: An examination of the limitations of contemporary classification systems

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ABSTRACT

Classifying patients with chronic low back pain (CLBP) may facilitate targeted treatment, and optimise outcomes. Most classification systems (CS) do not consider multiple, interacting dimensions (for example, psychological or movement dimensions) involved in the lived experience of people with CLBP. A framework incorporating these multiple dimensions, and acknowledging individual variability, could provide a pathway to better assess and treat people with CLBP. Here we explored this proposition, presenting four cases (P1–4), profiling their clinical presentations within a multidimensional framework.

P1's profile was characterised by localised lumbar sensitisation consistent with dominant peripheral nociception. P2 presented a 'mixed' profile characterised by localised lumbar hypersensitivity, combined with factors suggestive of centrally-mediated facilitation of nociception. P3's profile suggested widespread hypersensitivity possibly reflective of dominant centrally-mediated pain mechanisms. P4's profile was characterised by dominant psychosocial factors and comorbidities.

These cases are discussed in relation to contemporary CLBP CS, highlighting the complexity of these disorders and limitations of CS for people with CLBP and their treating health professionals. This paper reinforces the need for a consensus CS for people with CLBP that is flexible, has clinical utility and considers all relevant dimensions.

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1. Introduction

Treatment outcomes for people with chronic low back pain (CLBP) are moderate at best (Balagué and Dudler, 2011). Factors underpinning modest outcomes include assumed sample homogeneity (Hush and Marcuzzi, 2012) and lack of consideration of the complex biopsychosocial nature of CLBP, potentially contributing to a lack of treatment specificity (Rusu et al., 2012). Classifying patients with low back pain (LBP) using multiple dimensions contributing to pain persistence may facilitate targeted treatment and offer better outcomes than unmatched treatments (Brennan et al., 2006). However, only one such study has included people with CLBP (Long et al., 2004), limiting generalisability to this population.

While it is recognised that CLBP is a multidimensional, biopsychosocial disorder (Waddell, 2004), only 10% of classification systems (CS) incorporate a biopsychosocial framework (Billis et al., 2007). Research into pain mechanisms (Woolf, 2010) underlying CLBP is limited, possibly because specific mechanisms are difficult to correlate with clinical presentations (Baron et al., 2012). Most CS do not consider the multiple, interacting dimensions necessary for a comprehensive classification of CLBP (Ford et al., 2007; Rusu et al., 2012), despite such consideration being likely required to deliver improved outcomes (Foster et al., 2011). Dimensions for consideration include those associated with greater pain and disability in CLBP, those prognostic of poor outcomes or predictive of chronicity, and those potentially indicative of pain mechanisms underlying CLBP (pain characteristics, psychophysical, psychological, social, comorbidities, lifestyle, movement) (Woolf and Mannion, 1999; Hayden et al., 2009, 2010; Scholz et al., 2009; Baron et al., 2012; Giamberardino and Jensen, 2012; Karayannis et al., 2012).

Early LBP CS focused on pathoanatomy, with attempts to determine a structure contributing to peripheral nociceptive input, using anaesthetic diagnostic blocks (Laslett et al., 2005). However, nociceptive "sources" could only be determined in approximately half of subjects with CLBP (Laslett et al., 2005). However this system is limited by poor correlation of pathoanatomy with symptoms in people with CLBP (Kjaer et al., 2005) and the limited capacity of this

Table 1
Definitions of pain types and mechanisms.

Pain type	Definition	Pain mechanisms	Example	Discussion
Nociceptive	Pain "from actual or threatened damage to non-neural tissue … due to … activation of nociceptors" (IASP Taxonomy Working Group, 2011)	In response to noxious stimuli, C or Aδ afferents stimulate central nervous system nociceptive pathways (Woolf, 2004, 2011; Costigan et al., 2009)	Acts as an early warning to provoke appropriate behavioural responses/limit damage e.g. lifting hot objects provokes release	Some consider nociceptive pain non-pathological (Costigan et al., 2009; Woolf, 2010), separate from inflammatory pain. IASP states nociceptive pain is "to contrast with neuropathic pain" (IASP Taxonomy Working Group, 2011). It is commonly used in this manner (Bennett et al., 2006; Smart et al., 2010a). IASP states nociceptive describes "pain occurring with a normally functioning somatosensory nervous system" contrasting with "abnormal function seen in neuropathic pain." (IASP Taxonomy Working Group, 2011) It is debatable whether mechanisms in inflammatory pain constitute normal, baseline function (Costigan et al., 2009; Woolf, 2010).
Inflammatory	Pain due to tissue injury and subsequent inflammation (Costigan et al., 2009; Woolf, 2010)	Innocuous stimulation of low-threshold afferents can produce pain (allodynia). Responses to noxious stimuli are magnified (hyperalgesia). Receptive fields expand. Spontaneous and evoked pain (Costigan et al., 2009; Woolf, 2010). Underlying allodynia and hyperalgesia is chemically-mediated peripheral nociceptor sensitisation and CS (Costigan et al., 2009; Woolf, 2010; IASP Taxonomy Working Group, 2011)	Leads to hypersensitivity, a biologic function favouring healing e.g. pain causing reduced weight bearing after an ankle sprain	See above
Neuropathic	"Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (Treede et al., 2008, p. 1631). Diagnostic criteria include: pain in areas consistent with nervous system lesions; clinical suspicion of such lesions; temporal links between lesions and pain; correlating demonstrable signs and diagnostic tests (Treede et al., 2008)	For review of pain mechanisms in neuropathic pain see Costigan et al. (2009) Characterised by spontaneous pain, and pain evoked by noxious and innocuous stimuli (Woolf, 2010)	Lumbar radiculopathy with demonstrable motor weakness and associated findings on imaging	Where impossible to prove a lesion, conditions should not be deemed neuropathic (Treede et al., 2008).
Functional	In functional pain there is no known source of noxious stimuli and minimal evidence of inflammation. Abnormal central nervous system processing is considered the disease itself (Costigan et al., 2009).	Characterised by spontaneous pain, and pain evoked by noxious and innocuous stimuli (Woolf, 2010)	CLBP, fibromyalgia	Inflammatory or neuropathic pain may be involved in the initiation of pain hypersensitivity in this disorder, however it is unclear what maintains functional pain (Costigan et al., 2009)
Central sensitisation	"Amplification of neural signalling within the central nervous system that elicits pain hypersensitivity" (Woolf, 2011) (p. S5)	Involves peripherally triggered, activity-dependent, predominantly heterosynaptic plasticity causing long-lasting spinal cord hyperexcitability (Latremoliere and Woolf, 2009; Woolf, 2011)	Not applicable	Central sensitisation is common to inflammatory, neuropathic and functional pain. Typically central sensitisation normalises as peripheral lesions resolve; however it may become aberrant, persisting beyond initiating stimuli (Woolf and Salter, 2000; Woolf, 2004). Central sensistisation may be involved in, but not the sole mechanism for WH (Latremoliere and Woolf, 2009). These terms should not synonymously but commonly are (Yunus, 2008; Nijs et al., 2010; Smart et al., 2010a; Kumar and Saha, 2011; Smart et al., 2012). Also not synonymous with "'psychosocial' or 'chronic'" (Zusman, 2008, p. 59).

International Association for the Study of Pain (IASP); widespread hypersensitivity (WH); chronic low back pain (CLBP).

approach to offer guidance for management as it does not consider contributors to pain persistence (O'Sullivan, 2005). Because of these limitations CS evolved based upon pain responses to movement and tissue loading, e.g. Delitto et al. (1995). Many such CS assume dominant peripheral nociception, and are unidimensional in their approach. Greater understanding of psychosocial contributions to pain and disability have resulted in CS that target prognostic risk factors (Hill et al., 2008), although not consistently addressing broader multidimensional contributors to CLBP.

Parallel to development of CS for LBP has been a quest to determine neurophysiological mechanisms underlying pain (Woolf and Mannion, 1999) (Table 1). Initial work acknowledged nociceptive aspects of CLBP but expanded to consider neuropathic and central nervous system mechanisms underlying persistent nociception. The CS proposed by Smart et al. (2011) categorises subjects' pain as 'nociceptive', 'peripheral neuropathic' or 'central sensitisation'. However, this system has not been validated against quantitative sensory testing, and while it considers the psychological and social dimensions it fails to consider the lifestyle and movement dimensions.

A framework incorporating multiple dimensions, allowing individual variability and enabling clinicians to recognise specific 'clusters' could provide a pathway to better inform clinical assessment and management (O'Sullivan, 2012b). We explored this proposition, presenting four cases within such a framework.

Four subjects with diverse multidimensional axial CLBP presentations (>60%LBP:40% leg pain (Wai et al., 2009)) were selected from a larger study (Curtin University Human Research Ethics Committee Approval HR112/2012). Dominant leg pain was excluded due to the specific nature of a diagnosis of radiculopathy. Subjects completed questionnaires to ascertain disability (Roland and Morris, 1983), pain levels (Scholz et al., 2009), psychosocial (Waddell et al., 1993; Lovibond and Lovibond, 1995; Sullivan et al., 1995; Brown and Ryan, 2003; Nicholas, 2007; Hill et al., 2008; Fish et al., 2010) and lifestyle (Buysse et al., 1989; Linton and Boersma, 2003; Hasenbring et al., 2009; Van Weel et al., 2012) profiles (Table 2, Fig. 1, Appendix 1). Laboratory testing included the Standardised Evaluation of Pain (Scholz et al., 2009), a bedside sensory testing protocol performed at the lumbar spine. Quantitative sensory testing (pressure pain threshold, cold pain threshold, heat pain threshold) at the wrist and lumbar spine were undertaken to discriminate localised versus widespread hypersensitivity

(Table 3, Appendix 2). Twenty forward and backward bending movements were video recorded for analysis of movement patterns (O'Sullivan, 2005), behavioural responses to pain (e.g. bracing the hand on the knee, grimacing) (Sullivan et al., 2006), perceived summation of pain (change in pain rating on an 11-point numeric rating scale) during repeated movements (Sullivan et al., 2009) and identification of directional influences of movement upon pain (Table 4, Appendix 3).

1.1. Patient one (P1)

P1 was a 42 year old female with insidious onset LBP 20 years ago. She reported symptoms aggravated by bending, turning in bed and moving from sitting to standing. She believed her symptoms were due to "compacted discs". P1 had no comorbid medically-diagnosed disorders.

P1 demonstrated reduced lumbar region heat pain threshold, with normal heat pain threshold at the wrist. She had no abnormalities with Standardised Evaluation of Pain testing.

P1 had an active extension movement pattern (O'Sullivan, 2005), maintaining a lordosis throughout forward bending. Reported summation of pain during repeated movements suggested a directional pain provocation pattern (McKenzie and May, 2003): pain increased from 6/10 to 9/10 during forward bending, but decreased from 9/10 to 6/10 during backward bending. Behavioural responses to pain were only observed during forward bending.

P1 demonstrated elevated catastrophising (Sullivan et al., 1995) and was rated medium-risk using the STarTBack Screening Tool (Hill et al., 2008).

1.2. Patient two (P2)

P2 was a 62 year old female with insidious onset LBP 10 years ago. She reported symptoms aggravated by moving from sitting to standing, prolonged standing, turning in bed, lifting, psychological stress and cold temperatures. She perceived her symptoms were due to psychological stress and uneven weight-bearing secondary to knee pain. P2 had 12 comorbidities including fibromyalgia, irritable bowel syndrome and chronic fatigue syndrome; all classified as functional pain disorders (Mayer and Bushnell, 2009).

Table 2
Demographic and background profiles.

	Comparative data	Case 1	Case 2	Case 3	Case 4
Baseline NRS	CLBP: 6.2 (Nicholas et al., 2008)	6	8	5	3
RMDQ (Roland and Morris, 1983)	CLBP: 13.5 (Nicholas et al., 2008)	6	8	9	19
Body chart squares filled (see Fig. 1)	Subjects sick-listed for >6 weeks due to LBP: 12.8 (Öhlund et al., 1996).	8	4	17	20
Aggravated by (formulated from the StEP (Scholz et al., 2009) and RMDQ (Roland and Morris, 1983))		Too much activity, rest, bending, putting on socks, bending, sit to stand, turn in bed	Too much activity, stress, cold, sit to stand, stand, turn in bed, lifting, putting on socks	Too much activity, walking, standing, lifting, stress, anger, low mood, poor sleep	Too much activity, rest, walking, stairs, standing, lifting, stress, cold, low mood, anger, poor sleep
Paroxysmal pain (Bennett, 2001)		No	No	Yes	Yes
Comorbidities		1	12 (Including fibromyalgia, depression, irritable bowel syndrome, chronic fatigue syndrome, incontinence)	16 (Including irritable bowel syndrome, temporomandibular joint pain, allergy, palpitations)	8 (Including anxiety, depression)

All comparative data are mean values unless otherwise stated. Chronic low back pain (CLBP); low back pain (LBP); numeric rating scale (NRS); Roland Morris Disability Questionnaire (RMDQ); Standardised Evaluation of Pain (StEP).

Patient 1   Patient 2

Patient 3   Patient 4
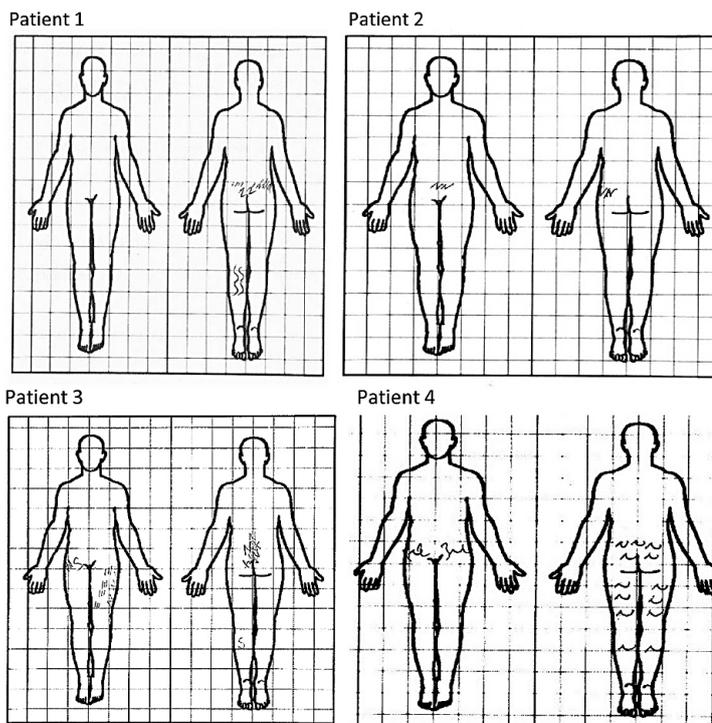
Fig. 1. Body charts.

Quantitative sensory testing demonstrated altered pressure, heat and cold pain thresholds consistent with hypersensitivity and a painful response to repeated nylon monofilament stimulation, all localised to the lumbar spine.

P2 had an active extension movement pattern. Pain increased from 4/10 to 7/10 during repeated forward bending, and slightly increased (6/10 to 7/10) during backward bending. Behavioural responses to pain were observed only during forward bending.

P2 scored highly on the Fear-Avoidance Beliefs Questionnaire (Waddell et al., 1993) indicating movement-related fear of pain/(re)

injury (Crombez et al., 1999); and for psychological stress in the past year (Littman et al., 2006). P2 was rated medium-risk using the STarTBack Screening Tool.

1.3. Patient three (P3)

P3 was a 55 year old female. Symptoms began due to lifting 17 months earlier. She reported symptoms aggravated by prolonged standing and walking, lifting, poor sleep, psychological stress, low mood and anger. This was a compensable case with three months

Table 3
Overview of differentiating factors taken from multidimensional profiles.

	Case 1	Case 2	Case 3	Case 4
PPT (kPa)		L+	W+	
			L+	
HPT (°C)	L+	L+	W+	
			L+	
CPT (°C)		L+	L+	
Change in pain rating (NRS)	F+	F+	F+	
with repeated movements	B−	Directional	B+	
	Directional		Multidirectional	
Other		Increasing pain with repeated nylon monofilament stimulation Psychosocial+	Allodynia Pinprick hyperalgesia Increasing pain with repeated nylon monofilament stimulation Psychosocial++	Increasing pain with repeated nylon monofilament stimulation Psychosocial++

Wrist (W); lumbar spine (L); forward bending task (F); backwards bending task (B); pressure pain threshold (PPT); kilopascals (kPa); heat pain threshold (HPT); cold pain threshold (CPT); degrees centigrade (°C); elevated scores (+); reduced scores (−); numeric rating scale (NRS).

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Table 4
Published data from studies undertaking quantitative sensory testing in subjects with low back pain.

Reference	Patient sample	Lumbar QST	Distant QST
(Lewis et al., 2010)	LBP ± leg pain; variable chronicity ($n = 15$)	Higher CPT (i.e. pain threshold at warmer temperatures).	Higher CPT (deltoid)
(Giesbrecht and Battie, 2005)	CLBP ± leg pain; >6 months duration; >4/10 on NRS; recruited from primary care ($n = 30$)	Lower PPT (i.e. pain threshold at lower pressures)	Lower PPT (C5 paraspinal muscles, wrist extensor muscles, calf muscle, middle phalanx of second finger)
(O'Neill et al., 2011)	LBP > 30 days LBP in past year; recruited from general population ($n = 57$)	Lower PPT	Lower PPT (tibialis anterior, brachioradialis)
(Blumenstiel et al., 2011)	LBP > 45 days last 3 months; recruited from general population ($n = 23$)	Lower PPT; higher VPT (i.e. vibration threshold at greater amplitudes)	
(Puta et al., 2012)	LBP > 6 months duration, no spinal disorders or disc pathology on MRI, females ($n = 14$)	Pinprick hyperalgesia (i.e. greater pain intensity reported on pinprick stimulation)	Pinprick hyperalgesia (dorsal and palmar hand)
(Neziri et al., 2012)	LBP > 6 months duration ($n = 40$)	Lower PPT, higher CPT and lower HPT (i.e. pain threshold at lower temperatures)	Lower PPT (second toe and suprascapular), higher CPT (lateral leg and suprascapular)
(Farasyn and Meeusen, 2005)	LBP ± leg pain; >3 weeks/<12 weeks duration; recruited from physiotherapy centre ($n = 87$)	Lower PPT	PPT equal to control subjects (triceps brachii)
(Imamura et al., 2013)	Unilateral CLBP > 12 weeks duration; recruited from hospital and general population ($n = 20$)	Lower PPT	Lower PPT (iliopsoas, L1-S2 dermatomes both legs; except contralateral iliopsoas and S1 dermatome)
(Hübscher et al., in press)	Acute LBP ± leg pain; <6 weeks duration; or CLBP ± leg pain; >3 months duration; recruited from hospital physiotherapy departments and general population (acute LBP $n = 20$; CLBP $n = 30$)	Acute LBP: CPT, HPT, cold pain tolerance, heat pain tolerance, temporal summation of repeated heat stimuli all equal to controls CLBP: Higher CPT. HPT, cold pain tolerance, heat pain tolerance, temporal summation of repeated heat stimuli all equal to controls	Acute LBP: CPT, HPT, cold pain tolerance, heat pain tolerance, temporal summation of repeated heat stimuli all equal to controls (volar forearm) CLBP: Higher CPT, lower cold pain tolerance. HPT, heat pain tolerance, temporal summation of repeated heat stimuli all equal to controls (volar forearm)

(LBP) low back pain; (CLBP) chronic low back pain; (NRS) numeric rating scale; (CPT) cold pain threshold; (HPT) heat pain threshold; (PPT) pressure pain threshold; (VPT) vibration perception threshold. (Note: frank radiculopathy, and studies with no lumbar test site excluded.)

off work during the last year because of CLBP. P3 believed her symptoms were due to repeated lifting and poor "core strength". P3 had 16 comorbidities including irritable bowel syndrome and temporomandibular pain.

Quantitative sensory testing demonstrated altered pressure, heat and cold pain thresholds at the lumbar spine, and pressure and heat pain thresholds at the wrist consistent with widespread hypersensitivity. Some Standardised Evaluation of Pain testing was provocative (allodynia upon nylon monofilament contact, increasing pain with repeated monofilament stimulation, pinprick hyperalgesia).

P3's movement pattern was multi-directional. Repeated forward bending increased perceived pain from 5/10 to 7/10. Symptoms further increased to 8/10 with backwards movements. Behavioural responses to pain were observed in both directions.

The Depression Anxiety Stress Scale (Lovibond and Lovibond, 1995) revealed moderate depressive and anxiety symptoms, and elevated psychological stress in the past year. P3 scored highly for fear-avoidance. Scores for the Chronic Pain Acceptance Questionnaire (Fish et al., 2010) and Pain Self-Efficacy Questionnaire (Nicholas, 2007) were low, indicating poor ability to undertake activities despite pain and ongoing attempts to avoid or control pain (McCracken et al., 2004; Foster et al., 2010). P3 was rated as high-risk by the STarTBack Screening Tool.

1.4. Patient four (P4)

P4 was a 33 year old male. Symptoms began due to lifting eight years ago and his pain was aggravated by prolonged walking and standing, moving from sitting to standing, bending, lifting, poor

sleep, stress, low mood, anger, and cold temperatures. P4 ceased employment (electrical technician) six months previously because of CLBP. He believed his symptoms were "... initially mechanical, but .... now more complex". P4 had eight comorbidities.

P4 had normal quantitative sensory testing at both sites, and no abnormalities with Standardised Evaluation of Pain testing.

P4 demonstrated normal movement patterns, no behavioural responses to pain and no symptom change with repeated movement.

P4 had moderate depressive and anxiety symptoms, elevated psychological stress in the past year, elevated fear-avoidance, low acceptance and low self-efficacy. P4 was rated as medium-risk using the STarTBack Screening Tool.

2. Interpretation of cases in relation to classification systems

The variability of these four profiles across multiple dimensions highlights the need for a framework that is flexible and acknowledges clinical heterogeneity. However, it is also acknowledged that these four cases were purposefully selected to highlight limitations within contemporary CS for CLBP, and as such it may not be possible to draw inferences to the wider CLBP population. P1's profile was characterised by dominant localised heat hypersensitivity associated with a directional maladaptive (active extension) movement pattern and minimal psychosocial factors. P2 presented a 'mixed' profile characterised by localised lumbar pressure, heat and cold hypersensitivity, and a dominant directional pain response (active extension pattern) with associated behavioural responses to pain. This presentation was combined with factors

suggestive of centrally-mediated nociceptive facilitation (painful response to repeated monofilament stimulation, psychosocial factors and comorbidities (Mayer and Bushnell, 2009; Rhudy, 2009; Joergensen et al., 2013)). P3's profile demonstrated widespread hypersensitivity, allodynia, and thermal and mechanical hyperalgesia. P3 also exhibited numerous psychosocial factors and comorbidities possibly associated with centrally-mediated pain mechanisms (Mayer and Bushnell, 2009; Rhudy, 2009), and maladaptive movement patterns with associated behavioural responses to pain and perceived pain summation with forward and backward bending. P4's profile was characterised by normal quantitative sensory testing and movement profiles. However, he also had multiple psychosocial factors and comorbidities that are associated with significant CLBP and disability.

Rather than fitting clear subgroups, these cases have differing multidimensional profiles, highlighting the limitations of current CS for CLBP and the need for a multidimensional framework that attributes different weighting to the various dimensions in order to better inform clinical management. We interpret the cases both within extant CS and a multidimensional biopsychosocial framework.

2.1. Peripheral nociceptive generator-based classification

Traditional diagnoses for CLBP were based upon identification of pathoanatomy. However, "abnormal" findings are common in asymptomatic subjects (Jensen et al., 1994) and correlate poorly with LBP and disability (Kjaer et al., 2005). Diagnostic anaesthetic blocks only determine a nociceptive "source" in approximately half of subjects with CLBP and agreement between clinical examination and diagnostic injections is poor (Laslett et al., 2005). The lack of evidence that CLBP is due to persistent peripheral sensitisation of spinal structures may explain poor outcomes for interventions based upon this premise.

Both P1 and P2 demonstrated localised lumbar quantitative sensory testing findings suggesting some degree of local structural sensitisation. In contrast, P3 demonstrated widespread hypersensitivity rather than a focal nociceptive "source". P4 had no findings to suggest ongoing peripheral nociception (Woolf, 2010). These cases highlight the variable nature of tissue sensitivity.

2.2. Movement-based classification

These CS consider movement-induced tissue loading a reason for ongoing peripherally-mediated nociception. McKenzie's CS of mechanical diagnosis (McKenzie and May, 2003) advocates assessment of pain responses to lumbar mechanical loading, including repeated movements. Examination determines whether a directional preference (a particular direction of repeated movement improves or aggravates symptoms) or 'centralisation' response (spinal loading causes progressive, distal-to-proximal reduction in pain) exists. Patients are classified as "mechanical responders" or "non-responders" (McKenzie and May, 2003, p. 138). In this context, P1 showed increased pain with forward bending and decreased pain with backward bending, consistent with the premise of this CS. However, P2 and P3 did not demonstrate clear directional preferences with pain provocation during forward and backward bending, and P4 demonstrated an absence of pain with repeated movement. This highlights the difficulty of classifying these cases using this CS, consistent with a systematic review suggesting 'centralisation' only occurs in 52% of subjects with CLBP (Aina et al., 2004).

The Movement Impairment Syndrome CS (Sahrmann, 2002) is based upon the premise that abnormal movement results in tissue damage and pain. Presentations are classified in terms of the direction of movement into which the patient is "susceptible"

(Sahrmann, 2002, p. 4). Treatments aim to 'normalise' movement to reduce tissue strain. A recent randomised controlled trial compared treatment matched to this CS with non-specific treatment. Both groups achieved improvement in disability levels, but no between group comparisons were reported (Van Dillen et al., 2013). Applying this CS, P1 and P2 could be classified as extension movement impairments (Sahrmann, 2002), however P3 and P4 would both be difficult to classify. P3's symptoms were exacerbated by both directions of movement suggestive of multi-directional sensitivity, not considered in the CS. While this could be interpreted as causing peripherally-mediated stimulation of nociceptors in tissues loaded in both directions, in P3 allodynia, hyperalgesia and increasing pain with repeated monofilament stimulation suggest pain mechanisms other than peripherally-mediated nociception. P4's symptoms were not influenced by movement. Neurophysiological, psychosocial factors and comorbidities are not considered in this CS (Karayannis et al., 2012) limiting its utility in directing multidimensional management strategies in P2–4.

2.3. Treatment-based classification

Delitto et al. (1995) advocate examination of pain responses to movements to determine classifications indicating one of four interventions: mobilisation, traction, repeated movement exercises or stabilisation exercises (Fritz and George, 2000). While treatments matched to this CS in acute/sub-acute LBP offer better results than unmatched treatments (Brennan et al., 2006), in CLBP this CS produced results only equivalent to guideline-based care (Apeldoorn et al., 2012). To facilitate management of more complex CLBP this CS evolved to consider the psychosocial dimension, primarily emphasising fear-avoidance (Karayannis et al., 2012). Isolating one psychosocial factor may mean people with CLBP are excluded from interventions or incorrectly grouped together (Karayannis et al., 2012). This approach is unlikely to be adequate in directing management of patients with more complex multidimensional profiles.

2.4. Psychosocial classification

Other CS focus on identification of psychosocial factors prognostic of poor outcome in CLBP. The STarTBack Screening Tool is a stratification tool for LBP in primary care settings, using risk profiling based upon pain characteristics, functional impairment and psychosocial factors (Hill et al., 2008). When classifying these cases according to the STarTBack Screening Tool scores P1, P2 and P4 were classified as medium-risk indicating psychologically-informed physiotherapy would not be advocated, whereas for P3 (high-risk), it would (Hay et al., 2008). However, based upon examination of their multidimensional profiles, psychologically-integrated management would arguably be appropriate for all four cases, and particularly relevant for P4. While there is strong evidence to support the use of this tool to better target care (Hill et al., 2011), the lack of consideration of movement and quantitative sensory testing in this CS may limit the ability to tailor treatment to individual presentations. This highlights the potential to integrate the STarTBack Screening Tool with other CS in order to enhance targeted care for CLBP.

2.5. Neurophysiological classification

Smart et al. (2010a) derived a checklist to discriminate three groups (Smart et al., 2010b) (nociceptive, peripheral neuropathic, central sensitisation) based upon hypothesised pain mechanisms. The nociceptive group were defined by responses to physical tests or aggravating/easing factors proportionate to the presentation. The peripheral neuropathic group were described as having a

history of nerve injury, positive neural provocation testing and dermatomal presentations. The central sensitisation group presented with disproportionate pain responses to movement, widespread hypersensitivity, and significant psychosocial factors. While these groupings suggest underlying mechanisms, clinical manifestations may involve multiple interacting mechanisms (Woolf and Mannion, 1999) thus compromising this CS. P1 would fit the nociceptive classification, and P2 and P3 would fit the central sensitisation classification based upon psychosocial factors and pain characteristics, despite differences in movement and quantitative sensory testing profiles. P4 would not fit this CS.

The Standardised Evaluation of Pain (Scholz et al., 2009) protocol assists postulation of pain mechanisms underlying CLBP and helps differentiate two groups with axial LBP. One group had paraesthesia, burning pain and a painful response to repeated monofilament stimulation (all present in P3) while the other did not (Scholz et al., 2009). Allodynia on monofilament contact and pinprick hyperalgesia would differentiate P3 from the other cases. Non-mechanical aggravating factors determined by the Standardised Evaluation of Pain and painful responses to repeated monofilament stimulation would assist differentiation of cases with a dominant centrally-mediated component (P2–4) from P1, however they would classify P2 and P4 in the same subgroup despite differing psychosocial and movement profiles.

Comprehensive laboratory quantitative sensory testing has been used to explore nociceptive processes (Baron et al., 2012). Quantitative sensory testing has been used to discriminate subgroups in low back-related leg pain (Schäfer, 2009) but to our knowledge not axial CLBP. Quantitative sensory testing demonstrated evidence of localised lumbar hypersensitivity in P1 and P2, with P2 hypersensitive to a greater number of stimuli. In isolation this may lead clinicians to conclude both cases presented with dominant peripherally-mediated nociception, and implement identical management. However, it is likely that consideration of psychosocial factors and comorbidities in P2's presentation would facilitate more effective management. P3 presented with widespread hypersensitivity to multiple sensory stimuli. Management based purely on quantitative sensory testing would be sub-optimal without knowledge of relevant psychosocial, movement and comorbidity factors. P4 presented with normal quantitative sensory testing, offering no guidance for management if solely relying on this assessment, yet P4 was significantly disabled. P4's profile is not documented in the CLBP quantitative sensory testing literature (Table 4) and may be "washed out" if occurring less frequently than the hypersensitivity demonstrated in most quantitative sensory testing studies.

2.6. Comorbidities

A recent paper calls for a stepped approach to managing CLBP in the presence of comorbidities (Hartvigsen et al., 2013). Despite evidence for the role of comorbidities in underlying mechanisms, prognosis and management of CLBP (Giamberardino and Jensen, 2012), consideration of comorbidities is not made by the aforementioned CS. P2–4 presented with comorbidities considered to reflect common underlying central nervous system-mediated mechanisms (Mayer and Bushnell, 2009), and may guide management to encompass broader aspects of a person's health.

2.7. Biopsychosocial classification

A flexible, biopsychosocial CS may allow profiling across multiple relevant dimensions, to facilitate targeted care based on the dominant factors present in individual profiles. For example,

in P1, the dominance of localised, likely peripherally-mediated, symptoms associated with maladaptive movement patterns and behaviours associated with pain, may suggest intervention should be directed towards normalisation of pain provocative movements and behaviours while addressing her pathoanatomical beliefs and catastrophic thoughts. P2's movement profile is very similar to that of P1. However, where P1's profile displays minimal associated psychosocial factors, P2 displays factors suggestive of centrally-mediated processes favouring nociceptive facilitation including numerous psychosocial factors and comorbidities (Mayer and Bushnell, 2009; Rhudy, 2009; Joergensen et al., 2013). Therefore in the case of P2, intervention may target the negative beliefs, fear and distress, by providing a biopsychosocial understanding of pain, body mindfulness, normalisation of movement and pain behaviours, physical activation and building self-efficacy. Comparatively, in the case of P3 the dominance of widespread hypersensitivity, combined with a multidirectional maladaptive movement pattern and pain behaviours, a more complex psychosocial profile and greater number of comorbidities, may direct care towards a multi-disciplinary management approach. This may include: pharmacological management to reduce sensitisation, physiotherapy to provide a biopsychosocial understanding of pain, relaxation strategies, normalising movement and pain behaviours, and psychological management to manage anxiety and depression. In P4, the dominance of psychosocial factors in this profile would direct care towards a biopsychosocial understanding of pain, targeting fear and distress reduction strategies integrated with functional activation and reduction in body hypervigilance. The CS described by O'Sullivan (O'Sullivan, 2012a; O'Sullivan et al., in press) adopts a flexible biopsychosocial approach (Karayannis et al., 2012). One randomised trial for subjects with CLBP demonstrated superior long term clinical outcomes for this approach compared to physiotherapist-lead manual therapy and exercise (Vibe Fersum et al., 2013). However, this trial needs replication and the relative contributions and interactions of psychosocial, lifestyle and quantitative sensory testing profiles within this CS require further objective analysis independent of the potential bias of clinical judgement.

3. Conclusion

These four cases were purposefully selected to highlight the limitations of contemporary CS for CLBP pertaining to each case. As such it is not possible to draw inferences to the wider population of people with CLBP. However, these cases do highlight the relative variations in the multiple dimensions associated with CLBP disorders and the potential limitations of contemporary CS to direct targeted care. There is growing support for a consensus CS for people with CLBP that is flexible, adaptive and considers all relevant dimensions (pain characteristics, psychophysical, psychological, social, lifestyle, movement, comorbidities). Further development and refinement of such a CS to ensure clinical utility and to enhance person-centred, multidimensional management of CLBP is needed.

Appendix 1. Psychosocial profiles

	Comparative data	Case 1	Case 2	Case 3	Case 4
PSQI (Buysse et al., 1989)	HC: 4.7 (Buysse et al., 1989); CLBP: 10.4–13 (Marin et al., 2006; Marty et al., 2008; O'Brien et al., 2010), >5 represents sleep disturbance (Buysse et al., 1989)	10	6	16	12
Waking due to pain		On movement	On movement	On movement, at rest	On movement, at rest
Depression, anxiety, stress (DASS) (Lovibond and Lovibond, 1995)	HC: 1–5.7, 2–3.8, 5–9.5 (Henry and Crawford, 2005; Mitchell et al., 2009); CLBP: 13.3, 7.7, 14.9 (Nicholas et al., 2008).	0, 4, 2	8, 2, 6	16, 10, 20	16, 10, 9
Stress past year (life events/ hassles) (Littman et al., 2006)	HC: 3.5/6 (Littman et al., 2006)	2	5	4	5
FABQ-PA (Waddell et al., 1993)	CLBP: 12–13.6 (Meyer et al., 2009; George et al., 2010)	12	19	18	21
FABQ-W	CLBP: 13.9–19.4 (Meyer et al., 2009; George et al., 2010)	17	0	40	28
PCS (Sullivan et al., 1995)	HC: 9.5–16.5 (Van Damme et al., 2002; Mitchell et al., 2009; de Boer et al., 2012) CLBP: 15–22 (Van Damme et al., 2002; Meyer et al., 2009; George et al., 2010) CP: 23.7 (de Boer et al., 2012)	20	38	21	31
CPAQ-8 (pain willingness, activity engagement) (Fish et al., 2010)	CP: 23.4 (8.9, 14.5) (Fish et al., 2010)	28 (7, 21)	26 (10, 16)	15 (6, 9)	15 (4, 11)
PSEQ (Nicholas, 2007)	CLBP: 24.9–49 (Nicholas et al., 2008; Costa et al., 2011)	39	32	21	23
STarTBack (psychosocial sub –scale) (Hill et al., 2008)	Low risk < 3; medium risk > 3, but <4 on psychosocial subscale; high risk ≥ 4 for psychosocial subscale (Hill et al., 2008)	4 (2)	4 (2)	6 (4)	7 (3)

All comparative data are mean values unless otherwise stated. Chronic low back pain (CLBP); low back pain (LBP); healthy controls (HC); mixed chronic pain states (CP); Pittsburgh Sleep Quality Index (PSQI); short-form Chronic Pain Acceptance Questionnaire(CPAQ-8); Depression, Anxiety, Stress Scales (DASS); Fear Avoidance Beliefs Questionnaire, Physical Activity subscale (FABQ-PA); Fear Avoidance Beliefs Questionnaire, Work subscale (FABQ-W); Pain Catastrophising Scale (PCS); Pain Self-Efficacy Questionnaire (PSEQ).

Appendix 2. Quantitative sensory testing profiles

	Comparative data	Case 1	Case 2	Case 3	Case 4
PPT (kPa)	W HC 557 (Suttrup et al., 2011) L HC 352–910 L CLBP 168–801 (Lewis et al., 2010; O'Neill et al., 2011; Neziri et al., 2012)	W 192 L 402	W 317 L 169	W 89 L 268	W 595 L 513
HPT (°C)	W HC 44.1–44.9 (Moloney et al., 2011; Suttrup et al., 2011) L HC 40.7–47.1 L CLBP 39.5–46 (Lewis et al., 2010; Neziri et al., 2012)	W 45.9 L 40.0	W 46.3 L 40.4	W 35.7 L 34.5	W 47.0 L 46.6
CPT (°C)	W HC 9–13.9 (Moloney et al., 2011; Suttrup et al., 2011) L HC 3.3–9.3 L CLBP 11.0–13.2 (Lewis et al., 2010; Neziri et al., 2012)	W 4 L 4	W 6.2 L 24.0	W 6.4 L 30.0	W 4.3 L 4
StEP sensory tests (Scholz et al., 2009)				Increasing pain with repeated nylon monofilament stimulation from 0 to 2	Pain evoked by nylon monofilament contact rated 6–10/10 Pinprick hyperalgesia Increasing pain with repeated nylon monofilament stimulation from 7 to 8
CPM change score	Median HC −2.9 (Pud et al., 2009)	−1	−1	0	+1

All comparative data are mean values unless otherwise stated. Chronic low back pain (CLBP); low back pain (LBP); healthy controls (HC); wrist (W); lumbar (L); Standardised Evaluation of Pain (StEP); centimetres (cm); pressure pain threshold (PPT); kilopascals (kPa); heat pain threshold (HPT); cold pain threshold (CPT); degrees centigrade (°C); conditioning pain modulation (CPM).

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Appendix 3. Movement profiles

	Comparative data	Case 1	Case 2	Case 3	Case 4
Change in pain rating (NRS) with repeated movements (Sullivan et al., 2009)		F 6—9 (+3)	F 4—7 (+3)	F 5—7 (+2)	F 0
		B 9—6 (−3)	B 6—7 (+1)	B 7—8 (+1)	B 0
Movement pattern (O'Sullivan, 2005)		Active extension	Active extension	Multidirectional	
Pain behaviour flexion (Sullivan et al., 2006)		Communicative 8	Communicative 1	Communicative 22	Protective 1
		Protective 20	Protective 20	Protective 29	
Pain behaviour extension			Communicative 1	Communicative 12	

Forward bending task (F); backwards bending task (B).

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Preface to Chapters Four to Six

The primary aims of this research were to explore statistical subgrouping using standardised, valid and reliable, clinically-applicable measures from multiple dimensions within a large cohort with axial CLBP, and to profile subgroups using these data.

LCA was chosen as the appropriate unsupervised statistical procedure, meaning that it allows derivation of previously unknown subgroups from cross-sectional data, independent of any known subgroups or future outcomes (Kent et al., 2010), and because it has advantages over other existing statistical clustering techniques (e.g. hierarchical and non-hierarchical cluster analysis) (Magidson and Vermunt, 2002, Collins and Lanza, 2010). These advantages include:

i) Statistical evaluation of the optimal number of subgroups.

ii) Accommodation of variables of mixed measurement types: e.g. in this dataset measurement of pressure pain threshold (PPT) is continuous, while measurement of endurance behaviour (AEQ classification) is categorical.

iii) Accommodation of missing data, which varies between included indicator variables (Appendix 2).

iv) Calculation of classification probabilities for each individual, which allows the uncertainty of subgroup allocation to be a consideration in subsequent analyses.

LCA may therefore afford greater overall model validity (Magidson and Vermunt, 2002, Kent et al., 2014), and may be more accurate in determining cluster membership than other cluster analysis methods (Kent et al., 2014, Magidson and Vermunt, 2002).

Sample size requirements for LCA are not definitive and depend upon many factors, including the size and number of latent classes, and the model complexity in terms of number, type and correlation of indicator variables (Nylund et al., 2007). However, simulation studies have suggested a minimum of 200 participants for LCA

with continuous variables (Nylund et al., 2007) and 300 participants for LCA with dichotomous variables (Swanson et al., 2012). Therefore, the aim of this current body of research was to recruit 300 participants to achieve the minimum acceptable sample size. Although a larger sample would have afforded greater power for LCA, this was not feasible within the timescale and budget available for this study. A flowchart detailing participant recruitment, and descriptive statistics for included participants, people who did not satisfy the inclusion / exclusion criteria, and those who dropped out before completion of the baseline assessment battery, are presented in Appendix 2.

Complex statistical procedures such as LCA entail the use of an iterative approach, where successive sets of parameter estimates are evaluated using a search algorithm, rather than most simple statistical parameters, which are able to be estimated simply by solving an equation. To estimate model parameters, the statistical software used in this study, LatentGold (Statistical Innovations Inc., Belmont, USA) uses a combination of the expectation-maximisation and Newton-Raphson algorithms to maximise the likelihood function, which is the likelihood of the observed data, conditional on the models parameter estimates. The maximum of the likelihood function represents the set of parameter values most supported by the data. A common problem of LCA is the risk of converging on a "local" rather than "global" maximum likelihood solution. The estimation algorithm begins the search for the maximum likelihood solution at a random initial set of parameter values. The search from this starting point continues until either the model converges (changes in successive iterations become trivial), or the maximum number of iterations specified is reached. If a model does not have a definitive maximum likelihood estimate (global solution) different sets of starting values may produce different sets of parameter estimates, some of which are local maxima rather than the true maximum. In this case, the model is considered to be underidentified, meaning that although a maximum likelihood solution does exist it may be difficult to identify, or even that there is no unique maximum likelihood, in which case the model is unidentified. Underidentification can be a function of: i) absolute sample size (i.e. with a smaller sample, and less data in the data set, a

greater number of parameters will have to be estimated, making it more difficult to determine a global solution), ii) sparseness (i.e. small frequencies of cases in each of the cells in the contingency table formed by the data) which is a function of the number / type of variables plus the overall sample size, and iii) the strength of the association between the observed data and the latent classes (i.e how distinctive the groups are in the data) (Collins and Lanza, 2010).

Initially, in the current research, attempts were made to identify subgroups from a range of indicator variables from multiple dimensions (demographics, pain characteristics, tissue sensitivity, psychological, social, health, lifestyle, movement) using LCA. In all 66 possible indicator variables taken from measures of multiple dimensions were considered for entry into LCA (Table 1). These variables were clinically-applicable measures of factors associated with, or prognostic for, greater pain or disability in CLBP, predictive of poor treatment outcomes or otherwise having a strong biological rationale for consideration in the multidimensional model (Kamper et al., 2010), as determined by review of the literature. The methodology for each of these measures is included in subsequent chapters. Descriptive statistics and details regarding missing data management for each measure are provided in Appendix 2.

Table 1.

Measures of dimensions associated with chronic low back pain for which variables were considered for entry into latent class analysis.

Tissue sensitivity dimension	Demographics / pain characteristics dimension	Psychological dimension
Mechanical detection threshold (2 sites)	Age	Depression, Anxiety, Stress scales (3 subscales)
Pressure pain threshold (2 sites)	Sex	
	Pain intensity (NRS)	Fear-Avoidance Beliefs questionnaire (2 subscales)
Heat pain threshold (2 sites)	Roland Morris Disability questionnaire	
Cold pain threshold (2 sites)	Pain distribution	Pain Catastrophising scale (3 subscales)
	Symptom duration	
Two-point discrimination	Bothersomeness	Avoidance Endurance questionnaire (2 subscales)
Temporal summation	Pain behaviour:	
Baseline conditioned pain modulation pressure	i) aggravated by activity	Pain Self-Efficacy questionnaire
Conditioned pain modulation change in pain intensity	ii) aggravated by posture	Chronic Pain Acceptance questionnaire (2 subscales)
Decreased vibration perception		Perceived risk of pain persistence
Pinprick hyperalgesia		Mindful Attention Awareness scale
		Fremantle Back Awareness questionnaire

Social dimension	Movement dimension	Health / lifestyle dimensions
Occupation	Pain response following repeated forward and backward spinal bending	General health
Years in education		Comorbidity counts (4)
Compensation status	Time taken to complete five forward and backward bends	Painful areas marked on body chart count
Multidimensional Pain Inventory (4 subscales)	Protective and communicative behaviours associated with pain during bending tasks	Manchester definition of chronic widespread pain
Stressful life events count		Pittsburgh Sleep Quality index
		International Physical Activity questionnaire
		Smoking status
		Body mass index

This initial attempt to estimate models for one to six clusters, using 1000 random starts to reduce the possibility of local solutions, was unsuccessful in identifying a global solution. Since it was not possible to obtain a model that converged upon a clear maximum likelihood estimate (Collins and Lanza, 2010) using all indicator variables, data reduction using principal component analysis (PCA) was performed as a next step to decrease the number of indicator variables.

PCA was undertaken on the variables within each separate dimension where Bartlett's test of sphericity and the Kaiser-Meyer-Olkin measure of sampling adequacy indicated it was appropriate (Hair et al., 2010), and principal component (PC) scores were taken forward into LCA. Where PCA was not indicated, LCA was performed within each separate dimension and models were examined to determine which indicator variables had the greatest influence upon cluster membership within that single dimension. This process resulted in a combination of PC scores and individual variables totalling 25, which were used as indicator variables in the subsequent multidimensional LCA.

However, despite reducing the number of indicator variables to 25, LCA models would still not converge upon a clear maximum likelihood estimate, reflecting the complexity of the data set, and therefore possibly reflecting the complexity of CLBP as a disorder. Therefore, it was decided to examine the data set by deriving subgroups of people with different profiles based on three different dimensions separately: i) tissue sensitivity was evaluated using quantitative sensory testing (QST) to reflect central and peripheral nociceptive and non-nociceptive processing; ii) psychological questionnaire scores; iii) pain responses following repeated spinal forward and backward bending. Finally, these subgroups were profiled on the broader multidimensional data. These three dimensions were chosen as key, clinically modifiable dimensions within the clinical presentations of people with CLBP and the broader multidimensional understanding of CLBP, that have the potential to facilitate targeted interventions.

For examination of tissue sensitivity, QST was chosen to quantify somatosensory function in response to controlled psychophysical stimuli and to help characterise nociceptive and non-nociceptive processing (Baron et al., 2012). While QST is not recommended as a standalone tool for diagnosis, it does provide unique information about the functional status of somatosensory system (Backonja et al 2013), including static (thermal and mechanical) and dynamic processes (such as conditioned pain modulation). QST data allow characterisation of key clinical correlates of somatosensory sensitivity, i.e. allodynia and hyperalgesia to brush and to static mechanical or thermal stimuli, and temporal summation (a reflection of "wind up"). In this regard, QST data are complementary to the clinical profile for people with CLBP. The relevance of data from QST may extend to treatment outcomes (Coronado et al., 2014), however, QST findings have rarely been utilised to derive subgroups in people with CLBP, and their role as a diagnostic (Backonja et al 2013) or prognostic tool in CLBP is controversial (Hübscher et al., 2013). Due to multiple variables with differing scales, LCA was chosen as the optimal unsupervised statistical method for deriving subgroups based upon QST measures for reasons previously discussed.

Psychological findings were chosen because they consistently act as prognostic indictors for pain and disability in people with CLBP (Hayden et al., 2010). However, because the various subgrouping studies have examined differing psychological factors, which factors are most important for subgrouping remains unknown, and only limited subgroup multidimensional profiling has been undertaken to date. As with the QST data, due to multiple variables with differing scales from the psychological dimension, LCA was chosen as the optimal unsupervised statistical method for deriving subgroups based upon psychological measures.

Examination of pain responses following repeated spinal forward and backward bending were also chosen because exacerbation of pain, or provocation of pain, with movement is common in people with CLBP and is associated with greater disability acting as a barrier to rehabilitation (Sullivan et al., 2009). While *amelioration* of pain with repeated movements has been well examined, this phenomenon is reported to be less common in CLBP populations (May and Aina, 2012). In contrast while *provocation* responses to forward and backward bending tasks have been widely reported in CLBP populations (O'Sullivan, 2000, Hidalgo et al., 2014), little research has systematically investigated these responses following repeated movements using patient reports of pain intensity, without the influence of clinical judgement. When considering pain responses following movement, the use of valid and reliable, clinically-important, self-report levels of pain intensity (≥ two-point change on an 11 point NRS) during two standardised tasks, generated two binary variables. Unlike the QST and psychological data which necessitated more complex statistical subgrouping techniques, this allowed simple statistical subgrouping achieved by subgrouping participants according to their response on these two binary outcomes.

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Chapter Four – Study Two

4.1   Introduction To Study Two

Due to the aforementioned statistical estimation problems, when using a combination of measures from all dimensions, this research derived subgroups of people with CLBP on three separate dimensions. These three dimensions were: quantitative sensory testing (QST) data, psychological questionnaire scores and pain responses following repeated spinal bending. This chapter presents the first of these subgrouping studies, based upon QST measures. This was deemed an important dimension to examine, as although it has been suggested that QST offers a "window" to explore potential nociceptive and non-nociceptive processes (Baron et al., 2012) in CLBP subgroups with differing sensory phenotypes, they have rarely been utilised to derive subgroups in people with CLBP, and their role in CLBP is controversial (Hübscher et al., 2013).

Only two studies (Scholz et al., 2009, Coronado et al., 2014) to date have utilised unsupervised statistical techniques on QST data to derive subgroups in people with CLBP, however both used less optimal distance-based clustering procedures, had relatively small numbers of participants and considered only limited multidimensional profiling. The current study utilised LCA of data from a broad range of bedside and laboratory, nociceptive and non-nociceptive QST variables to derive subgroups in a large CLBP cohort, affording greater model validity, and possibly more accurate determination of cluster membership (Kent et al., 2014, Magidson and Vermunt, 2002). Subsequently subgroups were profiled on data from across each of the multiple dimensions associated with CLBP detailed in Chapter 2 (Table 1). While the tissue sensitivity dimension, reflecting central and peripheral nociceptive and non-nociceptive processing was examined using this broad QST battery, the clusters that were derived were based upon pressure and thermal pain sensitivity, and will henceforth be referred to as pain sensitivity clusters. Examination of the different clusters and their multidimensional profiles allows postulation regarding mechanisms contributing to the persistence of CLBP in each cluster and the clinical implications of these differing profiles.

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4.2   Study Two

**Somatosensory Nociceptive Characteristics Differentiate Subgroups In People
With Chronic Low Back Pain: A Cluster Analysis**

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This paper has been published as follows:

PAIN®

Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: a cluster analysis

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Abstract

The objectives of this study were to explore the existence of subgroups in a cohort with chronic low back pain (n = 294) based on the results of multimodal sensory testing and profile subgroups on demographic, psychological, lifestyle, and general health factors. Bedside (2-point discrimination, brush, vibration and pinprick perception, temporal summation on repeated monofilament stimulation) and laboratory (mechanical detection threshold, pressure, heat and cold pain thresholds, conditioned pain modulation) sensory testing were examined at wrist and lumbar sites. Data were entered into principal component analysis, and 5 component scores were entered into latent class analysis. Three clusters, with different sensory characteristics, were derived. Cluster 1 (31.9%) was characterised by average to high temperature and pressure pain sensitivity. Cluster 2 (52.0%) was characterised by average to high pressure pain sensitivity. Cluster 3 (16.0%) was characterised by low temperature and pressure pain sensitivity. Temporal summation occurred significantly more frequently in cluster 1. Subgroups were profiled on pain intensity, disability, depression, anxiety, stress, life events, fear avoidance, catastrophizing, perception of the low back region, comorbidities, body mass index, multiple pain sites, sleep, and activity levels. Clusters 1 and 2 had a significantly greater proportion of female participants and higher depression and sleep disturbance scores than cluster 3. The proportion of participants undertaking <300 minutes per week of moderate activity was significantly greater in cluster 1 than in clusters 2 and 3. Low back pain, therefore, does not appear to be homogeneous. Pain mechanisms relating to presentations of each subgroup were postulated. Future research may investigate prognoses and interventions tailored towards these subgroups.

Keywords: Low back pain, Sensory characteristics, Subgroups

1. Introduction

Treatment outcomes for people with chronic low back pain (CLBP) are modest at best.[9] Factors underpinning poor outcomes may include heterogeneity of the CLBP population and lack of consideration of the complex biopsychosocial nature of CLBP, contributing to poor treatment specificity.[62] Subgrouping people with CLBP with different clinical profiles is a research priority[15] to inform tailored interventions and improve outcomes.[74]

Clinical assessment of patients with pain includes sensory testing. Psychophysical tests provide a "window" to explore nociceptive and non-nociceptive processes underlying pain disorders,[4] inform prognosis,[69] and facilitate subgrouping to improve treatment specificity.[14,28,66] "Bedside" sensory testing and laboratory quantitative sensory testing (QST) are increasingly used to explore sensory characteristics.[3]

Given that different sensory stimuli are mediated by different primary afferents[34] and central nervous system pathways,[17]

multimodal testing is required to characterise sensory function. Although few studies of CLBP cohorts have examined multiple sensory modalities, early evidence suggests that heterogeneous sensory characteristics may exist in CLBP.[55]

Numerous factors influence sensory testing, including age, sex,[53,57] mood,[38] catastrophizing,[11] fear,[35] activity levels,[21] and sleep,[40] consistent with contemporary understanding of CLBP where interacting biopsychosocial factors influence pain sensitivity.[67] However, such potential confounders are not consistently addressed in QST literature, complicating data interpretation.

To minimise bias, CLBP subgroups should ideally be derived from large diverse samples using unsupervised rather than supervised statistical techniques, meaning previously unknown subgroups are identified from cross-sectional data, independent of any known subgroups or future outcomes.[37] Face validity of subgroups should be explored by analysing the differences between their biopsychosocial profiles.[37] While unsupervised statistical techniques have been used for subgrouping in other disorders, only 2 studies have involved people with low back pain (LBP).

Scholz et al.[66] used bedside tests examining pressure and thermal pain sensitivity, and pain characteristics, to examine a cohort with differing neurological diagnoses, lumbar radiculopathy, or CLBP. Participants with CLBP fell into 2 subgroups: one more likely to complain of paraesthesia and burning pain (n = 18) and the other more likely to exhibit temporal summation (n = 32). Interpretation of this study's outcomes was limited by the small sample, limited sensory testing, and lack of examination of between-cluster biopsychosocial differences. In a larger cohort

(LBP: n = 110; neck pain: n = 47), Coronado et al.[14] examined pain sensitivity and temporal summation. Three subgroups ([1]: high static pressure and dynamic heat pain sensitivity, [2]: high static heat pain sensitivity, and [3]: low pressure and heat pain sensitivity) were predictive of pain intensity change over a 2-week intervention but did not differ across baseline psychological measures.

In summary, sensory characteristics in people with CLBP may be heterogeneous. Identification of subgroups may inform tailored management. No studies have investigated the existence of subgroups in a large CLBP cohort using multimodal sensory testing and probabilistic unsupervised cluster analysis. Therefore, our first objective was to explore the existence of subgroups in a large CLBP cohort using latent class analysis (LCA). The second objective was to profile identified clusters according to demographic, psychosocial, lifestyle, and general health factors.

2. Materials and methods

This research was conducted in accordance with the Declaration of Helsinki.[80] All study procedures were approved by the institutional ethics committees of all participating institutions.

2.1. Study population

This was a cross-sectional study involving people with axial CLBP (n = 294; 57.1% female; median age: 50 years). Subjects were recruited from 2 metropolitan hospitals in Perth, Western Australia (physiotherapy and emergency departments [1.4%], private metropolitan physiotherapy [20.1%], pain management and general practice clinics [1.0%]) and through multimedia advertisements (newspaper, social media, television, radio) circulated throughout the general community, in both metropolitan and regional Western Australia (77.6%).

Potential participants were asked to contact one of the researchers (M.R.) directly by telephone or e-mail and were then sent an inclusion and exclusion criteria screening questionnaire through e-mail or mail. Ambiguous responses to any of the inclusion or exclusion criteria were clarified by telephone.

Inclusion criteria were as follows: males and females aged 18 to 70 years; LBP of >3 months' duration; a score of 2 or more on a numeric rating scale (NRS, 0-10) for pain intensity in the past week anchored with "No pain" at one end and "Worst pain imaginable" at the other; a score of 5 or more on the Roland–Morris Disability Questionnaire (RMDQ)[60]; a score of at least 60% LBP on the following question[76]: "Which situation describes your pain over the past 4 weeks the best? 100% of the pain in the low back; 80% of the pain in the low back and 20% in the leg(s); 60% of the pain in the low back and 40% in the leg (s); 50% of the pain in the low back and 50% in the leg(s); 40% of the pain in the low back and 60% in the leg(s); or 20% of the pain in the low back and 80% in the leg(s)." The latter question reliably differentiates participants with dominant leg pain or dominant LBP,[76] minimizing the likelihood of participants with primarily radiculopathy-related pain being entered into the cohort.

Exclusion criteria were as follows: previous extensive spinal surgery (greater than single-level fusion or instrumentation or discectomy) or spinal surgery within the past 6 months, serious spinal pathology (cancer, inflammatory arthropathy, or acute vertebral fracture), diagnosed neurological disease, bilateral pain at the dorsum of the wrist or hand, pregnancy, and inability to understand English.

2.2. Sensory testing protocol

A combination of clinical bedside tests and laboratory tests was chosen to examine somatosensory submodalities mediated by different primary afferents (C, A delta, A beta)[34] and to be indicative of alterations in central nervous system nociceptive and non-nociceptive processing.[17,46,82]

For all testing, participants were positioned prone. Testing was undertaken in the same order with every subject, beginning with the test deemed least likely to be provocative of pain, progressing to those more likely to be provocative. The tests are described below in that order. An experienced clinician (M.R.) conducted all testing.

All testing was undertaken in the area of maximal pain at the lumbar region as indicated by the subject.[31] Laboratory-based testing (mechanical detection threshold, pressure pain threshold [PPT], heat pain threshold [HPT], cold pain threshold [CPT], conditioned pain modulation [CPM]) was also performed at the dorsal wrist joint line[7] of a pain-free wrist (or if both wrists were pain-free, the nondominant wrist), with the participant's arm supported on the plinth. Testing was undertaken first at the wrist, then at the lumbar region. The same wrist also was used as the reference point for the Standardised Evaluation of Pain (StEP) protocol[66] of bedside sensory tests.

Testing used standardised instructions aligned to the StEP protocol[66] and the German Research Network on Neuropathic Pain QST protocol.[61]

2.2.1. Two-point discrimination

Two-point discrimination (TPD) was undertaken in the region of maximal lumbar pain only, using the method described by Moberg,[50] updated by Luomajoki and Moseley.[46] Subjects were instructed that a plastic calliper ruler (Aesthesiometer; DanMic Global, San Jose, CA) would be used to gently touch their lower back region. The amount of pressure applied was just enough to cause the "very first small blanching" around the calliper points (Ref. 50; page 128). All applications of the calliper were with the points aligned horizontally.[46] Each time they were touched, participants were instructed to indicate whether they perceived 1 or 2 points of the calliper touching them by saying "One" or "Two." Participants were also able to state that they were "Unsure." If a participant responded that they were "unsure," the distance between the 2 points of the calliper was changed by 5 mm, in either direction (dependent on whether it was an ascending/descending run), and testing continued until a clear threshold was determined. The TPD threshold was considered to be the minimum distance between the 2 calliper points at which the participant stated that they had been touched by 2 points rather than 1. Both ascending and descending runs, where the distance between the calliper points was increased or decreased by 5 mm at a time, respectively, were tested. A mean of 3 runs was used to calculate the threshold. "Trick" stimuli, where the callipers were applied at a distance that was out of sequence or where only 1 point made contact, were randomly applied to minimise the chances of participant guessing. The maximum distance between the 2 points of the calliper was 10 cm.

2.2.2. The Standardised Evaluation of Pain protocol

The following tests were applied as per the StEP protocol[66]:
(1) Detection of brush movement on the skin and brush-evoked pain were used to assess the response to dynamic tactile stimulation: A makeup brush (1 cm width) was moved over the skin 3 times at 3 to 5 cm per second. If a response similar to that perceived in the reference area occurred for 2 of 3 brush strokes, sensation was deemed intact. If 2 of 3 brush strokes provoked pain, participants were asked to rate its intensity on an NRS, as before.

(2) Detection of vibration using a standard 128 Hz tuning fork: The tuning fork was placed when vibrating, and when not vibrating, on a prominent bony point in the lumbar region, close to the area of maximal lumbar pain. Decreased vibration perception was documented when the participant could not perceive a difference between the tuning fork when it was vibrating and when it was not vibrating. The tuning fork was held in place for a maximum of 5 seconds for each test.

(3) Detection of pinprick and pinprick hyperalgesia using a toothpick: The original description of pinprick testing in the StEP describes using a safety pin.[66] However, to allow for single use of equipment for each participant, this testing was undertaken using sharp wooden toothpicks. The toothpick was applied with adequate pressure to elicit a painful response on normal skin without leaving an impression. The pressure was applied 4 times. If the participant did not describe a painful response on 3 of 4 occasions, they were deemed to have a decreased response. If the sensation perceived in the lumbar region was deemed to exceed the sensation perceived at the reference site, the participant was asked to rate its intensity on an NRS as before.

(4) Detection of perceived temporal summation upon repeated 26g Semmes–Weinstein monofilament stimulation: The participant was questioned whether the first application of the filament provoked pain. If so, they were asked to rate its intensity on an NRS as before. If not, pain intensity for the first stimulus was recorded as zero. The filament was then applied to the skin at a rate of 1 Hz for 30 seconds. Participants were then asked to rate the intensity of any pain at the end of the 30 seconds of stimulation on an NRS as before. A response for enhanced temporal summation to mechanical stimulation was deemed positive if participants perceived the initial stimulus as non-noxious, but it became noxious, increasing by at least 2 points on an NRS (equivalent to the minimum clinically important difference[63]) over the 30 seconds of repeated stimulation (n = 28, 9.5%) or if participants perceived the initial stimulus as noxious, and deemed the intensity of their response to the stimulus to have increased by at least 2 points on an NRS over the 30 seconds of stimulation (n = 4, 1.4%). These 2 groups were combined for future analysis (n = 32, 10.9%).

2.2.3. Mechanical detection threshold

This is the lowest mechanical force, applied to the skin using Semmes–Weinstein monofilaments that the subject can detect. The standardised filaments used for testing (Aesthesio; DanMic Global) exert between 0.08 and 2940 mN at the point of bending. Therefore, the Semmes–Weinstein monofilaments were applied perpendicularly to the skin, to the point of bending, and if the subject indicated that they sensed the light touch, gradually smaller filaments were tested until no response was elicited, or vice versa if the subject was unable to feel the light touch initially. Three threshold determinations of the minimum force necessary for the subject to detect the filament touching the skin were made, using ascending and descending stimulus intensities. The mean of these thresholds was used for analysis. Subjects kept their eyes closed throughout testing.

2.2.4. Pressure pain threshold

This was defined as the point at which the sensation of pressure perceived by the participant changed from pressure to a sensation of pressure and pain.[61] Pressure pain threshold was tested using an algometer with a probe size of 1 cm^2 (Somedic AB, Hörby, Sweden). Pressure was increased from 0 kPa, at 50 kPa/s, until the subject indicated their PPT by pressing a button. Thirty-second interstimulus intervals were adopted to reduce the possibility of temporal summation. The mean of 3 thresholds was used for analysis.

2.2.5. Heat pain threshold

Heat pain threshold, the temperature at which a sensation of warmth becomes the first sensation of heat and pain,[61] was tested using the Thermotest (Somedic AB). The contact area of the thermode was 2.5 × 5 cm. Testing began at 32°C. The temperature of the thermode increased by 1°C/s until the participant detected their threshold and pressed a button or the device's upper temperature limit (50°C) was reached. Thirty-second interstimulus intervals were adopted to reduce the possibility of temporal summation. The mean of 3 thresholds was used for analysis.

2.2.6. Cold pain threshold

Cold pain threshold was recorded as the point at which the sensation of cold became the first sensation of cold and pain.[61] Testing CPT used the same equipment as for testing HPT. Testing began at 32°C. The temperature of the thermode decreased by 1°C/s until the participant detected their threshold and pressed a button or the device's lower temperature limit (4°C) was reached. Thirty-second interstimulus intervals were adopted to reduce the possibility of temporal summation. The mean of 3 thresholds was used for analysis.

2.2.7. Conditioned pain modulation

The following test stimulus (TS) was applied at the most painful area in the lumbar region; pressure was applied using the aforementioned algometer. Pressure increased from 0 kPa at 50 kPa/s, until the participant indicated that the pressure was equal to a pain intensity of 6 of 10 on the NRS[24,52] by triggering the algometer button. This pressure was recorded. The conditioning stimulus (CS) was noxious heat applied to the dorsal hand using the aforementioned thermode, adjusted to ensure optimal contact. The CS commenced at 40°C and increased 1 degree at a time until the participant indicated that the stimulus was too uncomfortable to tolerate, then it was reduced by 1 degree. The participant then received the following explicit instructions: "I am going to apply three further pressure tests to your back. You rated the last pressure as 6/10. Now I want you to give me a score out of 10 compared to that first rating for each of these next three pressures." No indication was given as to whether the pressures to be applied would vary from the initial pressure, or not. The specific wording of the instructions allowed determination of whether the participant perceived whether baseline pain intensity (6/10) was altered in the presence of the CS. The TS was then reapplied, at the same application rate, to the same point, at the predetermined pressure indicated by the participant (±10 kPa). The participant then indicated another NRS score for the pain intensity of the TS while the CS was ongoing.[58] The TS was tested after the CS had been ongoing for 3 time points at 30, 60, and 90 seconds. The mean of these 3 NRS ratings was analysed. Conditioned pain modulation was coded as missing in cases where it was not possible to achieve a pain intensity rating of 6 of 10 on the baseline pressure test.

2.3. Demographic, psychosocial, and clinical data

Age, sex, and body mass index were collected for each participant.

2.3.1. Pain intensity

Pain intensity over the past week was determined from the aforementioned NRS. The validity and reliability of this measure have been demonstrated.[19]

2.3.2. Low back pain–related disability

Level of disability was measured using the RMDQ,[60] comprising 24 items, in which the participant may tick items to indicate whether the item is relevant to their experience (maximum score: 24, indicating high disability). The items examine the effects of LBP on physical activities and activities of daily living. The RMDQ is valid and reliable.[59,60]

2.3.3. Pain duration

Participants were asked, "How long have you had your back pain for?" All answers were converted into months.

2.3.4. Opioid analgesic usage

Ethical approval was contingent on not influencing participant's medication; therefore, participants were allowed to continue all medications as prescribed (non-opioid analgesics, n [%]: 78 [26.5]; opioid analgesics: 48 [16.3]; co-analgesics: 55 [18.7]). To consider the possible effects of opioid intake on pain sensitivity,[20] the number of participants taking opioid analgesics was recorded and between-cluster differences in this variable were assessed.

2.3.5. Depression Anxiety Stress Scales

The Depression Anxiety Stress Scales 21 (DASS-21) is the short-form version of the original DASS.[45] The score is doubled to give a possible maximum score of 42 points. It is a valid and reliable questionnaire evaluating depression, anxiety, and stress-related symptoms.

2.3.6. Life events

The impact of life events was measured on an NRS anchored at one end by "0" and "No stress" and at the other by "6" and "Extreme stress" for the question, "In the past year, how would you rate the amount of stress in your life (at home and at work)?" This is a valid and reliable question for assessing the presence of stressful life events and daily hassles.[44]

2.3.7. Fear-Avoidance Beliefs Questionnaire

The Fear-Avoidance Beliefs Questionnaire (FABQ) is a measure of pain-related fear, comprising 2 subscales (Physical Activity [FABQ-PA] and Work [FABQ-W]). It is reliable[75] and valid.[22] This study used only the FABQ-PA, as one quarter of the participants were not working.

2.3.8. Pain Catastrophising Scale

The Pain Catastrophising Scale is a questionnaire examining patients' thoughts and feelings about pain in terms of magnification, rumination, and helplessness. This questionnaire is valid and reliable.[70]

2.3.9. Fremantle Back Awareness Questionnaire

The Fremantle Back Awareness Questionnaire[77] examines patient perception of the low back region. It consists of 9 statements regarding perception of the lumbar region such as, "My back feels as though it is not part of the rest of my body," for which the participants indicate the degree of agreement with the statement using an NRS anchored at one end by "0" and "Never" and at the other by "4" and "Always." There is a maximum score of 36 points indicating higher perceptual dysfunction. This questionnaire demonstrates adequate reliability, construct, and discriminative validity.[77]

2.3.10. Comorbidities

To assess the presence of differing types of comorbidities, participants were asked to indicate on a checklist which of 25 medical conditions known to be associated with LBP they had been diagnosed with (heart disease, diabetes, ulcer or stomach disease, anaemia or other blood disease, cancer, osteoarthritis, rheumatoid arthritis, fibromyalgia, hypertension, depression, neurological disorders, eczema, osteoporosis, incontinence or bladder problems, respiratory disorders, migraine or recurrent headache, irritable bowel syndrome, chronic fatigue syndrome, pelvic pain or vulvodynia, temporomandibular joint pain, hay fever or some other allergy, eating disorders, anxiety disorders, visual or hearing disorders, thyroid disorders).[6,18] A simple count of comorbidities reported by the individual was used for analysis.[27]

2.3.11. Multiple pain sites

The presence of multiple pain sites was assessed using a quantifiable grid-based body chart. Subjects were asked to fill in all areas of pain. A count of squares of the body chart containing any marking was generated using a validated and reliable method described by Öhlund et al.[56]

2.3.12. Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index comprises 17 questions that assess sleep quality, quantity, disturbance and its effect on daily living. This index has acceptable reliability and validity.[10]

2.3.13. International Physical Activity Questionnaire

The International Physical Activity Questionnaire (Short Form)[33] is a measure of activity levels. It allows determination of the number of walking, moderate and vigorous minutes of activity per week. The measure is valid and reliable.[16] Subjects were categorised as being above or below the Australian Government's Department of Health guidelines of a minimum of 300 minutes of moderate activity (or equivalent) per week.[8]

2.4. Statistical analysis

2.4.1. Data management before latent class analysis

For calculation of total scores for questionnaires, missing data management was undertaken as suggested in original manuscripts, where described. The imputed average of other items was used in the calculation of the questionnaire total when 1 item was missing. Questionnaire totals were coded as missing, when 2 or more items were missing.

Before LCA, pressure and heat pain threshold scores were reversed so that a higher score reflected higher sensitivity across

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all sensory measures. Data from bedside tests where the frequency of a positive response was very low (decreased brush movement perception: n = 1 [0.3%], brush-evoked allodynia: n = 1 [0.3%], decreased pinprick perception: n = 3 [1.0%]) were not used in subsequent LCA. As 76.2% of the sample was currently working, data from the FABQ (Work subscale) were excluded from analysis.

2.4.2. Latent class analysis

Latent class analysis is an unsupervised statistical technique examining inherent relationships between variables within the data set independent of any previously known groups or outcome measures. This was used to estimate the number of distinct groups with differing responses to multimodal sensory testing. This is a probabilistic form of clustering using maximum likelihood estimation, which has advantages over traditional distance-based cluster procedures in that it allows statistical evaluation of the optimal number of subgroups, utilisation of variables of mixed measurement types, and provision of classification probabilities for each individual.[13,49] Sample size requirements for LCA are not definitive and are dependent on many factors, including the size and number of true latent classes and model complexity in terms of number, type, and correlation of indicator variables. However, simulation studies for LCA have suggested a minimum of 200 participants for LCA with continuous variables[54] and 300 participants for LCA with dichotomous variables.[71]

Initially, LCA was performed using 13 indicator variables from the sensory tests, but due to difficulties in obtaining clear maximum likelihood estimates (ie, identifying global rather than local solutions), principal component analysis was used as a data reduction technique. Principal component analysis with varimax rotation was performed on the polychoric correlation matrix of the 13 indicator variables of mixed measurement type. Principal components (PCs) with eigenvalues >1 were retained.[29] Before LCA, PC scores for those PCs representing pressure, heat, and cold pain thresholds were residualised for age and sex (male or female, > or <50 years old) to reduce variability explained by these factors. Previous studies have confirmed significant sex and age differences in measures of pressure, heat, and cold pain thresholds and that sex differences in these measures may be reduced in participants older than 50 years.[53,57]

Subsequent LCA used PC scores as indicator variables. Models for 1 to 6 clusters were estimated, using 1000 random starts to reduce the possibility of local solutions. Models were developed with examination and consideration of unique log-likelihood solutions, degree of contributions of each indicator PC, and residual correlations within classes. Model fit was assessed by comparison of model fit statistics (consistent Akaike information criterion and adjusted Bayesian information criterion) and posterior probability diagnostics (average posterior probability for each latent class, odds of correct classification and classification error). Individuals were then assigned cluster membership based on posterior probability.

2.4.3. Profiling of clusters

Between-cluster differences in QST variables were examined using linear regression analysis for normally distributed variables, Kruskal–Wallis 1-way analysis of variance for variables with skewed data, and χ^2 analysis for dichotomous data. Profiling of biopsychosocial and demographic (age and sex) variables was performed using univariable multinomial logistic regression with cases weighted according to their probability of class membership.

Latent class analysis was undertaken using Latent GOLD 4.5 (Statistical Innovations Inc, Belmont, CA), and all other statistical procedures were performed using Stata 13.1 (StataCorp, College Station, TX). Statistically significant differences were considered to be at $\alpha < 0.05$.

3. Results

3.1. Principal component analysis

Principal component analysis derived 5 PCs accounting for 68.8% of the total variation in the data. Variable loading on each component was considered significant if >0.3[29] (**Table 1**). These PCs can be summarised as representing the dimensions temperature (PC1), pressure (PC2), CPM, temporal summation, and pinprick hyperalgesia (PC3), mechanical detection (PC4), and TPD and vibration perception (PC5). Principal component scores were calculated for each participant using the component loadings.

3.2. Latent class analysis

Initial latent class models included all 5 PC scores, but due to difficulties in obtaining clear unique maximum log-likelihood solutions models indicating global rather than local solutions, the maximum likelihood solutions for models were examined and only those PCs with a substantial contribution to models ($R^2 > 0.3$) were retained as indicator variables for further model estimations.

Table 1

Principal component analysis of QST variables.

Variable	Component 1	Component 2	Component 3	Component 4	Component 5
PPT w	0.01	**0.64**	0.01	0.01	0.02
PPT lx	0.01	**0.66**	0.01	0.01	0.02
HPT w	**0.39**	0.15	0.03	0.12	0.04
HPT lx	**0.48**	0.06	0.08	0.01	0.01
CPT w	**0.48**	0.07	0.02	0.02	0.03
CPT lx	**0.54**	0.03	0.01	0.07	0.04
MDT w	0.04	0.03	0.04	**0.71**	0.08
MDT lx	0.06	0.06	0.01	**0.64**	0.12
CPM change score	0.03	0.19	**0.54**	0.04	0.02
Temporal summation	0.02	0.21	**0.51**	0.22	0.10
Pinprick hyperalgesia	0.03	0.00	**−0.66**	0.10	0.04
Vibration detection	0.08	0.14	0.00	0.03	**0.71**
TPD	0.09	0.12	0.02	0.03	**−0.68**

Variable loading on each component was considered significant if >0.3 (indicated in bold).[28]

QST, quantitative sensory testing; CPT, cold pain threshold; CPM, conditioned pain modulation; HPT, heat pain threshold; MDT, mechanical detection threshold; PPT, pressure pain threshold; TPD, two-point discrimination.

These PCs included PC1 (combined wrist and lumbar HPTs and CPTs) and PC2 (combined wrist and lumbar PPTs). Using these 2 indicators, a series of 1 to 6 class models was estimated. Fit statistics indicated that a 3-class solution was optimal, with the adjusted Bayesian information criterion value being 1647, 1470, 1452, 1465, 1481, and 1501 and the consistent Akaike information criterion value being 1652, 1479, 1466, 1484, 1505, and 1530 for the 1 to 6 class models, respectively. The mean (SD) probability of membership was 0.96 (0.09), 0.88 (0.11), and 0.88 (0.14) for clusters 1, 2, and 3, respectively, which is well over the recommended minimum for model adequacy of 0.7.[51] The odds of correct classification were 26.0, 14.9, and 31.3 for C1, C2, and C3, respectively. Larger values indicate better assignment accuracy, and a minimum value of 5 has been suggested to represent high assignment accuracy.[51] The classification error of the 3-class solution was acceptable at 0.07.

Figure 1 displays the 3-class solution according to the 2 indicator PCs, and **Figure 2** displays the underlying thermal and pressure pain thresholds for each cluster, using standardised values for easier interpretation. Cluster 1 (n = 94, 31.9%) was characterised by average to high temperature and pressure pain sensitivity. Cluster 2 (n = 153, 52.0%) was characterised by average to high pressure pain sensitivity. Cluster 3 (n = 47, 16.0%) was characterised by low temperature and pressure pain sensitivity. **Table 2** shows descriptive statistics for each cluster, in the form of raw data, stratified for age and sex, for each of the QST scores that were combined to form PCs used as indicator variables in the final cluster solution. As only 2 PCs were used as indicator variables in the final cluster solution, not all sensory tests examined contributed to these 2 PCs and subsequent identification of the clusters. Sensory tests not incorporated into these 2 PCs have their descriptive statistics detailed in **Table 3**. Temporal summation was the only other QST variable to show a significant difference between the 3 clusters, occurring significantly more frequently in cluster 1.

3.3. Profiling of clusters

Descriptive statistics for each cluster, for demographic, pain characteristic, and biopsychosocial profiling variables, are shown in **Tables 4 and 5**. Profiling of biopsychosocial factors with the
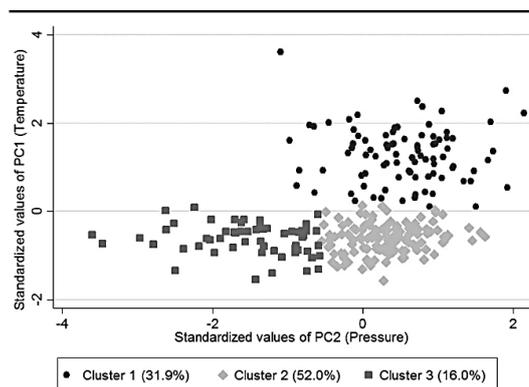
Figure 1. Results of latent class analysis showing 3 clusters derived from thermal and pressure principal component scores. PC1, principal component 1 (from wrist and lumbar heat and cold pain thresholds); PC2, principal component 2 (from wrist and lumbar pressure pain thresholds).
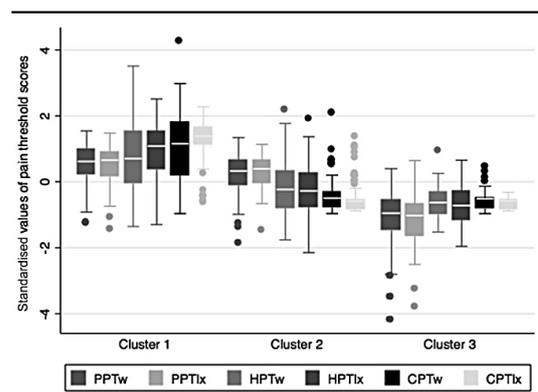
Figure 2. Sensory profiles of 3 clusters derived from latent class analysis of thermal and pressure pain thresholds. CPTw, cold pain threshold, wrist; CPTlx, cold pain threshold, lumbar; HPTlx, heat pain threshold, lumbar (reverse scored); HPTw, heat pain threshold, wrist (reverse scored); PPTw, pressure pain threshold, wrist (reverse scored); PPTlx, pressure pain threshold, lumbar (reverse scored).

analyses weighted by probability of cluster membership identified that clusters 1 and 2 had a significantly higher proportion of females and higher depression and sleep disturbance scores than cluster 3, and the proportion of participants undertaking <300 minutes of moderate activity per week was significantly greater in cluster 1 than in clusters 2 and 3 (**Table 5**). There were no other differences between the clusters.

4. Discussion

This study derived subgroups in a CLBP cohort differentiated by somatosensory nociceptive characteristics, adjusted for age and sex. This is consistent with the proposal that CLBP is heterogeneous.

Interpreting data in the context of putative mechanisms underlying somatosensory characteristics requires these considerations: numerous interacting mechanisms may generate similar clinical signs; similar sensory characteristics may exist despite divergent mechanisms[79]; genetics and epigenetics influence CLBP intensity, nociception, and QST[64,72]; psychosocial factors influence pain sensitivity[21,38,40]; nociception and its association with attention are in constant flux[39]; comparisons with other studies are complicated by a lack of normative data for our test sites[48,53,57,61] and varied protocols.[14,66]

Cluster 1 was characterised by average to high pressure and thermal pain sensitivity at the lumbar region and remotely, suggesting multisensory nociceptive hypersensitivity of superficial and deep tissues (thermal sensitivity, tested using a thermode, stimulates superficial structures; pressure sensitivity is mediated by deep tissue stimulation[17,26]). Combined with a higher proportion of participants exhibiting temporal summation, this suggests involvement of central pain mechanisms,[78,82] but does not exclude peripheral sensitisation, and dorsal horn sensitisation to afferent lumbar region input acting concurrently.[25] On visual inspection, this subgroup's data (**Table 2**) appear consistent with local and remote hypersensitivity compared with normative data.[48,53,57,61]

Cluster 2 was characterised by average to high pressure pain sensitivity and average or below average thermal sensitivity. Mechanisms underlying mechanosensitivity in persistent pain

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Table 2

Pressure, heat, and cold pain threshold raw data for the 3 clusters derived from thermal and pressure PCs, by age and sex.

Indicator variable	Cluster 1 (n = 94, 31.9%)	Cluster 2 (n = 153, 52.0%)	Cluster 3 (n = 47, 16.0%)	P
PPT (wrist), median (IQR), kPa				
Female <50 y old	161[a] (105-256)	210[b] (162-297)	372[c] (336-470)	<0.001*
Female >50 y old	184[a] (156-212)	253[b] (182-309)	544[c] (430-600)	<0.001*
Male <50 y old	203[a] (157-279)	305[b] (249-402)	614[c] (482-905)	<0.001*
Male >50 y old	261[a] (189-293)	303[b] (232-344)	614[c] (471-642)	<0.001*
PPT (lumbar), median (IQR), kPa				
Female <50 y old	110[a] (76-160)	177[b] (119-240)	491[c] (433-594)	<0.001*
Female >50 y old	186[a] (114-276)	228[b] (168-317)	617[c] (542-687)	<0.001*
Male <50 y old	240[a] (92-269)	387[b] (241-459)	811[c] (741-952)	<0.001*
Male >50 y old	292[a] (237-523)	344[a] (262-494)	864[b] (759-1092)	<0.001*
HPT (wrist), median (IQR), °C				
Female <50 y old	39[a] (38-43)	44[b] (43-46)	45[b] (44-47)	<0.001*
Female >50 y old	41[a] (38-44)	45[b] (43-46)	48[c] (46-50)	<0.001*
Male <50 y old	45[a] (39-46)	46[b] (45-49)	49[c] (48-50)	<0.001*
Male >50 y old	45[a] (41-48)	47[b] (46-49)	49[c] (48-50)	<0.001*
HPT (lumbar), mean (SD), °C				
Female <50 y old	39[a] (3)	43[b] (3)	43[b] (2)	<0.001†
Female >50 y old	39[a] (3)	44[b] (3)	47[c] (2)	<0.001†
Male <50 y old	38[a] (3)	44[b] (3)	46[b] (3)	<0.001†
Male >50 y old	40[a] (4)	44[b] (2)	46[c] (2)	<0.001†
CPT (wrist), median (IQR), °C				
Female <50 y old	23[a] (15-27)	6[b] (4-11)	4[b] (4-5)	<0.001*
Female >50 y old	16[a] (11-22)	4[b] (4-8)	4[c] (4-4)	<0.001*
Male <50 y old	14[a] (6-16)	4[b] (4-4)	4[b] (4-4)	<0.001*
Male >50 y old	12[a] (6-24)	4[b] (4-5)	4[b] (4-4)	<0.001*
CPT (lumbar), median (IQR), °C				
Female <50 y old	28[a] (25-29)	4[b] (4-6)	4[b] (4-4)	<0.001*
Female >50 y old	26[a] (25-28)	4[b] (4-5)	4[b] (4-4)	<0.001*
Male <50 y old	26[a] (24-28)	4[b] (4-4)	4[b] (4-4)	<0.001*
Male >50 y old	24[a] (17-27)	4[b] (4-4)	4[b] (4-4)	<0.001*

Superscript letters (a, b, and c) define significantly different groups, ie, results with different letters are significantly different.
* Kruskal–Wallis 1-way analysis of variance.
† Linear regression.
CPT, cold pain threshold; HPT, heat pain threshold; IQR, interquartile range; PC, principal component; PPT, pressure pain threshold.

remain unclear.[5] A specific mechanosensitive pathway has been postulated,[1] supported by afferent neurones found in animals, responsive to mechanical, but not thermal, stimuli,[47] and similarly responsive human thalamic cells.[42] Pressure hypersensitivity may involve peripheral sensitisation of group III or IV deep tissue (likely myofascial) afferents.[26] Involved in mechanotransduction,[12] acid-sensing ion channels in an animal muscle injury model mediate mechanical but not thermal hyperalgesia.[68] Although acidosis may be associated with altered disc metabolism, evidence for myofascial acidosis in humans with LBP is lacking.[43] Localised

lumbar pressure pain sensitivity, without thermal pain sensitivity, has been described in one small CLBP cohort.[7] When visually compared with normative data,[48,53,57,61] this subgroup's PPTs appear consistent with hypersensitivity at both sites, while thermal pain sensitivity appears similar to normative data.[48,53,57,61]

Cluster 3 was characterized by low pressure and thermal sensitivity. Coronado et al.[14] identified one subgroup (mixed neck or back pain cohort) with low pressure and heat sensitivity and an HPT comparable with cluster 3. The remainder of their stimuli were suprathreshold. As indicated by Neziri et al. (Ref. 53; page

Table 3

Descriptive statistics for other QST variables for the 3 clusters derived from thermal and pressure PCs.

Indicator variable	Cluster 1 (n = 94, 31.9%)	Cluster 2 (n = 153, 52.0%)	Cluster 3 (n = 47, 16.0%)	P
MDT wrist, median (IQR) (min-max), mN	3.9 (3.9-5.9) (0.4-19.6)	3.9 (3.9-5.9) (0.1-19.6)	5.9 (3.9-9.8) (0.7-19.6)	0.47*
MDT lumbar, median (IQR) (min-max), mN	5.9 (3.9-9.8) (0.7-58.8)	5.9 (3.9-13.7) (0.1-58.8)	5.9 (3.9-13.7) (0.2-58.8)	0.89*
TPD, mean (SD) (min-max), cm	6.09 (2.22) (0.5-10.0)	5.56 (2.16) (0.5-10.0)	5.82 (1.90) (3.0-10.0)	0.17†
CPM change score (NRS), mean (SD) (min-max)	1.0 (1.3) (−2.0-4.0)‡	0.9 (1.2) (3.0-3.7)§	1.1 (1.3) (−3.0-4.0)‖	0.41†
Temporal summation, n (%)	29[a] (30.8)	22[b] (14.4)	5[b] (10.9)¶	0.002#
Pinprick hyperalgesia, n (%)	18 (19.2)	20 (13.1)	6 (12.8)	0.39#
Decreased vibration detection, n (%)	28 (29.8)	37 (24.2)	7 (14.9)	0.15#

Superscript letters (a and b) define significantly different groups, ie, results with different letters are significantly different.
* Kruskal–Wallis 1-way analysis of variance.
† Linear regression.
‡ Missing in 3 cases.
§ Missing in 5 cases.
‖ Missing in 9 cases.
¶ Missing in 1 case.
# χ^2 analysis.
CPM, conditioned pain modulation; IQR, interquartile range; MDT, mechanical detection threshold; NRS, numeric rating scale; PC, principal component; QST, quantitative sensory testing; TPD, two-point discrimination.

Demographic and pain characteristic data for the entire cohort with axial CLBP and for the 3 clusters derived from thermal and pressure pain PCs.

Variable	Entire cohort (n = 294)	Cluster 1 (n = 94, 31.9%)	Cluster 2 (n = 153, 52.0%)	Cluster 3 (n = 47, 16.0%)	P*
Age, median (IQR) (min-max), y	50 (38-60) (18-70)	50.5 (35-60) (18-70)	50 (37-59) (18-70)	54 (43-61) (21-69)	0.38
Female, n (%)	168 (57.1)	61[a] (64.9)	90[a] (58.8)	17[b] (36.2)	0.004
Pain intensity (NRS), mean (SD) (min-max)	5.8 (1.9) (2-10)	5.9 (2.0) (2-10)	5.9 (2.0) (2-10)	6.0 (1.7) (2-9)	0.49
RMDQ score, median (IQR) (min-max)	9 (6-13) (5-24)	9 (7-13) (5-21)	9 (6-13) (5-24)	9 (6-12) (5-20)	0.75
Duration of CLBP, median (IQR) (min-max), mo	120 (36-240) (3-720)†	120 (39-240) (7-720)	120 (36-240) (3-600)	120 (60-300) (8-540)	0.34
Participants reporting 60% LBP/40% leg pain, n (%)	35 (11.9)	14 (14.9)	18 (11.8)	3 (6.4)	0.36
Participants reporting opioid analgesic usage, n (%)	48 (16.3)	17 (18.1)	28 (18.3)	3 (6.4)	0.16

Superscript letters (a and b) define significantly different groups, ie, results with different letters are significantly different.
* Evaluation of statistical differences was performed using univariable multinomial logistic regression with cases weighted according to their probability of class membership.
† Missing in 1 case.
CLBP, chronic low back pain; IQR, interquartile range; LBP, low back pain; NRS, numeric rating scale; PC, principal component; RMDQ, Roland–Morris Disability Questionnaire.

379), "The incidence and meaning of hyposensitivity to mechanical and thermal painful stimuli are…unclear." On visual inspection, the data of cluster 3 appear similar to normative data,[48,53,57,61] consistent with a lack of pain sensitivity.

Demographic and biopsychosocial profiling revealed between-group differences for sex, depression, sleep, and activity levels. Depression and sleep scores were higher for clusters 1 and 2 than for cluster 3, as was the proportion of female participants. Depression scores for all subgroups appear normal,[45] making the clinical significance unclear. Higher depression scores in clusters 1 and 2 are interesting considering data suggesting that diagnosed depression is associated with increased pressure[41] and cold[38] sensitivity. Sleep scores for all subgroups indicate sleep disturbance.[10] Sleep scores in clusters 1 and 2 were similar to a previous study of people with CLBP,[73] while cluster 3 fell below this level. Experimental data suggesting that increased thermal and pressure sensitivity occurs when healthy participants

are sleep deprived[40] may align with the hypersensitivity evident in clusters 1 and 2. The proportion of participants undertaking <300 minutes of moderate activity per week was greater in cluster 1. Experimental data suggest that higher activity levels may be associated with lower pressure and thermal pain sensitivity,[21] as seen in clusters 2 and 3.

Because age and sex are strongly associated with QST, we removed all variation due to age and sex in threshold data before LCA. Accordingly, normative values are recommended to be reported by age and sex.[48,53,57,61] This allowed evaluation of patterns of relative high and low thresholds referenced to that expected for someone of the same age and sex.

Although an alternative method of dealing with age and sex would involve including them as "active" covariates, allowing age and sex to influence probability of cluster membership, identification of clusters characterized by differences in threshold magnitude would still have been strongly driven by age and

Multidimensional profiles of the 3 clusters derived from thermal and pressure PCs.

Variable	Cluster 1 (n = 94, 31.9%)	Cluster 2 (n = 153, 52.0%)	Cluster 3 (n = 47, 16.0%)	P*
Psychosocial dimension				
DASS depression score, median (IQR) (min-max)	9[a] (2-16) (0-42)	6[a] (2-12) (0-42)	4[b] (0-8) (0-40)	0.03
DASS anxiety score, median (IQR) (min-max)	4 (2-8) (0-34)	4 (2-8) (0-42)	2 (0-6) (0-24)	0.14
DASS stress score, median (IQR) (min-max)	12 (8-20) (0-38)	12 (6-20) (0-42)	10 (2-18) (0-34)	0.26
FABQ-PA, mean (SD) (min-max)	15.1 (6.2) (1-24)	14.2 (5.8) (0-24)	14.0 (5.8) (0-24)	0.51
PCS, median (IQR) (min-max)	16 (8-25) (0-46)	19 (10-29) (0-52)	16 (6-26) (1-43)	0.49
Life events (0-6), mean (SD) (min-max)	3.8 (1.4) (0-6)	3.6 (1.4) (0-6)	3.5 (1.7) (0-6)	0.59
Other dimensions				
Body chart squares, median (IQR) (min-max)	13 (8-20) (2-84)	13 (7-20) (2-68)	9 (4-22) (1-75)	0.69
Total comorbidity count, median (IQR) (min-max)	2 (1-4) (0-11)	2 (0-3) (0-10)	2 (0-3) (0-6)	0.80
BMI, mean (SD) (min-max), kg/m²	27.3 (5.8) (18.4-50.3)	27.1 (5.0) (17.7-43.2)	26.5 (3.7) (18.9-36.4)	0.70
Moderate and vigorous activity†, N (%), min/wk				0.02
≤300	77[a] (83.7)	103[b] (68.7)	31[b] (67.4)	
>300	15 (16.3)	47 (31.3)	15 (32.6)	
PSQI‡, mean (SD) (min-max)	9.2[a] (4.1) (2-20)	9.6[a] (4.2) (2-19)	7.6[b] (3.5) (2-14)	0.02
FreBAQ, mean (SD) (min-max)	10.2 (6.9) (0-30)	9.7 (6.6) (0-32)	9.0 (6.2) (0-23)	0.68

Superscript letters (a and b) define significantly different groups, ie, results with different letters are significantly different.
* Evaluation of statistical differences was performed using univariable multinomial logistic regression with cases weighted according to their probability of class membership.
† Missing in 6 cases.
‡ Missing in 11 cases.
BMI, body mass index; DASS, Depression Anxiety Stress Scales; FABQ-PA, Fear-Avoidance Beliefs Questionnaire—Physical Activity; FreBAQ, Fremantle Back Awareness Questionnaire; IQR, interquartile range; PC, principal component; PCS, Pain Catastrophising Scale; PSQI, Pittsburgh Sleep Quality Index.

sex. This does not mean that sex could still not be associated with cluster membership, as LCA identifies groups with a combination of both different magnitudes and patterns of relative difference across indicators. Therefore, clusters with differing patterns of difference across age- and sex-adjusted indicators could still differ by age and sex, as per cluster 3 having significantly fewer females. This can be interpreted as indicating people lower on both pressure and thermal sensitivity for their age and sex are more likely to be male.

While subgroups based on pain sensitivity were identified, pain and disability did not differ between subgroups, consistent with a systematic review[32] that found low correlations between pain thresholds and pain intensity and disability. These authors noted that few studies included dynamic QST (CPM, temporal summation),[32] which may better reflect pain modulation[82] and are associated with clinical pain morbidity.[82] In our protocol, there was no significant between-group difference for CPM. As there is no consensus on the optimal CPM protocol,[81] our stimuli were based on previous research.[52,58] However, using different stimuli may have influenced outcomes.[52] Although cluster 1 had a greater proportion of participants demonstrating temporal summation, this was not associated with pain or disability. In other pain disorders, QST is indicative of poor prognosis,[69] and in low back–related leg pain, membership of subgroups with different sensory characteristics predicts treatment responses.[65] Future investigation should consider whether membership of these subgroups is prognostic and influences management outcomes.

The majority of the participants were recruited through community advertisements, facilitating generalizability to the wider community. Differing results may have occurred had a clinical sample been examined.

Inclusion criteria included a question identifying dominant LBP,[76] minimizing the likelihood of inclusion of participants who primarily had radiculopathy. It is acknowledged there was potential, that people with some degree of radiculopathy may have been in those 11.9% of participants who rated their pain as 60% LBP. However, there was no significant difference in the proportion of participants across clusters according to relative percentages of LBP vs leg pain.

This study combined bedside and laboratory QST. We used pressure and thermal pain thresholds to facilitate discrimination of subgroups compared with set temperatures and pressure used in the StEP.[66] These measures facilitated subgroup derivation. While alternative more sensitive methods exist for assessment of CPM, pinprick hyperalgesia, temporal summation, and vibration,[23,52,61] which may have influenced subgrouping, using bedside sensory tests was important to facilitate translation of results into practice and reduce participant burden.

Two comparable studies using cluster analysis of sensory tests to identify subgroups of people with LBP exist.[14,66] Scholz et al.[66] identified 2 subgroups; however, their study contained small number of participants with LBP (n = 18, n = 32), used only bedside sensory testing, was not age- and sex-adjusted, and did not consider between-group differences in biopsychosocial factors. Coronado et al.[14] investigated a larger cohort (n = 157), but participants with LBP were not separated from participants with neck pain. Participants were excluded if they had chronic conditions unrelated to LBP, despite comorbidities being clinically common and influencing management.[30] Both studies used distance-based clustering procedures, rather than the probabilistic method used in this study, which may afford greater model validity.[36,49] Assessment of power of LCA to identify true latent classes is in development, and it is likely that the sample size in this study may be inadequate. Although

recommendations for minimum samples (200-300) exist, power may be influenced by model-specific factors, including the size and number of true latent classes and model complexity. Utilisation of 13 indicator variables of differing types presented difficulty in obtaining unique maximum likelihood solutions indicating global rather than local solutions and necessitated data reduction techniques. Clusters with more variable profiles on the 13 indicators may exist, but larger sample sizes would be necessary to explore this possibility.

Multiple comparisons in this study increase the possibility of type I error.[2] However, as LCA is an exploratory technique for determining the existence of clusters,[13] when profiling derived clusters, it may be more appropriate at this stage of this research to maintain P values such that there may be a greater chance of a type I error, but less chance of a type II error.[2] As such, no correction for multiple comparisons was undertaken.

In conclusion, this study that used LCA of data from multimodal somatosensory testing in a large CLBP cohort, and profiled subgroups on multiple potentially interacting biopsychosocial variables, may offer insight into the complexity of CLBP.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Chapter Five – Study Three

5.1   Introduction To Study Three

Due to statistical estimation problems when using a combination of measures from all dimensions, this research derived subgroups of people with CLBP on three separate dimensions. This chapter presents results of subgrouping based upon the psychological dimension, which was chosen because many psychological factors are prognostic of pain and disability in people with chronic low back pain (CLBP) (Hayden et al., 2010) and some reflect mental health disorders comorbid with CLBP (Bair et al., 2008, Pincus and McCracken, 2013). Psychological factors may also be associated with biological and behavioural factors such as higher pain sensitivity (Klauenberg et al., 2008), impaired motor control (Lewis et al., 2012) and endurance behaviours (Hasenbring et al., 2012).

There is a long history of using statistical cluster analysis of psychological data to derive subgroups of people with CLBP, initially based upon data from one psychological construct, or a single questionnaire (e.g. Minnesota Multiphasic Personality Inventory (Bradley et al., 1978, McGill et al., 1983)). More recently CLBP subgroups have been statistically-derived using data from multiple, cognitive and affective psychological factors (e.g. fear-avoidance beliefs, pain self-efficacy, anxiety, depression and troublesomeness (Barons et al., 2014)), however, it remains unclear which psychological factors, or combinations thereof, may be most important for determining subgroups in people with CLBP. Furthermore, the small range of profiling variables examined across subgroups derived to date provides limited insight into the multidimensional nature of CLBP within these subgroups.

A statistical subgrouping method was chosen to reduce clinical interpretation and its potential bias (Kent et al., 2010). LCA was chosen as the optimal unsupervised statistical technique for determining psychologically-derived subgroups because it allows statistical evaluation of the optimal number of subgroups, and accommodates missing data (Magidson and Vermunt, 2002, Collins and Lanza, 2010, Kent et al., 2014). Derived subgroups were subsequently profiled on variables from multiple dimensions associated with CLBP. Examination of the different

psychological subgroups and their multidimensional profiles allows postulation regarding mechanisms contributing to the persistence of CLBP in each subgroup and may facilitate development of interventions targeted towards these different profiles.

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5.2   Study Three

Differing Psychologically-Derived Clusters In People With Chronic Low Back Pain Are Associated With Different Multidimensional Profiles.

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5.2.1 Abstract

Objectives.

To explore the existence of subgroups in a cohort with chronic low back pain (n=294) based upon data from multiple psychological questionnaires, and profile subgroups on data from multiple dimensions.

Methods.

Psychological questionnaires considered as indicator variables entered into latent class analysis included: Depression, Anxiety, Stress scales, Thought Suppression and Behavioural Endurance subscales (Avoidance Endurance questionnaire), Chronic Pain Acceptance questionnaire (short-form), Pain Catastrophising Scale, Pain Self-Efficacy questionnaire, Fear-Avoidance Beliefs questionnaire. Multidimensional profiling of derived clusters included: demographics, pain characteristics, pain responses to movement, behaviours associated with pain, body perception, pain sensitivity and health and lifestyle factors.

Results.

Three clusters were derived. Cluster 1 (23.5%) was characterised by low cognitive and affective questionnaire scores, with the exception of fear-avoidance beliefs. Cluster 2 (58.8%) was characterised by relatively elevated thought suppression, pain catastrophising and fear-avoidance beliefs, but lower pain self-efficacy, depression, anxiety and stress. Cluster 3 (17.7%) had the highest scores across cognitive and affective questionnaires.

Cluster 1 reported significantly lower pain intensity and bothersomeness than other clusters. Disability, stressful life events and low back region perceptual distortion increased progressively from Cluster 1 to Cluster 3, while mindfulness progressively decreased. Clusters 2 and 3 had more people with an increase in pain following repeated forward and backward spinal bending, and more people with increasing pain following bending, than Cluster 1. Cluster 3 had significantly greater lumbar

pressure pain sensitivity, more undiagnosed comorbid symptoms and more widespread pain than other clusters.

Discussion.

Clinical implications relating to presentations of each cluster are postulated.

5.2.2 Introduction

There is growing evidence that a broad range of psychological factors are associated with pain and disability, and may mediate the relationship between pain and disability, in people with chronic low back pain (CLBP) (Hayden et al., 2010, Lee et al., 2015). Unhelpful psychological factors include both cognitive (e.g. kinesiophobia, pain catastrophising, endurance behaviours, low acceptance, low pain self-efficacy) and affective factors (e.g. depressed mood, anxiety, stress) (Campbell et al., 2013, Pincus and McCracken, 2013). There is evidence that rather than acting independently, psychological factors overlap in people with CLBP, leading to calls to consider them as broader constructs (e.g. pain-related distress) (Foster et al., 2010, Campbell et al., 2013).

Understanding the influences of psychological factors has led to psychologically-based interventions for people with CLBP. However, to date treatment outcomes for these interventions in people with CLBP are moderate at best (Ramond-Roquin et al., 2014), possibly reflecting the heterogeneity of study samples or because other dimensions associated with CLBP (e.g. pain characteristics, health, lifestyle, tissue sensitivity, movement) are not targeted by these interventions (Rusu et al., 2012). To facilitate better understanding of the complexities of CLBP, a research priority is to determine subgroups of people with CLBP with different clinical profiles (Costa et al., 2013), to facilitate development of tailored interventions and improve outcomes (Vibe Fersum et al., 2013). To achieve this, analysis should consider a range of factors from multiple, relevant dimensions (Rusu et al., 2012), and to minimise bias CLBP subgroups should be "data-driven": identified within large, diverse samples using unsupervised statistical techniques derived from cross-

sectional data, independent of previously determined associations or potential outcomes (Kent et al., 2010).

While CLBP subgroups have been statistically-derived previously using data from psychological measures (Viniol et al., 2013, Strong et al., 1995), these studies have both examined a limited number of different measures making it unclear which psychological factors are most important for deriving subgroups.

Where interventions have been tailored towards CLBP subgroups, derived predominantly from psychological factors, outcomes have still been suboptimal (Bergbom et al., 2014, Verra et al., 2015) suggesting other dimensions may contribute to persistence of the disorder, and be important for optimising targeted management. For example, unhelpful cognitive and affective factors have been associated with greater pain intensity levels during repeated lifting (Sullivan et al., 2009), more widespread pain (Öhlund et al., 1996), higher local and widespread pain sensitivity (O'Sullivan et al., 2014, Campbell and Edwards, 2009), impaired motor control (Lewis et al., 2012), protective (Sullivan et al., 2006), avoidance and endurance behaviours (Hasenbring et al., 2012), and distorted perception of the low back region (Beales et al., 2015). These associations highlight the complexity of multidimensional interactions underlying the lived experience of CLBP (Simons et al., 2014), and the potential importance of profiling subgroups across multiple interacting dimensions.

Therefore the aims of this study were:

1) Using latent class analysis of a broad range of psychological indicator variables, to determine the existence and number of clusters in a cohort of people with axial CLBP.
2) To profile identified clusters according to demographics, pain characteristics, health and lifestyle factors, body perception, tissue sensitivity, pain responses to movement and behaviours associated with pain.

5.2.3 Materials And Methods

This research was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committees of Curtin University, Royal Perth Hospital and Sir Charles Gairdner Hospital in Perth, Western Australia.

Study population.

This cross-sectional study involved people with axial CLBP (n=294; 57.1% female; median age 50 years old) recruited from the aforementioned public metropolitan hospitals (1.4%); private metropolitan pain management and general practice clinics (1.0%) and physiotherapists (20.1%), and via multi-media advertisements in metropolitan and rural Western Australia (77.6%).

Potential participants contacted one researcher (MR) by telephone or e-mail. They were subsequently sent a self-report inclusion / exclusion criteria screening questionnaire. Ambiguous responses to any criteria were clarified by telephone.

Inclusion criteria were: aged 18-70 years old; > 3 months duration of LBP; pain intensity of ≥ two-points on a numeric rating scale (NRS) (0, "no pain"-10, "worst pain imaginable") in the past week; ≥ five-points scored on the Roland Morris Disability Questionnaire (RMDQ) (Roland and Morris, 1983); a score of at least 60% LBP on the question (Wai et al., 2009), "Which situation describes your pain over the past 4 weeks the best? 100% of the pain in the low back; 80% of the pain in the low back and 20% in the leg(s); 60% of the pain in the low back and 40% in the leg(s); 50% of the pain in the low back and 50% in the leg(s); 40% of the pain in the low back and 60% in the leg(s); or 20% of the pain in the low back and 80% in the leg(s)." This final question reliably differentiates dominant leg pain from dominant LBP (Wai et al., 2009), minimizing the likelihood of recruitment of participants with radiculopathy.

Exclusion criteria were: previous extensive spinal surgery (greater than single level fusion / instrumentation or discectomy); spinal surgery within the past six months, serious spinal pathology (cancer, inflammatory arthropathy, acute vertebral

fracture); diagnosed neurological disease; bilateral dorsal wrist / hand pain; pregnancy; inadequate command of English.

For included participants paper copies of all questionnaires were mailed for completion at their convenience at home (duration approximately 30 minutes). An appointment (duration 60-90 minutes) was made for them to attend the Pain Research Laboratory at Curtin University within approximately two weeks, for completion of the physical examination. Questionnaires were checked for missing data when the participant attended the study centre. All participants completed the following physical examination in this order: two-point discrimination, pain sensitivity testing (temporal summation; pressure, heat and cold pain thresholds) and repeated bending tasks.

Ethical approval was contingent upon not influencing participant's medication use, and therefore participants were allowed to continue all medications as prescribed.

Indicator variables for derivation of psychologically-based subgroups.

A broad range of psychological factors associated with pain and disability in people with CLBP were considered as indicator variables for entry into latent class analysis (LCA). Despite conceptual overlap between such variables (Foster et al., 2010, Campbell et al., 2013) subscales of each individual questionnaire considered have been shown to measure unique constructs (Parkitny et al., 2012, Fish et al., 2013, Van Damme et al., 2002, Hasenbring et al., 2009, Waddell et al., 1993) and it is unknown which constructs may be most important for psychological subgroup derivation. While these variables may be associated with each other in a cohort as a whole, LCA allows derivation of subgroups based upon differing response patterns across the indicator variables. For example, while depression may be associated with fear-avoidance beliefs (Campbell et al., 2013), LCA may allow the derivation of a subgroup who exhibit low levels of depression but high levels of fear-avoidance beliefs, which may be important for the future development of tailored interventions. The following variables were considered as indicator variables in LCA.

Depression, anxiety and stress.

The short-form version of the Depression Anxiety Stress scales (DASS-21) (Lovibond and Lovibond, 1995) is a valid and reliable questionnaire with three subscales, each containing seven statements evaluating depression, anxiety and stress symptoms. Each statement is rated on a 0 - 3 scale, and the score is doubled to give a score of 0 - 42 points per subscale, with higher scores reflecting greater symptoms.

Fear-avoidance beliefs.

The Fear-Avoidance Beliefs questionnaire (FABQ) measures of fear of pain / re-injury. It is reliable (Waddell et al., 1993) and valid (2010). The physical activity (FABQ-PA subscale) contains four statements regarding fear of pain / re-injury for which participants indicate their level of agreement on a 0 - 6 scale giving a score of 0 - 24 points. The work subscale (FABQ-W) contains seven such statements giving a score of 0 - 42 points. Higher scores reflect higher fear-avoidance beliefs.

Endurance behaviours.

The Avoidance Endurance questionnaire (AEQ) (Hasenbring et al., 2012) is a valid and reliable measure of endurance behaviours. The Thought Suppression sub-scale (TSS) comprises four statements, which examine suppression of thoughts regarding pain. The Behavioural Endurance Sub-scale (BES) comprises 12 statements, which examine persistence behaviours. Participants are asked to respond to each statement such as, "I distract myself with physical activity," on a 0 - 6 scale from, "Never," to, "Always." A mean score is derived for each subscale, with higher scores reflecting greater thought suppression or behavioural endurance.

Pain catastrophising.

The Pain Catastrophising scale (PCS) is a valid and reliable (Sullivan et al., 1995) questionnaire examining a person's thoughts and feelings in terms of magnification, rumination, and helplessness about pain. On a 0 - 4 scale participants indicate the frequency at which they experience these different types of catastrophic thoughts described in 13 statements, giving a total score of 0 - 52 points, with higher scores reflecting greater pain catastrophising. The rumination subscale comprises four statements, the magnification subscale three statements, and the helplessness subscale six statements, giving scores of 0 - 16, 0 - 12 and 0 - 24 respectively.

Pain self-efficacy.

The Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas, 2007) is a valid and reliable measure of a person's beliefs regarding their ability to undertake activities despite pain (Kaivanto et al., 1995, Asghari and Nicholas, 2001). Participants rate how confident they are of undertaking actions described in 10 statements, on a 0 - 6 scale, giving a score of 0 - 60 points, with higher scores indicating higher pain self-efficacy.

Acceptance.

The short-form Chronic Pain Acceptance Questionnaire (CPAQ-8) (2010) is a valid and reliable measure of a person's ability to have ongoing pain without attempting to avoid or control it. Participants indicate their level of agreement with eight statements relating to acceptance of chronic pain, scored on a 0 - 6 scale. It has two subscales (four statements each): pain willingness (not engaging in behaviours that lead to the avoidance of pain, particularly when this may limit functioning or reduce quality of life) and activity engagement (engaging in activities whilst in pain). There is therefore a score of 0 - 24 points for each subscale, and an overall total of 48 points indicating greater acceptance.

Multidimensional profiling variables.

CLBP is a multidimensional disorder (Simons et al., 2014), therefore variables from multiple dimensions were considered as profiling variables, to be compared between subgroups. As per the indicator variables, profiling variables were selected based on established associations with CLBP, taken from the demographic / pain characteristic dimension, health and lifestyle dimensions, tissue sensitivity dimension and movement dimension.

Demographics / pain characteristic dimension.

Assessment of the demographic / pain characteristic dimension considered age, sex, pain intensity, pain duration, CLBP-related disability, bothersomeness, and perceived risk of persistent pain.

Age and sex were collected for each participant.

Average pain intensity (during the past week) was determined using a valid and reliable NRS (0 (no pain) - 10 (worst pain imaginable)) (Dworkin et al., 2005).

Duration of symptoms was determined by asking participants, "How long have you had your back pain for?" Responses were converted into months.

CLBP-related disability was measured using the Roland Morris Disability questionnaire (RMDQ) (Roland and Morris, 1983), which examines the influences of LBP on physical activities during daily life. It is valid and reliable (Kuijer et al., 2005, Roland and Morris, 1983). The RMDQ comprises 24 items, which the participant may tick to indicate whether the item is relevant to their presentation. Scores range from 0 - 24, with higher scores indicating higher disability.

The following single question was used as a measure of the bothersomeness of any reported CLBP, "Overall, how bothersome has your back pain been in the last 2 weeks?" Responses on a five-point scale from, "not at all," to, "extremely," were dichotomised with participants answering from, "not at all," to, "moderately," forming one group, and those answering, "very much," or, "extremely" forming another (Dunn and Croft, 2005).

To assess the participant's perceived risk of persistent pain a 0 - 10 scale from the valid and reliable Örebro Musculoskeletal Pain Questionnaire was used; anchored at one end by, "No risk," and at the other by, " Very large risk," for the question, "In your view, how large is the risk that your current pain may become persistent?" (Linton and Boersma, 2003)

Health and lifestyle dimensions.

Assessment of the health and lifestyle dimensions considered stressful life events, sleep quality, mindfulness, physical activity levels, comorbidities, multiple pain sites, and perception of the low back region.

The self-perceived impact of stressful life events was measured on an NRS (0, "No stress," - 6, "Extreme stress") for the question, "In the past year, how would you rate the amount of stress in your life (at home and at work)?" This is a valid and reliable single question assessing life events and hassles (Littman et al., 2006).

The Pittsburgh Sleep Quality index (PSQI) contains 17 questions examining sleep quality, quantity, disturbance and its effect on daily living. A scoring schema is described by the original authors, which generates a final score from 0 – 21 points. If this score is above five points it suggests significant sleep disturbance. It is reliable and valid (Buysse et al., 1989).

The Mindful Attention Awareness Scale (MAAS) (Brown and Ryan, 2003) is a valid and reliable measure of mindfulness. It consists of 15 statements regarding mindfulness such as, "I break or spill things because of carelessness, not paying attention, or thinking of something else." People are asked to rate the frequency with which these statements relate to their day-to-day activities on a 0 - 6 scale. A mean score is calculated, with higher scores indicating greater mindfulness.

For the short-form version of the International Physical Activity questionnaire (IPAQ) (IPAQ Group, 2005) participants estimate the amount of activity they have done in the past seven days and the scoring guidelines (IPAQ Group, 2005) allow calculation of the number of moderate and vigorous minutes of physical activity per week. It is valid and reliable (Craig et al., 2003).

To assess the presence of comorbidities associated with CLBP, participants were asked to self-report whether they had a number of diagnosed medical conditions (specifically heart disease, diabetes, ulcer or stomach disease, anaemia or other blood disease, cancer, osteoarthritis, rheumatoid arthritis, fibromyalgia, hypertension, depression, neurological disorders, eczema, osteoporosis, incontinence or bladder problems, respiratory disorders, migraine or recurrent headache, irritable bowel syndrome, chronic fatigue syndrome, pelvic pain or vulvodynia, temporomandibular joint pain, hay fever or some other allergy, eating disorders, anxiety disorders, visual or hearing disorders, thyroid disorders) (Beales et al., 2012, Dominick et al., 2012); or undiagnosed symptoms (constipation, diarrhoea, palpitations, dizziness, chest pain, stomach discomfort, breathing difficulties, tiredness, flushes / heat sensations) (Tschudi-Madsen et al., 2011, Hagen et al., 2006). Total counts of the number of diagnosed conditions (0 - 25) and undiagnosed symptoms (0 - 9) were used for analysis.

Assessment of the regions of the body where pain was perceived was undertaken by completion of a quantifiable body chart. A grid allowed a total count of squares (0 - 256) of the body chart containing any marking to be generated. This method is valid and reliable (Öhlund et al., 1996).

The Fremantle Back Awareness questionnaire (FreBAQ) (Wand et al., 2014) examines patient perception of body schema in relation to the low back region. It consists of nine statements regarding perception of the lumbar region such as, "My back feels as though it is not part of the rest of my body," for which the participants indicate the degree of agreement with the statement using an NRS anchored at one end by, "0," and, "Never," and at the other by, "4," and, "Always". There is a maximum score of 36 points, a higher score indicating higher perceptual dysfunction. This questionnaire demonstrates adequate reliability, construct and discriminative validity (Wand et al., 2014).

Tissue sensitivity dimension.

Psychophysical sensory tests were chosen to examine somatosensory submodalities mediated by different primary afferents (C, A delta, A beta) (Jensen and Baron, 2003), and assess central nervous system nociceptive and non-nociceptive processing (Cruz-Almeida and Fillingim, 2014). This included assessment of two-point discrimination, temporal summation and pressure and thermal pain thresholds. All participants were positioned prone during testing, which was undertaken in the same order with each participant beginning with the test deemed least likely to be provocative of pain, progressing to those more likely to be provocative. An experienced clinician (MR) undertook all testing.

All tests (pain thresholds, temporal summation, two-point discrimination) were undertaken in the area of maximal lumbar pain indicated by the participant (Ho et al., 2006). Pain threshold testing (pressure, heat, cold) was also performed at the dorsal wrist joint line (Blumenstiel et al., 2011) of a pain-free wrist (if both wrists were pain-free, the non-dominant wrist), with the participant's arm supported on the plinth. The wrist was tested before the lumbar region. Testing utilised standardised instructions aligned to the Standardised Evaluation of Pain (Scholz et al., 2009) or German Research Network on Neuropathic Pain QST protocol, as

relevant (Rolke et al., 2006). Current best practice for quantitative sensory testing was adhered to (Backonja et al., 2013). Standard protocols for pain threshold testing include a 30-second inter-stimulus interval to reduce the likelihood of temporal summation (Brennum et al., 1989, Graven-Nielsen et al., 2012). Therefore, between temporal summation testing, and the application of each stimulus during pain threshold testing (pressure, heat and cold) 30-second inter-stimulus intervals were adopted. Testing of pressure pain thresholds prior to thermal pain thresholds, was also adopted to reduce the likelihood of increasing sensitisation with repeated testing (Gröne et al., 2012).

Two-point discrimination (TPD) was undertaken in the region of maximal lumbar pain only, using the method described by Moberg (1990), updated by Luomajoki and Moseley (2011). Participants were instructed that a plastic calliper ruler (Aestheisometer, DanMic Global, San Jose, USA), would be used to gently touch their lower back region. The amount of pressure applied was just enough to cause the, "very first small blanching," around the calliper points (Moberg, 1990)(p.128). Each time they were touched they were instructed to tell the examiner whether they believed they felt one or two points of the calliper touching them by saying, "One," or, "Two." Participants were also able to state that they were unsure as to whether they had felt one or two points. If they were unsure, testing simply continued, the distance between the callipers having been altered. All applications of the calliper were with the points aligned horizontally (Luomajoki and Moseley, 2011). The TPD threshold was taken as the minimum distance between the two calliper points at which the participant stated with certainty that they had been touched by two points rather than one. Both ascending and descending runs, where the distance between the calliper points were increased or decreased by 5mm at a time respectively, were tested. A mean of three runs was used to calculate the threshold. "Trick" stimuli, where the callipers were applied at a distance that was out of sequence, or where only one point made contact, were randomly applied to minimise the chances of the participant guessing. The distance between the two points of the calliper ranged from 0 - 10 centimetres.

Detection of perceived temporal summation was tested with a 26g Semmes-Weinstein nylon monofilament (Scholz et al., 2009). The participant was questioned whether the first application of the filament was painful. If so, they rated the pain intensity on the previously described NRS. If no pain was provoked, pain intensity for this stimulus was recorded as zero. The filament was then repeatedly applied (1 Hz, 30 sec). Participants rated the pain intensity again at the end of stimulation. Enhanced temporal summation was deemed to have occurred if participants perceived the initial stimulus as non-noxious, but it became noxious, increasing ≥2 points on the NRS (equivalent to the minimum clinically important difference (MCID) (Salaffi et al., 2004)) during repeated stimulation; or if participants perceived the first stimulus as noxious, and pain intensity increased ≥2 points during stimulation. A binary outcome of whether enhanced temporal summation did, or did not, occur was recorded.

Pressure pain threshold (PPT) was defined as the point when the sensation of pressure perceived by the participant changed to a sensation of pressure and pain (Rolke et al., 2006). PPT was tested using an algometer (probe size 1cm^2; Somedic AB, Sweden). Pressure increased from 0kPa, at 50 kPa/s, until the participant indicated their PPT by pressing a button. The mean of three thresholds was used for analysis.

Heat pain threshold (HPT), defined as the temperature at which a sensation of warmth becomes the sensation of heat and pain (Rolke et al., 2006), was tested using the Thermotest (Somedic AB, Sweden; thermode contact area 2.5cm x 5cm). Testing began at 32 ^{o}C, with the temperature increasing 1° C/s until the participant detected their threshold and pressed a button, or the device's upper limit (50 ^{o}C) was reached. The mean of three thresholds was used for analysis.

Cold pain threshold (CPT) was defined as the point when the sensation of cold became the sensation of cold and pain (Rolke et al., 2006). Testing CPT utilised the aforementioned contact thermode. Testing began at 32 ^{o}C, with the temperature decreasing 1 ^{o}C/s until the participant detected their threshold and pressed a

button, or the device's lower limit (4⁰C) was reached. The mean of three thresholds was used for analysis.

Movement dimension.

Assessment of the movement dimension incorporated two repeated spinal bending tasks, from which the following constructs were measured: pain provocation following repeated spinal bending, behaviours associated with pain and time taken to complete the tasks.

Participants were asked to perform the following two repeated spinal bending tasks:

1. To complete 20 forward spinal bends, with the cue to pick up a pencil from the floor.

   Repeated forward bending (20 repetitions) is a valid and reliable test of pain provocation for people with CLBP (Brouwer et al., 2003).

   Participants received standardised instructions to pick up a pencil that was placed on the floor in front of them. This counted as one forward bend. They then placed the pencil back on the floor, which counted as the second forward bend. They repeated this until a total of 20 forward bends was reached. Participants were told that they could undertake this task however they wished, and at whatever speed they wished.

2. To complete 20 backward spinal bends, with the cue to view a marker placed on the ceiling behind the participant.

   Repeated backward bending was included as it forms a common component of the physical examination for CLBP, and to determine whether pain provocation may be influenced in a directional manner (O'Sullivan, 2005).

   Participants received standardised instructions to take sight of the marker placed on the ceiling approximately 60cm behind them however they wished, at whatever speed they wished, but without turning around, and then to return to neutral before repeating the task up to a total of 20 times.

Standardised instructions were reiterated if the participant subsequently questioned whether they should perform the task in a certain manner. Participants were instructed that there would be a brief pause every five repetitions, during both tasks, to ask them to rate their pain intensity (see pain intensity during repeated movements below).

Participants were able to refuse to undertake these movements, or decline to complete the full 20 repetitions should they feel that their pain became too great, or fear exacerbation of symptoms because of these movements. The number of repetitions completed was recorded.

Video recordings were made of the repeated movements using two iPads (4th Generation) (Apple, California, USA) (1080p HD video recording) mounted on tripods. One iPad was directly in front of the participant; the second was repositioned to optimise the lateral view of the participant's lumbar region. These views allowed adequate visualisation to enable the coding of behaviours associated with pain provocation (Keefe and Block, 1982, Sullivan et al., 2006) (See below).

From these tasks it was determined whether the participant exhibited pain provocation following repeated spinal bending, and behaviours associated with pain using the methods detailed below:

Assessment of whether repeated movements influenced perceived pain intensity was undertaken by asking participants to rate their pain intensity on a valid and reliable NRS (0 (no pain) - 10 (worst pain imaginable)) (Dworkin et al., 2005), using a protocol adapted from Sullivan et al. (2009), allowing determination of whether pain increased with movement repetition. Participants rated their pain intensity before commencing the movements, then following every five repetitions. A change score was determined by subtracting the pain intensity score after the last set of repetitions completed (maximum 20) from the baseline score (adapted from (Sullivan et al., 2009)). Pain was subsequently deemed to have increased only if it had increased by the MCID (two-points) (Salaffi et al., 2004). Participants were subgrouped as follows: no increase in pain (<2-point change, both directions); increase in pain forward bending only (≥2-point change following forward bending,

<2-point change following backward bending); increase in pain backward bending only (≥2-point change following backward bending, <2-point change following forward bending); bidirectional increase in pain (≥2-point change both directions). Subgroup membership was used for profiling.

Assessment of behaviours associated with pain was undertaken by viewing video playback, using both angles, and repeated viewings where necessary, to obtain a total count of behaviours witnessed during the first five bends of each movement task (Sullivan et al., 2006, Keefe and Block, 1982). No minimum duration was stipulated for any behaviour (Sullivan et al., 2006). Assessment of these behaviours demonstrates good intra-rater agreement (Keefe and Block, 1982).

Protective behaviours included:

a) guarding - abnormally slow or rigid movements
b) bracing - using a limb for extra support during movement
c) rubbing or holding the affected area

Communicative behaviours included:

a) grimacing, or other facial expressions of pain
b) sighing, grunting, moaning etc.

From the video playback, the time (seconds), taken to complete the first five bends in each direction, was also recorded. This commenced at the initiation of the first bend, and was completed at the participant's return to a neutral standing position after the fifth bend.

5.2.4   Statistical Analysis

Data management prior to latent class analysis.

The number of participants with missing data for each variable are detailed in Tables 1-5. For questionnaires missing data management was undertaken as suggested in original manuscripts, where described. Otherwise, if one item was missing the imputed average of other items was used in the calculation of the questionnaire total, with the exception of the Pittsburgh Sleep Quality index for

which omission of certain single items means it is impossible to generate the total score. Questionnaire totals were coded as missing, when two or more items were missing. Only 76.2% of the sample was currently working, therefore data from the FABQ (Work) were excluded from analysis. Before LCA, the PSEQ score was reversed, so that a higher score reflected worse psychological functioning across all indicator variables. Two participants declined to undertake the movement task in both directions. For subgrouping purposes, these directions of movement were coded as provocative for these participants. For behaviours associated with pain, and time taken to complete bending tasks, these participants were coded as missing. Testing for temporal summation revealed 28 (9.5%) participants who perceived the initial stimulus as non-noxious, but it increased ≥ two-points on an NRS during stimulation. Four participants (1.4%) perceived the initial stimulus as noxious, and deemed the pain intensity to increase by ≥ two-points during stimulation. These two groups were combined for future analysis (n=32, 10.9%).

Latent class analysis.

LCA was used to estimate the number of clusters based upon responses to the psychological indicator variable questionnaires. LCA is a probabilistic form of cluster analysis using maximum likelihood estimation, which has advantages over traditional distance-based cluster procedures by allowing statistical evaluation of the optimal number of clusters, inclusion of variables with differing measurement types, and calculation of classification probabilities for each participant (Magidson and Vermunt, 2002, Collins and Lanza, 2010). Sample size requirements for LCA are not definitive, but depend upon many factors including the size and number of true latent classes, and the model complexity (number, type and correlation of indicator variables). However, simulation studies of LCA suggest >200 participants are preferable when using continuous variables (Nylund et al., 2007) and >300 participants with dichotomous variables (Swanson et al., 2012).

LCA was performed using 12 psychological indicator variables. A sample size of 300 participants allows accurate latent class derivation based upon inclusion of 12 indicator variables (Swanson et al., 2012). Models containing between one and five

clusters were estimated. One thousand random starts were estimated to reduce the possibility of local solutions. Models were developed with examination of unique log-likelihood solutions, degree of contributions of each indicator variable, and residual correlations within classes. Examination of model fit involved comparison of model fit statistics (Akaike information criterion (AIC), and Bayesian information criterion (BIC)) and posterior probability diagnostics. Cluster membership for each participant was then determined based upon posterior probability. To ensure the skewed nature of the ordinal data for some scales did not influence the latent class estimations, models were also estimated using quantiles of each indicator variable. As this procedure generated similar solutions the solution derived from raw data is presented, with increased confidence in validity of parameter estimates.

Multidimensional profiling.

Between-cluster differences in indicator and profiling variables were examined using analysis of variance for normally-distributed variables, Kruskal-Wallis one-way analysis of variance for variables with skewed data, and chi-squared analysis for dichotomous data.

No correction for multiple comparisons was undertaken. As LCA is an exploratory technique for deriving clusters within a sample (Collins and Lanza, 2010), we maintained p-values such that while there was a greater chance of type I error, there was less chance of type II error (Armstrong, 2014).

Latent class analysis was undertaken using Latent GOLD 4.5 (Statistical Innovations Inc., Belmont, USA), and all other statistical procedures performed using Stata 13.1 (Statacorp, Texas, USA).

5.2.5 Results

Latent class analysis.

Initial latent class models included 12 psychological indicator variables (Table 1), but due to an inability to obtain a unique log-likelihood solution, only those eight indicators contributing substantially to the models ($R^2 > 0.3$) were retained. The

indicator variables retained in the model were: DASS depression subscale, DASS anxiety subscale, DASS stress subscale, TSS of the AEQ, PCS rumination, PCS magnification, PCS helplessness and PSEQ (reverse scored). Using these eight indicators, models containing between one and five clusters were estimated.

The three and four cluster models were examined in detail. The three cluster model had the most unique log likelihood, and was supported by the BIC statistic (One cluster model: 14008, two cluster model: 13619, three cluster model: 13515, four cluster model: 13550, five cluster model: 13579). There was also an increase in classification error associated with the four cluster model (0.07) compared to the three cluster model (0.05). However, the four cluster model was supported by examining the results of the conditional bootstrapping procedure, which suggested that the four cluster model was a better fit than the three cluster model ($p=<.001$), and by the AIC statistic (one cluster model: 13927, two cluster model: 13454, three cluster model: 13265, four cluster model: 13215, five cluster model: 13159). Therefore, for both the three and four cluster models, cluster profiles were calculated using raw data from each retained indicator variable. These profiles, combined with their graphical representation, and the relative distributions of cluster membership, were visually inspected and compared between models. Interpretation of the cluster profiles in both models was informed by comparison to published data from healthy controls and, where available, from CLBP samples. In the four cluster model, there were two clusters with generally low scores across all indicator variables. These two clusters equated to splitting the lowest scoring cluster from the three cluster model. It was determined that retaining these 2 clusters would not facilitate the clinical interpretation of the cluster profiles. Therefore, the final solution chosen was the three cluster model, this being the most parsimonious.

For the three cluster model the mean (SD) probability of membership was .95 (.09), .94 (.10) and .93 (.11) for Clusters 1, 2 and 3 respectively. This exceeds the recommended minimum for model adequacy of .7 (Nagin, 2005). The odds of correct classification were 63.6, 11.3 and 60.5 for Clusters 1, 2 and 3 respectively. Larger measures indicate better assignment accuracy, and a minimum value of 5

has been suggested to represent high assignment accuracy (Nagin, 2005). The classification error of the three cluster model was acceptable at 0.05.

Figure 1 displays the three cluster solution. Cluster 1 (23.5%) was characterised by low scores across all retained indicator variables. Cluster 2 (58.8%) had relatively low scores related to negative affect (particularly the DASS depression and anxiety scores), with moderately high scores on the other indicator variables. Cluster 3 (17.7%) was characterised by high scores across all retained indicator variables.

Table 1 shows descriptive statistics for questionnaire scores for each cluster, for each of the eight retained indicator variables and four variables that did not contribute significantly to the final model. There were significant differences between clusters for each of the variables except the two CPAQ-8 subscales.
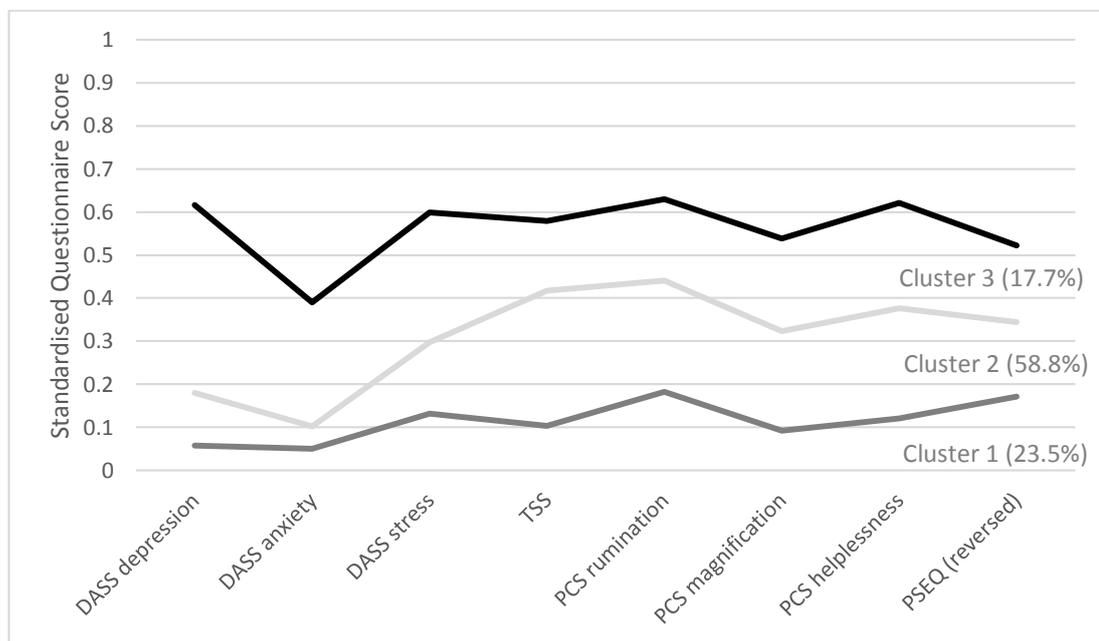
Figure 1. Final three cluster model derived using latent class analysis, with all psychological questionnaire scores standardised to a common scale (0-1). DASS depression etc. – Depression Anxiety Stress scales depression score etc., TSS – Thought Suppression subscale score, PCS rumination etc. – Pain Catastrophising scale rumination score etc., PSEQ – Pain Self-Efficacy questionnaire score (reversed).

Table 1

Psychological Indicator Variable Questionnaire Scores For The Three Clusters Derived Using Latent Class Analysis

Indicator variable	Cluster 1 (n=69, 23.5%)	Cluster 2 (n=173, 58.8%)	Cluster 3 (n=52, 17.7%)	*p*-value
DASS depression score* median (IQR) (min, max)	2[a] (0, 4) (0, 10)	6[b] (2, 12) (0, 24)	28[c] (20, 34) (0, 42)	**<.001[1]**
DASS anxiety score* median (IQR) (min, max)	2[a] (0, 4) (0, 10)	4[b] (2, 6) (0, 18)	16[c] (8, 24) (0, 42)	**<.001[1]**
DASS stress score* median (IQR) (min, max)	6[a] (2, 8) (0, 16)	12[b] (8, 18) (0, 36)	24[c] (20, 32) (12, 42)	**<.001[1]**
FABQ-PA mean (SD) (min, max)	12.5[a] (6.1) (0, 24)	14.3[b] (5.8) (0, 24)	17.7[c] (4.7) (6, 24)	**<.001[2]**
TSS* median (IQR) (min, max)	.2[a] (0, 1) (0, 2.5)	2.8[b] (1.5, 3.5)[3] (0, 6)	3.6[c] (2.8, 4.4) (0, 6)	**<.001[1]**
BES mean (SD) (min, max)	2.6[a] (1.1) (.3, 5.6)	3.2[b] (.9) (0, 5.9)	3.3[b] (1.2) (0, 6)	**<.001[2]**

Indicator variable	Cluster 1 (n=69, 23.5%)	Cluster 2 (n=173, 58.8%)	Cluster 3 (n=52, 17.7%)	p-value
PCS (Rumination)* median (IQR) (min, max)	2[a] (1, 5) (0, 9)	7[b] (4, 10) (0, 16)	10[c] (7, 13)[3] (0, 16)	**<.001[1]**
PCS (Magnification)* median (IQR) (min, max)	1[a] (0, 2) (0, 4)	4[b] (2, 5) (0, 12)	7[c] (4, 9)[3] (0, 12)	**<.001[1]**
PCS (Helplessness)* median (IQR) (min, max)	3[a] (1, 4) (0, 7)	9[b] (6, 12) (0, 21)	15[c] (12, 19)[3] (2, 24)	**<.001[1]**
PSEQ* median (IQR) (min, max)	50[a] (46, 54) (36, 60)	40[b] (32, 48) (7, 60)	28.5[c] (19.5, 37.5) (1, 57)	**<.001[1]**
CPAQ (Pain willingness) mean (SD) (min, max)	9.5 (5.0) (1, 22)	8.7 (4.7) (0, 21)	9.5 (5.1) (0, 20)	.41[2]
CPAQ (Activity engagement) median (IQR) (min, max)	18 (14, 20) (5, 2)	18 (15, 20) (0, 24)	17 (12.5, 22) (6, 24)	.89[1]

Note. [1] Kruskal-Wallis one-way analysis of variance; [2]analysis of variance; [3] missing in one case

* Indicates indicator variable included in final three cluster model

[a,b,c] Superscripted letters define significantly different groups, i.e. results with different letters are significantly different

DASS – Depression Anxiety Stress scales; FABQ-PA – Fear-Avoidance Beliefs questionnaire – Physical activity; CPAQ – Chronic Pain Acceptance Questionnaire; TSS – Thought Suppression Subscale; BES – Behavioural Endurance subscale; PCS – Pain Catastrophising scale; PSEQ – Pain Self-Efficacy Questionnaire

Multidimensional profiling.

Descriptive data are detailed in Tables 2-5 for each profiling variable including demographics, pain characteristics, health and lifestyle factors, tissue sensitivity, pain responses to movement and behaviours associated with pain.

Demographic / pain characteristic dimension.

There was a significant between-group difference for median age, with Cluster 1 being significantly older than Cluster 3. Cluster 1 reported significantly lower pain intensity in the past week, and had a significantly lower proportion of people who deemed their CLBP very or extremely bothersome than the other clusters. There was a significant progressive increase in disability levels from Cluster 1 to Cluster 3 (Table 2).

Health and lifestyle dimensions.

There was a significant progressive increase in reported stressful life events from Cluster 1 to Cluster 3. Conversely, there was a significant progressive decrease in mindfulness from Cluster 1 to Cluster 3. There was a significant progressive increase in FreBAQ scores (indicating greater distortion of perception of the low back region) from Cluster 1 to Cluster 3. Cluster 3 also had a significantly greater number of undiagnosed comorbid symptoms and more widespread pain (filled-in body chart squares) than Clusters 1 and 2 (Table 3).

Tissue sensitivity dimension.

Cluster 3 had significantly greater pressure pain sensitivity at the lumbar spine than Clusters 1 and 2 (Table 4).

Movement dimension.

Comparing pain responses to movement Cluster 1 was significantly different from Clusters 2 and 3, having a greater proportion of people with no increase in pain following repeated movements, and a lesser proportion of people with bidirectional increases in pain following repeated movement. Behaviours associated with pain (protective / guarding), and time taken to complete the bending tasks, were examined separately for forward and backward bending. However, there were no

significant differences found, therefore Table 5 contains summed data for these variables.

Table 2

Demographic and pain characteristic data for the three clusters derived using latent class analysis

Variable	Cluster 1 (n=69, 23.5%)	Cluster 2 (n=173, 58.8%)	Cluster 3 (n=52, 17.7%)	p-value
Demographics				
Age, years median (IQR) (min,max)	56[a] (41, 63) (20, 70)	50[ab] (39, 60) (18, 70)	45[b] (29, 55) (19, 68)	**.002[1]**
Female n(%)	41 (59.4)	93 (53.8)	34 (65.4)	.30[2]
Pain characteristics				
Pain intensity (NRS) mean (SD) (min,max)	5.1[a] (2.0) (2, 9)	6.0[b] (1.8) (2, 10)	6.2[b] (1.6) (3, 10)	**<.001[3]**
Duration of CLBP, months median (IQR) (min,max)	144 (60, 300) (6, 540)	120 (36, 240) (3, 720)[4]	96 (36, 150) (4, 516)	.10[1]
RMDQ Score median (IQR) (min,max)	6[a] (6, 9) (5, 18)	9[b] (7, 13) (5, 21)	12[c] (9, 16.5) (5, 24)	**<.001[1]**
Bothersomeness (very / extremely) n (%)	19[a] (27.5)	100[b] (57.8)	35[b] (67.3)	**<.001[2]**
Perceived risk of persistent pain (NRS) median (IQR) (min,max)	8 (7, 10) (3, 10)	9 (8, 10) (3, 10)	9 (8, 10) (6, 10)	.15[1]

Note. [1] Kruskal-Wallis one-way analysis of variance; [2] χ^2 analysis; [3] analysis of variance; [4] missing in four cases
[a,b,c] Superscripted letters define significantly different groups, i.e. results with different letters are significantly different
NRS – numeric rating scale; RMDQ – Roland Morris Disability questionnaire

Table 3

Health and lifestyle data for the three clusters derived using latent class analysis

Variable	Cluster 1 (n=69, 23.5%)	Cluster 2 (n=173, 58.8%)	Cluster 3 (n=52, 17.7%)	*p*-value
Stressful life events (0-6) mean (SD) (min, max))	2.9[a] (1.7) (0, 6)	3.7[b] (1.4) (0, 6)	4.5[c] (1.0) (2, 6)	**<.001[1]**
PSQI mean (SD) (min, max)	9.4 (4.0) (2, 17)[4]	9.1 (3.9) (2, 19)[6]	9.2 (4.7) (2, 20)	0.90[1]
MAAS mean (SD) (min, max)	4.7[a] (.7) (2.8, 6.0)[3]	4.1[b] (.7) (1.9, 5.9)[3]	3.5[c] (1.0) (1.3, 5.6)[3]	**<.001[1]**
Moderate and vigorous activity (min/week) median (IQR) (min, max)	120 (0, 360) (0, 1620)[5]	105 (0, 300) (0, 2100)[5]	180 (0, 360) (0, 1260)[5]	0.51[2]
Diagnosed comorbid disorders median (IQR) (min, max)	2 (0, 3) (0, 10)	2 (1, 3) (0, 11)	2 (1, 3) (0, 9)	0.91[2]
Undiagnosed comorbid symptoms median (IQR) (min, max)	2[a] (1, 4) (0, 9)	2[a] (1, 4) (0, 9)	4[b] (2, 5) (0, 9)	**0.003[2]**
Body chart squares filled in median (IQR) (min, max)	9[a] (5, 16) (2, 84)	13[a] (7, 20) (1, 75)	17[b] (11, 28) (4, 62)	**<.001[2]**
FreBAQ mean (SD) (min, max)	5.9[a] (4.2) (0, 18)	9.5[b] (5.8) (0, 25)	15.6[c] (7.6) (1, 32)	**<.001[1]**

Note. [1] analysis of variance; [2]Kruskal-Wallis one-way analysis of variance; [3] missing in one case; [4] missing in four cases; [5] missing in two cases; [6] missing in seven cases
[a,b,c] Superscripted letters define significantly different groups, i.e. results with different letters are significantly different
PSQI – Pittsburgh Sleep Quality index; MAAS – Mindful Attention Awareness scale

Table 4

Pain sensitivity data for the three clusters derived using latent class analysis

Variable	Cluster 1 (n=69, 23.5%)	Cluster 2 (n=173, 58.8%)	Cluster 3 (n=52, 17.7%)	*p*-value
Temporal summation n (%)	10 (14.7)	33 (19.1)	13 (25.0)	.36[1]
PPT wrist (kPa) median (IQR) (min,max)	269.0 (191.3, 385.3) (80.0, 1060.3)	268.0 (184.0, 344.7) (55.3, 1200.0)	271.0 (142.7, 330.2) (57.0, 939.0)	.42[2]
PPT lumbar (kPa) median (IQR) (min,max)	283.0[a] (197.3, 506.7) (36.7, 1349.0)	281.7[a] (168.7, 458.7) (37.0, 1600.0)	178.5[b] (95.7, 402.0) (49.0, 964.0)	**.007[2]**
HPT wrist (°C) median (IQR) (min,max)	45.5 (43.7, 48.1) (34.5, 50.0)	45.3 (42.5, 47.8) (33.9, 50.0)	45.0 (41.4, 47.6) (32.2, 50.0)	.52[2]
HPT lumbar (°C) mean (SD) (min,max)	42.4 (3.8) (34.6, 50.0)	42.7 (3.8) (33.6, 50.0)	41.5 (4.4) (33.6, 50.0)	.17[3]
CPT wrist (°C) median (IQR) (min,max)	5.6 (4.0, 13.9) (4.0, 27.9)	4.7 (4.0, 11.5) (4.0, 30.5)	6.5 (4.0, 14.8) (4.0, 30.6)	.42[2]
CPT lumbar (°C) median (IQR) (min,max)	4.0 (4.0, 20.7) (4.0, 30.5)	4.2 (4.0, 24.0) (4.0, 30.9)	8.6 (4.0, 24.7) (4.0, 31.2)	.14[2]
Two-point discrimination (cm) mean (SD) (min,max)	5.4 (2.1) (.5, 10)	5.9 (2.2) (.5, 10)	5.9 (2.1) (.5, 10)	.27[3]

Note. [1] χ² analysis; [2]Kruskal-Wallis one-way analysis of variance ; [3] analysis of variance

[a,b] Superscripted letters define significantly different groups, i.e. results with different letters are significantly different

PPT – pressure pain threshold; HPT – heat pain threshold; CPT – cold pain threshold; kPa – kilopascals; °C – degrees centigrade

Table 5

Pain responses to repeated spinal movements, and behaviours associated with pain for the three clusters derived using latent class analysis

Variable		Cluster 1 (n=69, 23.5%)	Cluster 2 (n=173, 58.8%)	Cluster 3 (n=52, 17.7%)	*p*-value
Pain responses to repeated movements n (column %)	No increase in pain	47 (68.1)	80 (46.2)	17 (32.7)	**<.001[1]**
	Increased pain, forward bend only	14 (20.3)	46 (26.6)	23 (44.2)	
	Increased pain, backward bend only	5 (7.2)	22 (12.7)	2 (3.8)	
	Bidirectional increase in pain	3 (4.4)	25 (14.4)	10 (19.2)	
Total guarding/bracing during repeated movements (bidirectional) median (IQR) (min, max)		5 (1, 9) (0, 15)	5 (0, 10) (0, 20)[3]	7.5 (0, 10) (0, 15)[4]	0.64[2]
Total time to complete forward/backward bending (sec) median (IQR) (min, max)		33 (28, 39) (18, 69)	35 (29.5, 42) (20, 95)[3]	38 (31, 50) (23, 225)[4]	0.15[2]

Note. [1] χ^2 analysis; [2] Kruskal-Wallis one-way analysis of variance; [3] missing in one case; [4] missing in three cases

5.2.6 Discussion

We derived three psychological clusters from a broad range of psychological measures in this CLBP cohort. Cluster 1 (23.5%) was characterised by low scores across all retained indicator variables. Compared to Cluster 1, cognitive scores for Cluster 2 (58.8%) included elevated thought suppression and pain catastrophising, and lower pain self-efficacy, while affective scores (depression, anxiety, stress) remained relatively low. Cluster 3 (17.7%) demonstrated higher scores across all retained indicator variables.

Data from our clusters can be compared to questionnaire cut-off scores and normative data. Depression, anxiety and stress can be classified as normal (Lovibond and Lovibond, 1995) for Clusters 1 and 2, and are similar to healthy controls, except stress which appears slightly elevated in Cluster 2 (Mitchell et al., 2009). Cluster 3 may be classified as having extremely severe depression, severe anxiety and moderate stress (Lovibond and Lovibond, 1995), with elevated scores compared to healthy controls (Mitchell et al., 2009).

Cluster 1 had lower median thought suppression (0.2) than the mean (SD) (3.5 (1.0)) reported in a previous LBP cohort (Scholich et al., 2012), consistent with their overall low-scoring psychological profile. Pain catastrophising scores were similar to healthy controls in Cluster 1, while in Cluster 2 scores appeared elevated but due to large standard deviations may still be within normal limits (Mitchell et al., 2009). In Cluster 3, pain catastrophising was elevated compared to healthy controls (Mitchell et al., 2009), being the only cluster with a median score >30 indicating clinically-relevant pain catastrophising (Sullivan, 1995). For pain self-efficacy, Cluster 3 scored similarly to a CLBP cohort attending pain management (Nicholas, 2007), Cluster 2 scored similarly to people seeking treatment in primary care (Costa et al., 2011), while the median score for Cluster 1 was significantly higher (e.g. greater self-efficacy) (Lee et al., 2015). Fear-avoidance beliefs were elevated in all clusters compared to healthy controls (Dedering and Börjesson, 2013), however, Cluster 3 scored notably higher than other CLBP cohorts (Wertli et al., 2014).

Although fear-avoidance beliefs and behavioural endurance did not contribute discriminatory information to cluster analysis, and therefore were not retained indicator variables, they differed between clusters. Contrastingly, pain acceptance was not retained and did not differ across clusters. Our findings are presented by considering psychologically-derived clusters, their multidimensional profiling and clinical implications.

Psychologically-derived clusters.

This study included the broadest range of psychological measures to date for the derivation of clusters in people with CLBP, where previous studies tend to cluster on a limited number of factors such as coping strategies, affect, somatisation or attitudes towards pain ((Viniol et al., 2013, Strong et al., 1995). This study included factors used in previous but less comprehensive clustering studies (e.g. depression, anxiety), but added novel factors (e.g. thought suppression).

In addition our study used LCA allowing optimised assignment of individuals to clusters and statistical evaluation of the optimal number of clusters (Collins and Lanza, 2010). LCA is more accurate at identifying clusters than the k-means cluster analysis (Magidson and Vermunt, 2002) used in isolation in two previous cluster analysis studies involving people with CLBP (Viniol et al., 2013, Strong et al., 1995).

While direct comparison with other psychological cluster analysis studies is complicated by variability in the measures and clustering techniques used, similarities exist suggesting possible common psychological presentations. Numerous studies deriving two, three or four cluster solutions describe broadly similar low and high-scoring psychologically-derived clusters in acute / sub-acute LBP (Boersma and Linton, 2005, Barons et al., 2014, Hirsch et al., 2014), LBP of variable duration (49% CLBP) (Beneciuk et al., 2015) and CLBP (Viniol et al., 2013, Strong et al., 1995)). Consistent with our findings, lower-scoring CLBP clusters presented with lower anxiety and depression; higher pain self-efficacy and positive coping strategies (Strong et al., 1995, Viniol et al., 2013). Higher-scoring clusters had higher anxiety and depression, and more negative coping strategies (Strong et al., 1995, Viniol et al., 2013). Further comparison with these studies is limited by use of

differing questionnaires (e.g. Coping Strategies questionnaire, Survey of Pain Attitudes (Strong et al., 1995)).

Three studies, with three or four cluster solutions, derived intermediate clusters scoring relatively low for affect (predominantly depression), and relatively high on fear-avoidance beliefs (Boersma and Linton, 2005, Barons et al., 2014, Hirsch et al., 2014); also having intermediate levels of pain intensity and disability broadly consistent with Cluster 2. These studies involved acute / sub-acute cohorts, suggesting characteristics shown by Cluster 2 may develop at an early stage. The identification of Cluster 2 where depression and anxiety were normal, but cognitive variables such as thought suppression, fear-avoidance beliefs and pain catastrophising were elevated and pain self-efficacy was lower, appears clinically important as these factors have previously been associated with greater pain and disability in CLBP, potentially warranting tailored management (Cook et al., 2006, Thibault et al., 2008, Foster et al., 2010, Crombez et al., 1999).

Multidimensional profiling.

The broad range of profiling variables in this study is novel, having been limited in other cluster analysis studies to demographics, pain characteristics, employment, healthcare utilisation and comorbidities (Hirsch et al., 2014, Boersma and Linton, 2005, Viniol et al., 2013, Strong et al., 1995, Barons et al., 2014, Beneciuk et al., 2015). Such novel multidimensional profiling adds a new level of validation to the derived clusters (Kent et al., 2010). Consistent with our findings, previous studies have reported higher pain intensity and disability, and more widespread pain and comorbidities associated with higher versus lower-scoring psychological clusters (Strong et al., 1995, Viniol et al., 2013). Although statistically significant, differences in pain intensity between clusters are below the MCID, so may not be clinically important (Salaffi et al., 2004), while the difference in disability between Clusters 1 and 3 is clinically important, being greater than the MCID on the RMDQ (Stratford et al., 1996).

Cluster 1 had the most localised pain, lowest pain intensity (5.1 / 10 on an NRS), least bothersomeness (27.5% rated their CLBP very / extremely bothersome) and

lowest disability levels (RMDQ score: 6). Cluster 1 had the highest proportion of participants with no increase in pain following repeated bending, and lowest proportion with increased pain following repeated forward and backward bending (bidirectional). While comparing pain sensitivity in these clusters with healthy controls should be undertaken cautiously due to different test sites / protocols and large standard deviations, Cluster 1 appears within normal limits for pain sensitivity (Neziri et al., 2011, Pfau et al., 2014, Rolke et al., 2006, Magerl et al., 2010). Cluster 1 had the lowest levels of stressful life events and undiagnosed comorbid symptoms, and highest mindfulness. While they had low scores for distorted body perception compared to other clusters and a previously reported CLBP cohort, they still scored higher than healthy controls (Wand et al., 2014).

Cluster 2 had more widespread pain, and higher pain intensity (6.0) and bothersomeness (57.8%) than Cluster 1, intermediate levels of disability (RMDQ score: 9) and the most even spread of pain provocation responses following repeated bending. Pain sensitivity appeared within normal limits (Neziri et al., 2011, Pfau et al., 2014, Rolke et al., 2006, Magerl et al., 2010). However, Cluster 2 had intermediate levels of stressful life events, mindfulness and distorted body perception.

Cluster 3 (17.7%) had higher pain intensity (6.2) and bothersomeness (67.3%) than Cluster 1, the most widespread pain and greatest disability (RMDQ score: 12). They had the highest proportion of participants with increased pain following repeated forward bending, and forward and backward bending (bidirectional), and lowest proportion with no pain increase following repeated bending. Cluster 3 had a significantly lower lumbar PPT suggesting increased sensitivity compared to normative data (Neziri et al., 2011, Pfau et al., 2014). They also had the highest levels of undiagnosed comorbid symptoms, and stressful life events and lowest mindfulness. Compared to Clusters 1 and 2, greater undiagnosed comorbid symptoms and stressful life events, combined with their higher psychological profile, suggests increased allostatic load may be relevant to Cluster 3's presentation (Dominick et al., 2012). Cluster 3 had the greatest distortion of body perception, higher than a previous CLBP cohort (Wand et al., 2014). Consistent with

this study, body perceptual distortion has been positively associated with pain intensity and pain catastrophising (Wand et al., 2014) possibly through altered interoception (Tsay et al., 2015). This cluster is similar to a previously reported CLBP subgroup demonstrating increased pain sensitivity, higher DASS scores, greater sleep disturbance and high levels / prolonged pain responses to movement (O'Sullivan et al., 2014).

There were no significant differences between clusters for protective behaviours despite previous associations between these behaviours and pain intensity and disability (Sullivan et al., 2006), which did differ between clusters. Two-point discrimination, reflecting body schema within the primary somatosensory cortex (S1) (Pleger et al., 2005), did not differ between clusters despite differing body perception (Wand et al., 2014), suggesting these measures reflect differing perceptual constructs. Sleep quality was similar across all clusters despite poor sleep being previously associated with greater stress (Åkerstedt, 2006) and depression (Boakye et al., 2015), both of which differed between clusters. However, PSQI scores represented significant sleep disturbance (Buysse et al., 1989) across all clusters, consistent with other people with CLBP (Marty et al., 2008).

Clinical implications.

As this study was cross-sectional, the nature and direction of associations between and within clusters is unknown. It is also unknown whether cluster membership predicts outcomes, however, previous research involving psychologically-derived clusters would suggest this is likely (Boersma and Linton, 2005, Barons et al., 2014, Hirsch et al., 2014).

Although our clusters were psychologically-derived, multidimensional profiling may provide greater direction for targeted care (Rusu et al., 2012). While the literature documents multiple psychological subgrouping studies, few have targeted treatments to psychologically-derived subgroups. Where matched treatments have been offered, long-term outcomes have been similar to control or unmatched treatments (Hill et al., 2011, Bergbom et al., 2014, Verra et al., 2015). One limitation of these approaches may be the lack of targeting other dimensions such as pain

responses to movement, distorted body perception and higher pain sensitivity. While there is early evidence suggesting management tailored towards findings from structured examination of multidimensional profiles in people with CLBP may offer improved outcomes compared to usual care (Vibe Fersum et al., 2013), further research is needed.

While speculative, targeted management for Cluster 1 could involve challenging fear-avoidance beliefs and protective behaviours, while employing strategies to improve sensorimotor perception and sleep quality. In Cluster 2, management could target cognitive factors such as pain catastrophising and pain-self efficacy, and sensorimotor disturbances, as well as enhancing stress resilience and sleep quality. Cluster 3's multidimensional profile suggests tailored multidisciplinary management might target psychological factors, sleep quality and sensorimotor disturbances in parallel with appropriate pharmacological management (Baron et al., 2013) and addressing comorbidities (Hartvigsen et al., 2013).

Strengths and limitations.

Most participants were recruited via advertisements, facilitating generalizability to the wider community. Only participants with dominant CLBP (Wai et al., 2009) were included, minimizing the likelihood of participants having radiculopathy. Other inclusion criteria included reporting pain intensity ≥two-points on an NRS and scoring ≥five-points on the RMDQ, which may have influenced cluster membership, reducing the size of the low-scoring cluster.

Clinical measures chosen to facilitate translation into practice and reduce participant burden were not necessarily gold standard measurements (e.g. PSQI scores versus polysomnography). Gold standard measurements may facilitate further understanding of multidimensional profiles, and subsequent management directions.

5.2.7 References

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Chapter Six – Study Four

6.1   Introduction To Study Four

This research derived subgroups of people with different clinical profiles on three key dimensions from within a multidimensional model of CLBP. This chapter presents the third subgrouping study, based upon pain responses following repeated forward and backward spinal bending. Examination of pain responses following repeated spinal bending were examined because provocation of pain with movement is common in people with CLBP, is associated with greater disability and acts as a barrier to rehabilitation (Sullivan et al., 2009). Also, while *amelioration* of pain with repeated movements has been well examined and may be considered predictive of greater improvements in pain and disability during conservative treatment for people with CLBP (Long, 1995), this phenomenon is less common in CLBP populations (May and Aina, 2012). Pain *provocation* following forward and backward bending has been reported to vary in people with CLBP based upon movement direction (Rabey et al., 2015, Fujiwara et al., 2010, Hidalgo et al., 2014), and judgementally-derived CS involving directional pain responses to movement have been described (McKenzie and May, 2003, Sahrmann, 2002, O'Sullivan, 2000). However, differing pain responses following repeated movements have not, to date, been examined in a non-judgemental manner, using valid and reliable measures of clinically important changes in pain (Dworkin et al., 2005, Salaffi et al., 2004), using a standardised protocol of repeated forward and backward bending in a large cohort of people with CLBP. While such pain responses following movement may be influenced by physical, psychosocial, neurophysiological and lifestyle factors, this remains relatively unexplored (Hodges and Smeets, 2015, Ung et al., 2014, Sullivan et al., 2006). Examination of multidimensional profiles of subgroups based upon pain responses following repeated movement may further understanding of these interactions.

Participants in the CLBP cohort were initially examined based upon whether they experienced a change in pain of at least two-points on an 11-point NRS following repeated forward and backward bending. Preliminary analysis revealed that

relatively few participants achieved pain amelioration with repeated movements, therefore subgroups were formed based upon pain increases only. Consideration of clinically important pain increases (≥ two-points on 11 point NRS) with repeated forward and backward spinal bending generated two binary variables, allowing participants to be simply grouped according to their response pattern as follows:

i) No increase in pain (either direction).

ii) Increased pain following repeated forward bending only.

iii) Increased pain following repeated backward bending only.

iv) Increased pain following forward and back bending (bidirectional).

The derived subgroups were profiled on variables from multiple dimensions associated with CLBP. Examination of the different pain responses following repeated bending and the multidimensional profiles associated with the derived subgroups allows postulation regarding mechanisms contributing to the persistence of CLBP in each subgroup and their clinical implications.

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6.2   Study Four

Pain Provocation Following Repeated Movements In People With Chronic Low Back Pain: Subgrouping And Multidimensional Profiles

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6.2.1 Abstract

Objectives.

To derive subgroups in people with chronic low back pain (n=294) based upon pain responses following repeated spinal bending.

Methods.

Subgroups were derived based upon clinically-important (≥two-points on an 11-point numeric rating scale), directional changes in pain intensity following repeated forward and backward bending. Subgroups were subsequently profiled on demographics, pain characteristics, protective behaviours, pain sensitivity (pressure, heat and cold pain thresholds, temporal summation), psychological, health and lifestyle factors.

Results.

Four subgroups were derived: one had no clinically-important increased pain bending in either direction (49.0%), another had increased pain with repeated forward bending only (28.2%), while another was provoked by repeated backward bending only (9.9%). The fourth had increased pain bending in both directions (12.9%). The first subgroup appeared normal for pain sensitivity, depression, anxiety, stress and pain catastrophising; but had elevated fear-avoidance beliefs and distorted body perception compared to healthy controls. Those provoked by forward bending had elevated disability and pain catastrophising, slower movement, and low pain self-efficacy compared to other subgroups; and elevated depression and fear-avoidance beliefs, and distorted body perception compared to healthy controls. Those provoked by backward bending had elevated fear-avoidance beliefs and distorted body perception compared to healthy controls. The fourth subgroup had higher pain intensity, pain catastrophising and lower pain self-efficacy than other subgroups; and elevated lumbar pressure and cold pain sensitivity, depression, fear-avoidance beliefs and distortion of body perception compared to healthy controls.

Discussion.

Pain provocation following repeated movements in people with chronic low back pain appears heterogeneous. Neurophysiological mechanisms relating to each subgroup are postulated.

6.2.2   Introduction

Clinicians commonly evaluate pain responses to repeated movement in people with chronic low back pain (CLBP), particularly forward / backward spinal bending (McKenzie and May, 2003), as exacerbation of pain in response to such functional movements commonly acts as a barrier to recovery (Sullivan et al., 2009, Reneman et al., 2002, Fujiwara et al., 2010). These pain responses are reported to vary based on movement direction, as well as patterns of amelioration and provocation. For some pain is influenced by forward bending or backward bending, while for others it is both directions, or not at all (Rabey et al., 2015, Fujiwara et al., 2010, Hidalgo et al., 2014). While directional patterns of pain amelioration and provocation with repeated movement have been reported in studies including people with CLBP (Long et al., 2004, Dankaerts et al., 2009) this has been based upon clinical judgement, rather than a standardised testing protocol, possibly introducing bias to the assessment (Ford et al., 2007).

It has been proposed that pain responses to movement are likely to reflect complex sensorimotor interactions potentially influenced by multiple dimensions including physical, psychosocial, neurophysiological and lifestyle factors (Hodges and Smeets, 2015, Ung et al., 2014). For example, in people with CLBP undertaking repeated lifting, pain intensity has been positively associated with kinesiophobia, pain catastrophising and depression, as well as protective behaviours (Sullivan et al., 2006). Kinesiophobia is also associated with greater back muscle activity and reduced lumbar flexion during forward bending (Geisser et al., 2004, Thomas and France, 2007). A recent systematic review reported that people with CLBP have reduced range of motion and move more slowly than healthy controls (Laird et al., 2014). Furthermore, people with CLBP who reported disproportionate pain provocation responses to spinal movement demonstrated higher localised lumbar

pressure pain sensitivity and local and remote cold pain sensitivity, and greater psychological distress compared to people with CLBP who reported proportionate pain responses to movement and had normal sensory profiles (O'Sullivan et al., 2014). These findings support the potential involvement of central pain processes in pain responses to movement in people with CLBP. Another study examining repeated lifting in people with CLBP demonstrated increasing self-reported pain intensity and increasing pressure pain sensitivity over 25 repetitions (Falla et al., 2014). These data support contemporary understanding of CLBP where multiple interacting dimensions (Simons et al., 2014) are associated with CLBP.

To date no study has determined whether different subgroups exist in a large CLBP cohort, based upon clinically-important pain responses following repeated forward and backward spinal bending utilising a standardised protocol. Furthermore, it is not known whether different pain responses to repeated movement are associated with different multidimensional profiles. This knowledge may provide insight to the factors underlying pain responses to repeated movement in order to enhance targeted management.

Therefore the aims of this study were:

i) To subgroup people with CLBP based upon clinically-important pain responses following a standardised protocol involving repeated forward and backward spinal bending.

ii) To determine whether these subgroups have differing multidimensional profiles based on demographics, pain characteristics, protective behaviours, pain sensitivity, psychological, health and lifestyle factors.

6.2.3 Materials And Methods

This research was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013). All study procedures were approved by the Human Research Ethics Committees of Curtin University, Royal Perth Hospital, and Sir Charles Gairdner Hospital in Perth, Western Australia.

Study population.

This was a cross-sectional study involving people with axial CLBP (n=294; 57.1% female; median age 50 years old). Participants were recruited via multimedia advertisements (newspaper, social media, television, radio) circulated throughout the general community, in both metropolitan and regional Western Australia (77.6%), and from private metropolitan physiotherapy clinics (20.1%), public metropolitan hospitals in Perth, Western Australia (physiotherapy and emergency departments) (1.4%) and private metropolitan pain management and general practice clinics (1.0%).

Potential participants were asked to contact one researcher (MR) directly, and were then sent an inclusion / exclusion criteria screening questionnaire. Ambiguous responses to any inclusion / exclusion criteria were clarified by telephone.

Inclusion criteria were as follows: aged 18-70 years old; LBP of greater than three months duration; a score of two or more on an 11-point numeric rating scale (NRS) for pain intensity in the past week; a score of five or more on the Roland Morris Disability Questionnaire (RMDQ) (Roland and Morris, 1983); a score of at least 60% LBP on the following question (Wai et al., 2009): "Which situation describes your pain over the past 4 weeks the best? 100% of the pain in the low back; 80% of the pain in the low back and 20% in the leg(s); 60% of the pain in the low back and 40% in the leg(s); 50% of the pain in the low back and 50% in the leg(s); 40% of the pain in the low back and 60% in the leg(s); or 20% of the pain in the low back and 80% in the leg(s)."

Exclusion criteria were as follows: previous extensive spinal surgery (greater than single level fusion / instrumentation or discectomy) or spinal surgery within the past six months, serious spinal pathology (cancer, inflammatory arthropathy, acute vertebral fracture), diagnosed neurological disease, bilateral pain at the dorsum of the wrist / hand, pregnancy, inability to understand English.

Participants were allowed to continue all medications as prescribed.

Movement tasks for subgrouping.

Participants were asked to perform two repeated bending tasks in the following order:

3. To complete 20 forward spinal bends, with the cue to pick up a pencil from the floor, and place it back down.
4. To complete 20 backward spinal bends, with the cue to view a marker placed on the ceiling approximately 60cm behind the participant.

Repeated forward bending (20 repetitions) is a valid and reliable test of pain provocation for people with CLBP (Reneman et al., 2002, Brouwer et al., 2003). Repeated backward bending was included as it forms a common component of the physical examination for people with CLBP, and to determine whether pain provocation may be influenced in a directional manner (O'Sullivan, 2005, Sahrmann, 2002, McKenzie and May, 2003).

Participants were able to refuse to undertake these movements, or decline to complete the full 20 repetitions should they feel that their pain became too great, or fear exacerbation of symptoms. The number of repetitions completed was recorded.

Participants received standardised instructions:

1. For the pencil task, participants were asked simply to pick up a pencil that was placed on the floor in front of them. This counted as one forward bend. They then placed the pencil back on the floor, which counted as the second forward bend. They repeated this until a total of 20 forward bends was reached. Participants were told that they could undertake this task however they wished, and at whatever speed they wished.
2. For the backward bending task, participants were instructed to take sight of the marker on the ceiling behind them however they wished, at whatever speed they wished, but without turning around, and then to return to neutral before repeating the task up to a total of 20 times.

These instructions were reiterated if the participant subsequently questioned whether they should perform the task in a certain manner. Participants were instructed that there would be a brief pause every five repetitions, during both tasks, to ask them to rate their pain intensity (see below).

Video recordings were made of the repeated bending tasks using two iPads (4th Generation) (Apple, California, USA) (1080p HD video recording) mounted on tripods. One iPad was directly in front of the participant. The second iPad was repositioned to optimise a lateral view of the participant's lumbar region. These placements allowed adequate visualisation to code behaviours associated with pain (Keefe and Block, 1982, Sullivan et al., 2006) (see below).

Pain intensity following repeated movements.

Assessment of whether repeated movement influenced the participant's perception of the intensity of their LBP was undertaken by asking participants to rate their pain intensity on an 11-point NRS following repeated bending (Sullivan et al., 2006). Participants were asked to rate the intensity of their pain before commencement of each task, and then during both tasks, following every five repetitions.

Profiling variables – demographics.

Age and sex were collected for each participant.

Profiling variables – pain characteristics.

Pain intensity.

Pain intensity over the past week was rated using the previously described 11-point NRS. The validity and reliability of this measure has been demonstrated (Dworkin et al., 2005).

Pain duration.

Participants were asked, "How long have you had your back pain for?" All answers were converted into months.

Low back pain related disability.

Level of disability was measured using the Roland Morris Disability questionnaire (RMDQ) (Roland and Morris, 1983), comprising 24 items, which the participant may tick to indicate whether the item is relevant to their presentation (maximum score 24 indicating high disability). The items examine the effects of LBP on physical activities and activities of daily living. It is valid and reliable (Roland, 2000, Kuijer et al., 2005, Roland and Morris, 1983).

Baseline pain intensity before commencement of movement tasks.

The initial pain intensity rating on the NRS, before commencement of the movement tasks, was recorded.

Profiling variables – behaviours associated with pain.

Behaviours associated with pain.

Assessment of behaviours associated with pain, was undertaken using a reliable method as described by (Keefe and Block, 1982), incorporating video analysis (Sullivan et al., 2006, Keefe and Block, 1982).

Protective behaviours associated with pain included:

  d) guarding - abnormally slow or rigid movements
  e) bracing - using a limb for extra support during movement
  f) rubbing or holding the affected area

Communicative behaviours associated with pain included:

  c) grimacing, or other facial expressions of pain
  d) sighing, grunting, moaning etc.

As per Sullivan et al. (2006), no minimum duration of any of the aforementioned behaviours was stipulated. Video playback, using both angles, and repeated viewings where necessary, were used to obtain an overall score for both protective and communicative behaviours associated with pain, during the first five bends of each of the movement tasks. Only the first five bends were assessed to allow comparison across all participants in case any discontinued the bending tasks prior to completion of the full number of repetitions.

Time taken to complete bending tasks.

From the video playback, the time in seconds, taken to complete the first five bends in each direction was recorded. This commenced at the initiation of the first bend, and was completed at the participant's return to a neutral standing position at the completion of the fifth bend.

Profiling variables – pain sensitivity.

A combination of quantitative sensory tests were chosen to examine somatosensory sub-modalities mediated by different primary afferents (C, A delta, A beta fibres) (Jensen and Baron, 2003). For all testing participants were positioned prone. Testing was undertaken in the same order with every participant, by the same experienced clinician (MR). All testing was undertaken in the area of maximal pain at the lumbar region, as indicated by the participant (Ho et al., 2006). Pain threshold tests were also performed at the dorsal wrist joint line (Blumenstiel et al., 2011) of a pain-free wrist (or if both wrists were pain-free, the non-dominant wrist), with the participant's arm supported on the plinth. Testing was undertaken at the wrist first, then the lumbar region.

Two-point discrimination.

Two-point discrimination (TPD) was undertaken in the region of maximal lumbar pain only, using the method described by Moberg (1990), updated by Luomajoki and Moseley (2011). Participants were instructed that a plastic calliper ruler (Aestheisometer, DanMic Global, San Jose, USA) would be used to gently touch their lower back region. The amount of pressure applied was just enough to cause the, "very first small blanching," around the calliper points (Moberg, 1990)(p.128). All applications of the calliper were with the points aligned horizontally (Luomajoki and Moseley, 2011). Each time they were touched, participants were instructed to indicate whether they perceived one or two points of the calliper touching them by saying, "One," or, "Two." The TPD threshold was considered the minimum distance between the two calliper points at which the participant stated that they had been touched by two points rather than one. Both ascending and descending runs, where the distance between the calliper points were increased or decreased by 5mm at a

time respectively, were tested. A mean of three runs was used to calculate the threshold. "Trick" stimuli, where the callipers were applied at a distance that was out of sequence, or where only one point made contact, were randomly applied to minimise the chances of the participant guessing. The maximum distance between the two points of the calliper was 10 centimetres.

Detection of perceived temporal summation.

This test was undertaken as described by Scholz et al. (2009) in the region of maximal lumbar pain only. The participant was questioned whether a single application of a 26g nylon monofilament, to the point of initial bending, provoked pain. If so, they were asked to rate its intensity on an 11-point NRS. If not, pain intensity for the first stimulus was recorded as zero. The filament was then applied to the skin at a rate of 1Hz for 30 seconds. Participants were then asked to rate the intensity of any pain at the end of the 30 seconds of stimulation on an NRS as before. Two possible responses, and their accompanying NRS scores could therefore be recorded:

> i) No pain from the first stimulus but pain provoked during 30 seconds of stimulation – Yes (NRS rating) / No
> ii) Following a painful response to the first stimulus pain increases with repeated stimulation – Yes (NRS rating) / No

Because the minimum clinically important difference (MCID) on an 11-point NRS is two-points (Salaffi et al., 2004) we only considered enhanced temporal summation to have occurred if participants reported a change in pain intensity following stimulation of two-points or more.

Pressure pain threshold (PPT).

All of the following pain threshold tests utilised standardised instructions aligned to the German Research Network on Neuropathic Pain QST protocol (Rolke et al., 2006).

Pressure pain threshold was the point when the sensation of pressure perceived by the participant changed to one of pressure and pain (Rolke et al., 2006). PPT was tested using an algometer (probe size 1cm^2) (Somedic AB, Hörby, Sweden). Pressure was increased from 0kPa, at 50 kPa/s, until the participant indicated their PPT by pressing a button. Inter-stimulus intervals of 30 seconds were adopted to reduce the likelihood of temporal summation. Three thresholds were measured and the mean used for analysis.

Heat pain threshold (HPT).

HPT, the temperature at which a sensation of warmth becomes the sensation of heat and pain (Rolke et al., 2006), was tested using the Thermotest (Somedic AB, Hörby, Sweden). The contact area of the thermode was 2.5cm x 5cm. Testing began at 32°C. The temperature increased by 1°C/s until the participant indicated their threshold by pressing a button (or the device's upper limit (50°C) was reached). Inter-stimulus intervals of 30 seconds were adopted to reduce the likelihood of temporal summation. Three thresholds were measured and the mean used for analysis.

Cold pain threshold (CPT).

CPT was the point at which the sensation of cold became the sensation of cold and pain (Rolke et al., 2006). Testing CPT utilised the Thermotest (Somedic AB, Hörby, Sweden). Testing began at 32°C. The temperature decreased by 1°C/s until the participant indicated their threshold by pressing a button (or the device's lower limit (4°C) was reached). Inter-stimulus intervals of 30 seconds were adopted to reduce the likelihood of temporal summation. Three thresholds were measured and the mean used for analysis.

Profiling variables – psychological factors.

Depression, anxiety and stress.

The Depression Anxiety Stress scales 21 (DASS-21) is the short-form version of the original DASS (Lovibond and Lovibond, 1995). There are seven questions, scored from 0 – 3 for each subscale – depression, anxiety and stress. The score is doubled

to give a possible maximum score of 42 points for each subscale, indicating greater affect. It is valid and reliable.

Fear-avoidance beliefs.

The Fear Avoidance Beliefs questionnaire (FABQ) is a measure of pain related fear, comprising two subscales (physical activity (FABQ-PA), work (FABQ-W)) with higher scores indicating greater fear-avoidance beliefs. The physical activity subscale (FABQ-PA) contains four statements, with which the participant indicates their level of agreement on an NRS anchored at one end by, "0," and, "Completely Disagree," and at the other by, "6," and, "Completely Agree" (maximum score 24 – points). The work subscale (FABQ-W) contains seven such statements (maximum score 42 – points). It is reliable (Waddell et al., 1993) and valid (George et al., 2010).

Pain Catastrophizing.

The Pain Catastrophising scale (PCS) is a questionnaire examining participants' thoughts and feelings about pain. Using an NRS anchored at one end by, "0," and, "Not at all," and at the other by, "4," and, "All the time," participants indicate the degree to which they experience catastrophic thoughts in response to statements such as, "I feel I can't go on." There are a total of 13 statements, giving a potential maximum score of 52 points, indicating high levels of pain catastrophising. There are three subscales measuring rumination (questions eight, nine, 10 and 11), magnification (questions six, seven and 13) and helplessness (questions one, two, three, four, five and 12). Rumination has been described as, "worry, and an inability to inhibit pain related thoughts", magnification is the exaggeration of the, "unpleasantness of pain situations and expectancies for negative outcomes," and helplessness refers to the "inability to deal with painful situations." (Sullivan et al., 1995)(p.525). It is valid and reliable (Sullivan et al., 1995).

Pain self-efficacy.

The Pain Self-efficacy questionnaire (PSEQ) (Nicholas, 2007) examines a person's beliefs regarding their ability to undertake activities despite pain. The questionnaire comprises 10 statements regarding pain self-efficacy such as, "I can enjoy things

despite the pain," for which participants rate how confident they are that they can undertake the action on an NRS anchored at one end by, "0," and, "Not at all confident," and at the other by, "6," and, "completely confident." The scores for each statement are summed, giving a potential maximum score of 60 points, indicating high pain self-efficacy. This questionnaire is valid and reliable (Kaivanto et al., 1995, Asghari and Nicholas, 2001).

Low back related body perception.

The Fremantle Back Awareness questionnaire (FreBAQ) (Wand et al., 2014) examines a person's perception of the low back region. It consists of nine statements regarding perception of the lumbar region such as, "My back feels as though it is not part of the rest of my body," for which the participants indicate the degree of agreement with the statement using an NRS anchored at one end by, "0," and, "Never," and at the other by, "4," and, "Always". There is a maximum score of 36 points indicating higher perceptual distortion. This questionnaire demonstrates adequate reliability, construct and discriminative validity (Wand et al., 2014).

Endurance behaviours.

The Avoidance Endurance questionnaire (AEQ) (Hasenbring et al., 2009, Hasenbring et al., 2012) is a valid and reliable measure of endurance behaviour. Two subscales from the AEQ are used to classify participants as demonstrating fear-avoidant behaviour, endurance behaviour (associated with eustress or distress) or adaptive coping. The Thought Suppression sub-scale (TSS) comprises four statements that examine suppression of thoughts regarding pain. The Behavioural Endurance Sub-scale (BES) comprises 12 statements that examine persistence behaviours. Participants are asked to respond to a statement such as, "I distract myself with physical activity," by selecting a number on an NRS anchored at one end by, "0," and, "Never," and at the other by, "6," and "Always," for each statement. A mean score is derived for each subscale. To complete this classification there is also a need to ascertain the degree of depressive symptoms exhibited by the participant. The authors of the AEQ utilised the cut-off score for mild depressive symptoms (or greater) from the Beck Depression Inventory (Beck et al., 1961). Since the DASS-21

was used in this study the cut-off score for mild depressive symptoms (nine-points) from the DASS-21 depression subscale (Lovibond and Lovibond, 1995) was utilised in conjunction with the scores from the AEQ subscales. Therefore to classify participants according to the AEQ participants scored as follows:

1) Fear-avoidance: ≥9 on the DASS-21 depressive subscale, and <3 on the TSS and BES.
2) Distress-endurance: ≥9 on the DASS-21 depressive subscale and ≥3 for a mean TSS and / or BES.
3) Eustress-endurance: <9 on the DASS-21 depressive subscale and >3 on the BES.
4) Adaptive coping: <9 on the DASS-21 depressive subscale, TSS and BES <3.

Profiling variables - health and lifestyle factors.

Sleep quality.

The Pittsburgh Sleep Quality index (PSQI) comprises 17 questions which assess sleep quality, quantity, disturbance and its effect on daily living. It has acceptable reliability and validity (Buysse et al., 1989). The scoring scheme described by the original authors generates a final score. If this score is above five it suggests significant sleep disturbance.

Physical activity.

The International Physical Activity questionnaire (IPAQ) (Short Form) (IPAQ Group, 2005) is a measure of activity levels. Participants estimate the amount of activity they have done in the past seven days. It allows determination of the number of moderate and vigorous minutes of activity per week. It is valid and reliable (Craig et al., 2003).

Total comorbidity count.

To assess the presence of differing types of comorbidities, participants were asked whether they had a number of diagnosed medical conditions known to be associated with LBP (heart disease, diabetes, ulcer or stomach disease, anaemia or

other blood disease, cancer, osteoarthritis, rheumatoid arthritis, fibromyalgia, hypertension, depression, neurological disorders, eczema, osteoporosis, incontinence or bladder problems, respiratory disorders, migraine or recurrent headache, irritable bowel syndrome, chronic fatigue syndrome, pelvic pain or vulvodynia, temporomandibular joint pain, hay fever or some other allergy, eating disorders, anxiety disorders, visual or hearing disorders, thyroid disorders) (Beales et al., 2012, Dominick et al., 2012, Tschudi-Madsen et al., 2011, Hagen et al., 2006, Mayer and Bushnell, 2009). A simple count of comorbidities (maximum of 25) present in the individual was used for analysis as such a count has been shown to correlate with physical function in participants with spinal disorders (Groll et al., 2005).

Multiple pain sites.

The presence of multiple pain sites was examined using a quantifiable, grid-based body chart. Participants filled in all areas of pain. A count of squares on the body chart containing any marking was generated using a validated and reliable method described by Öhlund et al. (1996).

6.2.4 Statistical Analysis

Missing data management.

The number of participants with missing data for each variable is detailed in Tables 1-5. For questionnaires, missing data management was undertaken as suggested in original manuscripts where described. Otherwise, the mean of other items was imputed in the case of one missing item, and the total score was considered missing in the case of two or more missing items.

Determination of subgroups based upon pain response following repeated bending.

A score for change in pain intensity was determined by subtracting the participant's score on the NRS after the last set of repetitions completed (maximum 20) from the baseline score (adapted from Sullivan et al. (2009)). Pain was subsequently deemed to have increased only if it had increased by the MCID of ≥two-points (Salaffi et al.,

2004). Subgroups of participants were derived based upon whether their pain intensity changed by two-points following repeated bending (Figure 1).

Multidimensional profiling.

Between-subgroup differences in profiling variables were examined using analysis of variance for normally distributed variables, Kruskal-Wallis one-way analysis of variance for variables with skewed data, and chi-squared analysis for categorical data.

Statistical analysis was performed using Stata 13.1 (Statacorp, Texas, USA).

6.2.5 Results

Subgroups.

For the forward bending task, 284 (96.6%) participants completed all 20 repetitions. Those not completing all repetitions were as follows (n (%)): 0 repetitions completed: 2 (0.7); 5 repetitions completed: 2 (0.7); 10 repetitions completed: 4 (1.4); 15 repetitions completed: 2 (0.7). For the backward bending task 277 (94.2%) participants completed all 20 repetitions. Those not completing all repetitions were as follows (n (%)): 0 repetitions completed: 2 (0.7); 5 repetitions completed: 7 (2.4); 10 repetitions completed: 6 (2.0); 15 repetitions completed: 2 (0.7).

Scores for the change in pain intensity were determined based upon the pain intensity rating following the last set of repetitions completed in both directions. Two participants declined to undertake the forward or backward bending task for fear of exacerbation of symptoms. For subgrouping purposes it was assumed that these movements were therefore provocative for these participants. Preliminary analysis revealed that provocative pain responses following repeated spinal bending were more common than ameliorative responses, therefore participants were classified into the following subgroups (Figure 1):

i.   No increase in pain (NIP) (n=144, 49.0%).

ii.   Increased pain following forward bending only (FB) (n=83, 28.2%).

iii.   Increased pain following backward bending only (BB) (n=29, 9.9%).

iv.   Increased pain following forward and backward bending (FB&BB) (n=38, 12.9%).
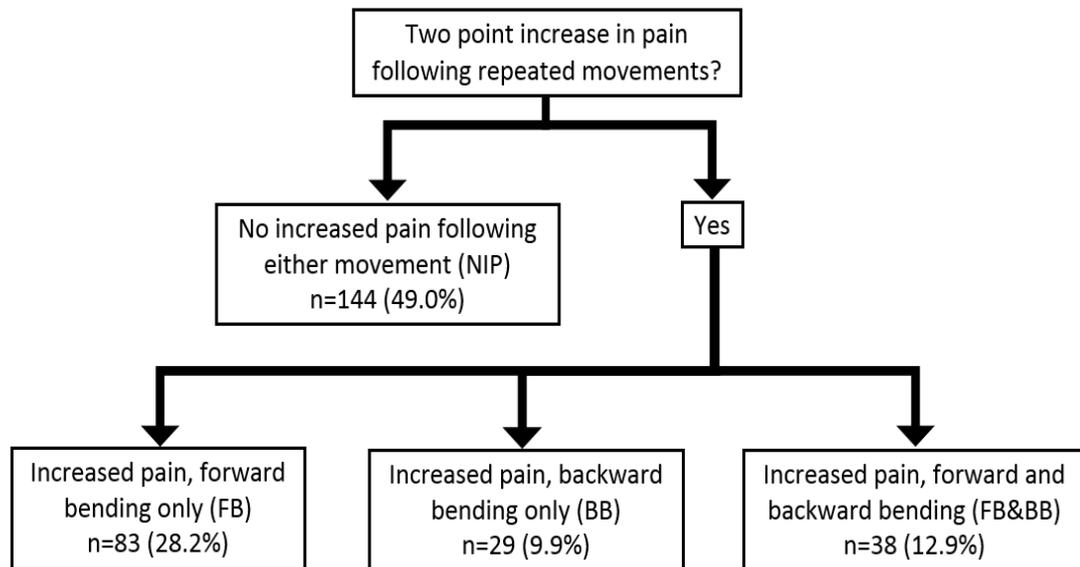
Figure 1. Tree diagram detailing the derivation of subgroups based upon changes in pain intensity following repeated spinal movement.

The increase in pain intensity (0-10 NRS) with repeated forward bending in the FB group ranged from 2 to 8 with a median of 3, similar to the degree of pain increase in the FB&BB group which ranged from 2 to 7 with a median of 2 (p=.44). The degree of pain increase with backward bending in the BB group ranged from 2 to 8 with a median of 2, similar to the degree of pain increase in the FB&BB group which ranged from 2 to 5 with a median of 2 (p=.45). There were 19 participants that displayed decreases in pain intensity with backward bending of ≥2-points. Interestingly, of these 19, 17 belonged to the FB subgroup (representing 20.5% of this subgroup) whilst the remaining two were in the NIP group. Conversely 13 participants displayed decreases in pain intensity of ≥2-points with forward bending, and of these six belonged to the BB subgroup (representing 20.7% of this subgroup), while the remaining seven were in the NIP group.

Multidimensional profiling.

Profiling variables – demographics.

There were no significant between-group differences for age or sex (Table 1).

Profiling variables – pain characteristics and disability.

The FB&BB subgroup had significantly greater pain intensity over the previous week than the other subgroups, and significantly shorter pain duration than the NIP and FB subgroups. There was no significant difference between subgroups for baseline pain intensity before commencement of the repeated movement tasks. The highest disability levels were seen in the FB subgroup, with their score on the RMDQ being significantly greater than that of the NIP and BB subgroups. The FB&BB subgroup also had significantly greater disability than the NIP subgroup (Table 1).

Profiling variables - behaviours associated with pain.

Data was coded as missing for two participants who declined to perform each movement task. Examination of the outcomes of the behaviours associated with the repeated movement tasks revealed that rubbing only occurred in 13 participants (4.4%), and the communicative behaviours of grimacing or sighing only occurred in 22 people (7.4%) These variables were excluded from subsequent analysis.

There were no significant between-group differences for protective behaviours. However, there were significant between-group differences for speed of movement. The NIP subgroup was significantly faster for all movements than other subgroups (Table 2). The FB group was significantly slower than all other subgroups for forward bending and was also slower during backward bending compared with the NIP and BB subgroups.

Table 1.

Demographic and pain characteristic data for the four subgroups determined by pain responses to repeated spinal movement tasks.

Variable	No increase in pain (n=144, 49.0%)	Increasing pain, forward bend (n=83, 28.2%)	Increasing pain, backward bend (n=29, 9.9%)	Bidirectional increase in pain (n=38, 12.9%)	*p*-value
Demographics					
Age, years median (IQR) (min,max)	50 (40, 59) (21, 69)	53 (40, 61) (18, 70)	50 (32, 63) (19, 69)	42 (29, 57) (18, 70)	.08[1]
Female n(%)	72 (50)	51 (61.4)	20 (69.0)	25 (65.8)	.09[3]
Pain characteristics					
Pain intensity past week (NRS) mean (SD) (min,max)	5.6[a] (2.0) (2, 9)	6.0[a] (1.8) (2, 10)	5.7[a] (1.8) (3, 10)	6.7[b] (1.6) (3, 10)	**.005[2]**
Duration, months median (IQR) (min,max)	120[a] (42, 264) (3, 624)[4]	120[a] (48, 240) (3, 720)[5]	120[ab] (42, 240) (18, 540)	51[b] (24, 96) (7, 480)[4]	**.004[1]**
RMDQ Score median (IQR) (min,max)	8[a] (6, 11) (5, 20)	11[b] (7, 14) (5, 21)	8[ac] (6, 10) (5, 21)	9[bc] (7, 13) (5, 24)	**<.001[1]**
Pain intensity (NRS) before movement tasks median (IQR) (min,max)	2 (1, 3) (0, 7)	2 (0, 3) (0, 8)	2 (0, 4) (0, 8)	2 (1, 3) (0, 5)	.37[1]

Note. [1] Kruskal-Wallis one-way analysis of variance; [2] analysis of variance; [3] χ² analysis; [4] missing in one case

[a,b,c] Superscripted letters define significantly different subgroups, i.e. results with different letters are significantly different, results containing the same letter are not significantly different

NRS – numeric rating scale; RMDQ – Roland Morris Disability questionnaire; Change in pain intensity – change in NRS score between first and last bend completed

Table 2.
Behaviours associated with pain data for the four subgroups determined by pain responses to repeated spinal movement tasks.

Variable	No increase in pain (n=144, 49.0%)	Increasing pain, forward bend (n=83, 28.2%)	Increasing pain, backward bend (n=29, 9.9%)	Bidirectional increase in pain (n=38, 12.9%)	*p*-value
Guarding behaviours, forward bend mean (SD) (min,max)	2.2 (2.4) (0, 5)	2.6 (2.5) (0, 5)	2.6 (2.4) (0, 5)	2.7 (2.5) (0, 5)[4]	0.53[1]
Guarding behaviours, backward bend mean (SD) (min,max)	1.3 (2.4) (0, 15)	1.2 (2.1) (0, 5)	1.8 (2.4) (0, 5)	1.6 (2.3) (0, 5)[4]	0.56[1]
Bracing behaviours, forward bend mean (SD) (min,max)	1.8 (2.3) (0, 5)	2.2 (2.3) (0, 5)	1.3 (2.1) (0, 5)	1.3 (2.0) (0, 5)[4]	0.16[1]
Bracing behaviours, backward bend mean (SD) (min,max)	0 (0.2) (0, 3)	0.1 (0.8) (0, 5)	0 (0) (0,0)	0 (0) (0,0)[4]	0.16[1]
Forward bend time (seconds) median (IQR) (min,max)	17[a] (13, 21) (9, 42)	20[b] (16, 27) (9, 186)	17[a] (14, 20) (12, 38)	18[a] (15, 20.5) (11, 108)[4]	**<.001[1]**
Backward bend time (seconds) median (IQR) (min,max)	15[a] (13, 18) (8, 57)	19[b] (16, 24) (9, 49)	16[c] (15, 19) (11, 44)	18[bc] (14.5, 22) (10, 34)[4]	**<.001[1]**

Note. [1] Kruskal-Wallis one-way analysis of variance; [2] analysis of variance ; [3] χ^2 analysis; [4] missing in two cases

[a,b,c] Superscripted letters define significantly different subgroups, i.e. results with different letters are significantly different, results containing the same letter are not significantly different

Forward bend speed / backward bend speed – time taken to complete five bends; Bracing / guarding behaviours – number of behaviours during the first five bends

Profiling variables – pain sensitivity.

Testing for enhanced temporal summation revealed that 28 (9.5%) participants perceived the initial stimulus as non-noxious, but it became noxious, increasing by at least two-points on an NRS, over the 30 seconds of repeated stimulation. Four participants (1.4%) perceived the initial stimulus as noxious, and deemed the intensity of their response to the stimulus to have increased by at least two-points on an NRS over the 30 seconds of stimulation. These two groups were therefore combined for further analysis (n=32, 10.9%). The proportion of participants exhibiting temporal summation was not significantly different between subgroups.

In the FB&BB subgroup, PPT at the lumbar region was significantly lower, and CPT at both the wrist and lumbar regions was significantly higher, than all other subgroups (i.e. higher sensitivity). In the FB subgroup, CPT at the lumbar spine was significantly more sensitive than the NIP subgroup (Table 3).

Table 3.

Pain sensitivity data for the four subgroups determined by pain responses to repeated spinal movement tasks.

Variable	No increase in pain (n=144, 49.0%)	Increasing pain, forward bend (n=83, 28.2%)	Increasing pain, backward bend (n=29, 9.9%)	Bidirectional increase in pain (n=38, 12.9%)	p-value
Two-point discrimination (cm) mean (SD) (min,max)	5.6 (2.0) (0.5, 10)	6.0 (2.3) (0.5, 10)	5.9 (2.3) (2.0, 10)	5.8 (2.3) (0.5, 10)	.59[2]
Temporal summation n (%)	23 (16.0)	17 (20.7)	4 (13.8)	12 (31.6)	.14[3]
PPT wrist (kPa) median (IQR) (min,max)	275.5 (189.8, 377.8) (67.3, 1060.3)	269.3 (181.3, 332.0) (57.0, 1200.0)	273.3 (159.7, 443) (80.0, 736.3)	226.7 (167.7, 306.0) (55.3, 1121.3)	.32[1]
PPT lumbar (kPa) median (IQR) (min,max)	286.2[a] (196.2, 480.8) (37.7, 1420.7)	256.7[a] (159.3, 440.0) (36.7, 1600.0)	311.3[a] (160.0, 532.0) (48.0, 1349.0)	125.3[b] (76.3, 283.0) (39.3, 1341.7)	**<.001[1]**
HPT wrist (°C) median (IQR) (min,max)	45.9 (43.7, 48.1) (34.5, 50.0)	45.0 (43.0, 48.1) (32.8, 50.0)	44.4 (41.3, 47.3) (35.9, 49.7)	44.6 (39.6, 46.7) (32.2, 50.0)	.06[1]
HPT lumbar (°C) mean (SD) (min,max)	42.9 (3.8) (34.1, 50.0)	42.2 (4.0) (33.6, 50.0)	42.5 (3.2) (35.4, 48.9)	41.1 (4.4) (33.6, 49.4)	.06[2]

Variable	No increase in pain (n=144, 49.0%)	Increasing pain, forward bend (n=83, 28.2%)	Increasing pain, backward bend (n=29, 9.9%)	Bidirectional increase in pain (n=38, 12.9%)	p-value
CPT wrist (^{o}C) median (IQR) (min,max)	4.3[a] (4.0, 11.0) (4.0, 28.3)	4.7[a] (4.0, 9.8) (4.0, 30.6)	4.1[a] (4.0, 11.5) (4.0, 26.8)	12.4[b] (4.0, 18.7) (4.0, 29.8)	**.01[1]**
CPT lumbar (^{o}C) median (IQR) (min,max)	4.0[a] (4.0, 16.5) (4.0, 30.5)	5.2[bd] (4.0, 24.1) (4.0, 31.2)	4.0[ad] (4.0, 10.1) (4.0, 29.9)	23.2[c] (4.0, 27.7) (4.0, 30.9)	**<.001[1]**

Note. [1] Kruskal-Wallis one-way analysis of variance; [2] analysis of variance ; [3] χ^2 analysis

[a,b,c,d] Superscripted letters define significantly different subgroups, i.e. results with different letters are significantly different, results containing the same letter are not significantly different

PPT – pressure pain threshold; HPT – heat pain threshold; CPT – cold pain threshold; kPa – kilopascals; ^{o}C – degrees centigrade

Profiling variables – psychological factors.

The DASS depression score and PCS score were both significantly higher in the FB and FB&BB subgroups than the other subgroups. The FB and FB&BB subgroups had significantly lower pain self-efficacy than the NIP subgroup, and the FB subgroup also had significantly lower pain self-efficacy than the BB subgroup. FreBAQ scores were significantly higher (i.e. more perceptual distortion) in the FB and FB&BB subgroups than the NIP subgroup. There were no differences in FABQ-PA scores across subgroups (Table 4). As only 76.2% of the sample was currently working data from the FABQ-W were excluded from analysis.

The number of participants per AEQ class was too small for analysis particularly in the BB and FB&BB subgroups, therefore the three non-adaptive classes (distress endurance, eustress endurance, fear-avoidance) were combined, and compared to those exhibiting adaptive behaviours. There were significantly fewer participants classified as adaptive in the FB&BB subgroup, when compared to the NIP and BB subgroups (Table 4).

Profiling variables – health and lifestyle factors.

There were no significant differences between subgroups for sleep quality, comorbidities, widespread pain or physical activity levels (Table 5).

Table 4.

Psychological data for the four subgroups determined by pain responses to repeated spinal movement tasks.

Variable	No increase in pain (n=144, 49.0%)	Increasing pain, forward bend (n=83, 28.2%)	Increasing pain, backward bend (n=29, 9.9%)	Bidirectional increase in pain (n=38, 12.9%)	p-value
DASS depression score median (IQR) (min, max)	6[a] (2, 12) (0, 42)	10[b] (4, 16) (0, 42)	4[a] (2, 10) (0, 40)	8[b] (4, 16) (0, 42)	**.007[1]**
DASS anxiety score median (IQR) (min, max)	4 (0, 6) (0, 42)	4 (2, 8) (0, 34)	4 (0, 6) (0, 32)	5 (2, 12) (0, 34)	.23[1]
DASS stress score median (IQR) (min, max)	10 (6, 18) (0, 42)	14 (6, 18) (0, 38)	10 (6, 16) (0, 38)	17 (6, 24) (0, 38)	.17[1]
FABQ-PA mean (SD) (min, max)	14.0 (5.8) (0, 24)	15.3 (6.3) (0, 24)	13.1 (6.2) (1, 24)	15.3 (4.8) (5, 24)	.20[2]
PCS score median (IQR) (min, max)	15[a] (8, 25) (0, 49)[4]	21[b] (11, 30) (0, 47)	15[a] (8, 22) (1, 52)	22[b] (12, 33) (3, 42)	**.03[1]**
PSEQ median (IQR) (min, max)	45[a] (35, 50.5) (7, 60)	36[b] (28, 48) (1, 60)	42[ac] (37, 50) (9, 59)	40[bc] (33, 46) (1, 58)	**.002[1]**

Variable		No increase in pain (n=144, 49.0%)	Increasing pain, forward bend (n=83, 28.2%)	Increasing pain, backward bend (n=29, 9.9%)	Bidirectional increase in pain (n=38, 12.9%)	p-value
FreBAQ mean (SD) (min, max)		8.6^a (6.1) (0, 24)	10.8^{bc} (7.3) (0, 32)	9.3^{ac} (6.4) (0, 23)	11.9^{bc} (6.4) (1, 30)	**.02[2]**
AEQ class n (%)	Adaptive (row %)	$46 (59.7)^a$	$17 (22.1)^{ab}$	$10 (13.0)^a$	$4 (5.2)^b$	**.03[3]**
	Non-adaptive combined	98 (45.6)	65 (30.2)	19 (8.8)	33 (15.5)	

[1] Kruskal-Wallis one-way analysis of variance; [2] analysis of variance ; [3] χ² analysis; [4] missing in one case

[a,b,c] Superscripted letters define significantly different subgroups, i.e. results with different letters are significantly different, results containing the same letter are not significantly different

DASS – Depression anxiety stress scales; FABQ-PA – Fear-Avoidance Beliefs questionnaire – Physical activity; PCS – Pain Catastrophising scale; PSEQ – Pain Self-Efficacy questionnaire; FreBAQ – Fremantle Back Awareness questionnaire; AEQ – Avoidance Endurance questionnaire

Table 5:

Health and lifestyle data for the four subgroups determined by pain responses to repeated spinal movement tasks.

Variable	No increase in pain (n=144, 49.0%)	Increasing pain, forward bend (n=83, 28.2%)	Increasing pain, backward bend (n=29, 9.9%)	Bidirectional increase in pain (n=38, 12.9%)	p-value
PSQI mean (SD) (min, max)	8.8 (4.1) (2, 19)[7]	9.9 (4.4) (2, 20)[5]	9.1 (4.3) (3, 19)	9.1 (2.9) (5, 16)[4]	.26[2]
Total comorbidity count median (IQR) (min, max)	4.5 (2, 7) (0, 15)	6.0 (3, 9) (0, 21)	5.0 (3, 6) (0, 14)	4.5 (3, 7) (0, 16)	.14[1]
Body chart squares median (IQR) (min, max)	13 (6, 21) (2, 84)	15 (8, 25) (2, 62)	12 (7, 18) (3, 75)	11 (6, 15) (1, 39)	.14[1]
Moderate and vigorous activity (min/week) median (IQR) (min, max)	120 (0, 345) (0, 1290)[6]	120 (0, 360) (0, 1620)[4]	90 (0, 240) (0, 1980)	145 (0, 240) (0, 2100)[4]	.98[1]

[1] Kruskal-Wallis one-way analysis of variance; [2] analysis of variance ; [3] χ^2 analysis; [4] missing in one case; [5] missing in three cases; [6] missing in four cases; [7] missing in seven cases

PQSI – Pittsburgh Sleep Quality index

6.2.6   Discussion

Our findings identified four subgroups of people with CLBP based upon pain provocation following repeated forward and backward spinal bending and demonstrated that these subgroups have differing multidimensional profiles. To our knowledge this is the first large CLBP cohort study to consider directional pain provocation responses following repeated movements utilising a statistical approach to subgrouping. While not directly comparable, in a randomised-controlled trial involving 107 people with CLBP, 40.2% reported pain provocation with flexion activities, 14.0% with extension activities, and 41.1% were bi-directionally provoked (Vibe Fersum et al., 2013) (Proportions were 28.2%, 9.9% and 12.9% respectively in this study). However, as proportions were derived from clinical examination rather than a standardised protocol, and did not necessitate a two-point change in pain intensity, they may vary from our four subgroups. When any self-reported change in pain intensity following repeated spinal bending was considered to indicate a directional pain response, the proportional responses in this cohort were similar to those reported by Vibe Fersum et al. (2013) (pain increased following forward bending only 33.2%, pain increased following backward bending only 13.4%, bidirectional increase in pain 29.4%). The proportion of people in both the FB and BB subgroups (approximately 20% for each group) demonstrating a clinically-significant amelioration of pain, when moving in the opposite direction to that which was provocative, appears lower than previously reported (60-74%)(Long et al., 2004, Werneke et al., 2011). This apparent discrepancy may reflect differences in pain duration (i.e. acute / sub-acute LBP versus CLBP) (May and Aina, 2012), movement procedures used (McKenzie and May, 2003), and / or use of a two-point change in pain intensity for deriving subgroups in the current study versus clinical judgement in the previous studies {Long, 2004 #334, Werneke et al., 2011).

Data from the multidimensional profiles of each subgroup are compared to previously published questionnaire cut-off scores and normative data, with clinical significance taken into account. The key multidimensional profile findings are summarised in Table 6.

Table 6.

Summary of key characteristics of each subgroup based upon questionnaire cut-off scores and previously published normative data, with likely clinical significance taken into account.

Increased pain following repeated spinal bending?	**No increase** in pain (NIP)	Increased pain with repeated **forward bending** only (FB)	Increased pain with repeated **backward bending** only (BB)	Increased pain with repeated **forward and backward bending (FB&BB)**
Pain characteristics				Shortest pain duration
Adaptive behaviours	Greatest proportion			Lowest proportion
Distorted perception of low back region	Abnormal*	Higher than NIP subgroup Abnormal*	Abnormal*	Greatest distortion Abnormal*
Psychological profile	Elevated fear-avoidance beliefs*	Elevated fear-avoidance beliefs* Moderate pain catastrophising Lowest self-efficacy Mild depressive symptoms	Elevated fear-avoidance beliefs*	Elevated fear-avoidance beliefs* Moderate pain catastrophising Self-efficacy lower than NIP subgroup
Pain sensitivity	Normal*	Normal*	Normal*	Elevated lumbar pressure and cold pain sensitivity
Movement characteristics		Slowest Pain amelioration following repeated backward bending (20.5%)	Pain amelioration following repeated forward bending (20.7%)	

Note. *Compared to healthy control data

No increase in pain following repeated bending (NIP) (49.0%).

The NIP subgroup has not been previously described. These findings contrast with studies where participants were not subgrouped and reported mean increases in pain intensity with repeated movements (Sullivan et al., 2009, Falla et al., 2014). The proportion of participants with NIP is substantial, potentially reflecting methodological factors. Firstly, the MCID for pain intensity was the cut-off for subgrouping. Tasks involving external loads may have been more provocative, consistent with previous reports (Sullivan et al., 2009). Participants were deliberately not instructed to move in a standardised manner, allowing adoption of various movement strategies including protective behaviours. While the frequency of protective behaviours was not different between subgroups, we cannot exclude the possibility that this subgroup may have adopted movement strategies effective in reducing pain provocation. Finally, while this subgroup did not report increased pain following every five repetitions, they may have experienced increased pain *during* movement that was unrecorded.

This subgroup also had the greatest proportion of participants classified as adaptive (suggesting an absence of fear-avoidance or endurance behaviours) by the AEQ (Hasenbring et al., 2012), however, the mean FABQ-PA score for this subgroup was higher than that reported in healthy controls (Dedering and Börjesson, 2013). While their mean FreBAQ score was lower than other subgroups, it was higher than that of healthy controls (Wand et al., 2014), indicating distorted body perception (e.g. difficulty perceiving body movements in space, perceiving the back as swollen / shrunken (Wand et al., 2014)).

Despite the absence of pain exacerbation following repeated movement, this subgroup had similar pain intensity (past week) to other groups. For this subgroup pressure and thermal pain sensitivity appeared within normal limits (Neziri et al., 2011, Pfau et al., 2014, Rolke et al., 2006, Magerl et al., 2010) and all other psychological data were unremarkable (Lovibond and Lovibond, 1995, Henry and Crawford, 2005, Mitchell et al., 2009, de Boer et al., 2014, Van Damme et al., 2002). The NIP subgroup appears similar to a previously described clinically-derived

subgroup demonstrating "proportionate" pain responses following aggravating movements, having similar pain sensitivity, DASS and PSQI scores (O'Sullivan et al., 2014).

Increased pain following repeated forward bending only (FB) (28.2%).

A number of findings characterise this subgroup. Firstly, they were the slowest bending forwards and backwards. Why participants with pain only aggravated following forward bending should be slowest bending backward is unknown. This is especially interesting given approximately 20% of this subgroup reported a clinically-significant pain reduction following repeated movement into backward bending. One study examined speed of forward / backward bending, finding both directions of movement slower in people with LBP than healthy controls. However pain responses to movement were not considered. The authors postulated the observed changes could be due to altered mechanics or fear of movement (McGregor et al., 1997). The FB subgroup had significantly higher disability than the NIP and BB subgroups. However, the difference between subgroups was three-points on the RMDQ, which is below the MCID (Stratford et al., 1996), making its clinical relevance questionable. The FB subgroup also demonstrated a higher mean FABQ-PA score than that reported in healthy controls (Dedering and Börjesson, 2013), moderate pain catastrophising (Sullivan, 1995), the lowest pain self-efficacy (Nicholas, 2007), and greater distortion of body perception than the NIP subgroup, which may influence forward bending movement patterns (Geisser et al., 2004, Thomas and France, 2007, Moseley and Hodges, 2006, Sullivan et al., 2009, Luomajoki and Moseley, 2011), or vice versa. While this subgroup had the highest median depression score reflecting mild symptomatology, anxiety and stress would both be classified as normal (Lovibond and Lovibond, 1995). Pain sensitivity appeared within normal limits (Neziri et al., 2011, Pfau et al., 2014, Rolke et al., 2006, Magerl et al., 2010). Although lumbar CPT was higher than the NIP subgroup, the difference was 1.2°C, making its clinical relevance questionable.

Increased pain following repeated backward bending only (BB) (9.9%).

The BB subgroup were not differentiated from other subgroups by our profiling variables. Approximately 20% of this subgroup reported a clinically-significant pain reduction following repeated movement into forward bending. While not statistically different from other subgroups, their mean FreBAQ and FABQ-PA scores were greater than those of healthy controls (Wand et al., 2014, Dedering and Börjesson, 2013) suggesting distorted body perception and elevated fear-avoidance beliefs. A previously described subgroup with CLBP aggravated by extension movements demonstrated different kinematics and electromyography from those with flexion-related pain and healthy controls (Dankaerts et al., 2009). Subgroups in our study may have exhibited differing electromyography and kinematics, and exclusion of these measures is a limitation of our study.

Increased pain following repeated forward and backward bending (FB&BB) (12.9%).

A number of profiling variables characterise this subgroup. The median pain sensitivity values in this subgroup suggested elevated lumbar pressure and cold pain sensitivity (Neziri et al., 2011, Pfau et al., 2014). This subgroup also had statistically greater wrist cold pain sensitivity, however, the median value was within normal limits (Magerl et al., 2010, Rolke et al., 2006). These findings contradict a meta-analysis (Hübscher et al., 2013) showing low correlation between pain thresholds and pain intensity, possibly reflecting that without subgrouping based on pain responses to movement, such associations may be effectively "washed out". Furthermore, pain sensitivity in CLBP may be associated with pain responses to movement, rather than baseline pain intensity, as observed in this study. Pain sensitivity in this subgroup was similar to a clinically-derived subgroup of people with CLBP reporting disproportionate pain provocation responses pain following aggravating movements (O'Sullivan et al., 2014).

This subgroup had the lowest proportion of adaptive participants (AEQ); and the greatest distortion of body perception, with their mean FreBAQ score being greater than that of healthy controls (Wand et al., 2014). They also demonstrated shorter

symptom duration than the NIP and FB subgroups (suggesting pain responses following repeated bending may, for unknown reasons, vary with time); elevated mean FABQ-PA scores compared to healthy controls (Dedering and Börjesson, 2013), moderate levels of pain catastrophising (Sullivan, 1995) (significantly higher than the NIP and BB subgroups) and lower pain self-efficacy than the NIP subgroup (Nicholas, 2007). While they scored significantly higher than the NIP and BB subgroups for depression, this difference may not be clinically relevant (Lovibond and Lovibond, 1995). The FB&BB subgroup also displayed a 1.1-point higher pain intensity (0-11 NRS, past week) than other groups, although this is below the MCID (Salaffi et al., 2004).

Potential mechanisms underlying pain responses following repeated movement.

The findings of this study support the heterogenous and multidimensional nature of pain responses to repeated movement in people with CLBP. While hypothetical, the profiling of these subgroups may provide some insight into potential underlying mechanisms associated with an individual's pain response to repeated movement. Altered body perception, present in all subgroups, but greatest in the FB and FB&BB groups, has been proposed to adversely influence movement patterns, possibly altering mechanical loading (Hodges and Smeets, 2015, Nijs et al., 2012), and has been associated with altered cortical function (Wand et al., 2011, Pleger et al., 2006) possibly influencing pain responses via altered cortical sensorimotor interactions (Hodges and Smeets, 2015, Nijs et al., 2012). In those subgroups demonstrating unidirectional pain provocation following repeated bending this may suggest peripherally-mediated nociception, associated with sensitisation of afferent stimuli from spinal structures secondary to altered mechanical loading (Hodges and Smeets, 2015). However, it may also reflect a learned association between stimuli (e.g. proprioception, vision) and psychological factors (e.g. fear-avoidance beliefs, anxiety) associated with that movement, influencing nociceptive processing at a cortical level (Moseley and Vlaeyen, 2015, Zusman, 2008). The FB subgroup's psychological profile may suggest enhanced central nociceptive facilitation (Simons et al., 2014, Zusman, 2002, Hodges and Smeets, 2015). In the FB&BB subgroup,

bidirectional pain increases and elevated pain sensitivity suggest involvement of peripheral sensitisation and / or central pain mechanisms (Sullivan et al., 2009, Cruz-Almeida and Fillingim, 2014, Graven-Nielsen and Arendt-Nielsen, 2010, Curatolo and Arendt-Nielsen, 2015).

The mechanisms underlying pain reduction following repeated movement reported by those subjects who also reported pain provocation responses in the opposite direction (FB and BB subgroups) are unclear. The rapidity of this response may suggest opposite direction movements may moderate pain via decreased sensitivity of afferent nociception from spinal tissues. However, it may also suggest cortical modulation of symptoms possibly due to a lack of perceived threat associated with these opposite movements (Zusman, 2008).

Factors not differing across subgroups.

A number of factors did not differ across subgroups, including age, sex, baseline pain before movement, behaviours associated with pain, two-point discrimination, some measures of pain sensitivity (temporal summation, PPT at the wrist, HPT at both the wrist and lumbar spine), anxiety, stress, fear-avoidance beliefs, sleep quality, comorbidities, multiple pain sites and activity levels. The findings support that these factors do not differentiate pain provocation responses following repeated movement in people with CLBP, and that these derived subgroups share some common characteristics. While some of these findings appear to be at odds with previous studies (O'Sullivan et al., 2014, Sullivan et al., 2009) this is likely to reflect methodological differences. These findings also highlight some interesting points for discussion. Firstly, pain intensity prior to movement and protective behaviours were equal between subgroups, indicating they were unrelated to pain provocation responses following repeated movement. Protective behaviours may reflect anticipation of pain and / or pain responses during movement not assessed in this study. When considering pain sensitivity temporal summation did not differ between groups, despite increasing pain following repeated lifting being hypothesised to relate to nociceptive summation (Sullivan et al., 2009). Furthermore, subgroups of people with CLBP have previously been derived based

upon thermal and pressure pain sensitivity (Rabey et al., 2015 , Coronado et al., 2014), however, interactions between pain sensitivity and movement were not considered in previous studies. Two-point discrimination, previously associated with altered motor control in people with CLBP (Luomajoki and Moseley, 2011), and considered to reflect body schema within the primary somatosensory cortex (S1) (Pleger et al., 2006) did not differ between subgroups despite FreBAQ scores (reflecting perception of the back) differing between the groups. It may be that these measures capture differing perceptual constructs. Despite significant differences in disability, pain catastrophising, and depression, which have been associated with fear-avoidance beliefs (Leeuw et al., 2007), no significant between-group differences were evident for fear-avoidance beliefs. This suggests levels of fear-avoidance beliefs, as measured by the FABQ, were not associated with pain provocation responses following repeated movement. However, fear-avoidance beliefs were higher than that reported in healthy controls (Dedering and Börjesson, 2013) in all subgroups.

Strengths and limitations.

The majority of participants were recruited via advertisements, enhancing generalizability of our data to the wider community. Inclusion criteria required having dominant LBP (Wai et al., 2009), thereby minimizing the likelihood of radiculopathy. Clinical measures utilised in this study for pragmatic reasons (reducing participant burden, facilitating translation into practice), were not necessarily gold standards (e.g. IPAQ rather than actigraphy). Use of gold standards may have allowed more accurate subgroup profiling. No correction for multiple comparisons was undertaken. As this was the first study of its kind, and exploratory in nature, maintaining such p-values may increase the chance of type I error, but reduced the chance of type II error (Armstrong, 2014).

Clinical implications.

This subgrouping is easily incorporated in clinical practice, and may help guide clinical assessment. For the NIP subgroup, clinicians could consider pain responses during movement and additionally assess spinal loading individually-matched to the

persons reported aggravating activities. Altered back perception, found in all subgroups, but greater in the FB and FB&BB subgroups, may support the role of targeted assessment and management of body perception in people with CLBP (Daffada et al., 2015).

Psychological factors contributed least to NIP and BB subgroup profiles, while the FB and FB&BB subgroups exhibited low pain self-efficacy and elevated pain catastrophising. The FB subgroup also exhibited mild depressive symptomatology (Lovibond and Lovibond, 1995), which can mediate pain and disability in CLBP (Hall et al., 2011). Determining that an individual fits the FB or FB&BB subgroups could prompt clinicians to further examine and target psychological profiles. Examination of movement patterns and motor control, not conducted in this study, may facilitate further understanding of the movement dimension's contribution to the broader multidimensional context of CLBP. This is particularly so for the NIP and BB subgroups, which lacked other differentiating factors, and the FB subgroup in order to facilitate an understanding of why they demonstrated the slowest movements. Increasing pain following repeated forward and backward bending may also cue clinicians to consider the likelihood of enhanced pain sensitivity possibly indicating a role for appropriate pharmacotherapy (Baron et al., 2013). The increased likelihood of an individual exhibiting non-adaptive behaviours (fear-avoidant or endurance) possibly indicates a role for behavioural interventions. The prognosis of these four subgroups is unknown, and warrants further investigation.

6.2.7   References

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Afterword To Chapters Four to Six

The previous three chapters present different subgroupings derived from within the same CLBP cohort using statistical techniques based upon tissue sensitivity, psychological questionnaire scores, and pain responses following repeated forward and backward spinal bending. Subgroups were subsequently profiled across multiple dimensions associated with CLBP.

The next step in the body of research was to investigate whether there was any cross over between the three subgrouping studies, i.e. did those participants grouped in the low pain sensitivity cluster, overlap with participants in the low-scoring psychological cluster?

To examine this, patterns of classification across the three subgroup dimensions were tabulated (Statistical procedures were performed using Stata 13.1 (Statacorp, Texas, USA)). Since an individual participant could be a member of one of three pain sensitivity clusters, one of three psychologically-derived clusters and one of four subgroups derived based upon pain responses following repeated bending, there were 36 possible different patterns of classification for any one individual across the three subgrouping studies.

Participants in this CLBP cohort demonstrated 33 out of the 36 possible patterns of classification (Figure 1), suggesting multidimensional presentations of people with CLBP are highly variable (Brown, 2009). The most common pattern, making up 16.0% of the sample, was "220" representing high pressure pain sensitivity, low affect and intermediate cognitive psychological scores, and no increase in pain following repeated bending. All other response patterns made up less than 10% of the sample. Response pattern "310" representing those in the low pain sensitivity cluster, and the low-scoring psychological cluster with no increase in pain following repeated bending, made up just 3.4% of the sample. Response patterns "131" and "133" representing those with high thermal and pressure pain sensitivity, in the higher-scoring psychological cluster, and with increased pain following forward bending only or increased pain following forward and backward bending combined, made up 4.1% and 2.7% of the sample respectively. Examination of the differing

response patterns suggests a high degree of variability in the presentations of people with CLBP when they are subgrouped based upon pain sensitivity, psychological questionnaire scores and pain responses following repeated spinal bending.

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Figure 1. Subgroup classification patterns across pain sensitivity and psychological clusters, and pain responses following repeated bending.

Frequency of subgroup classification patterns
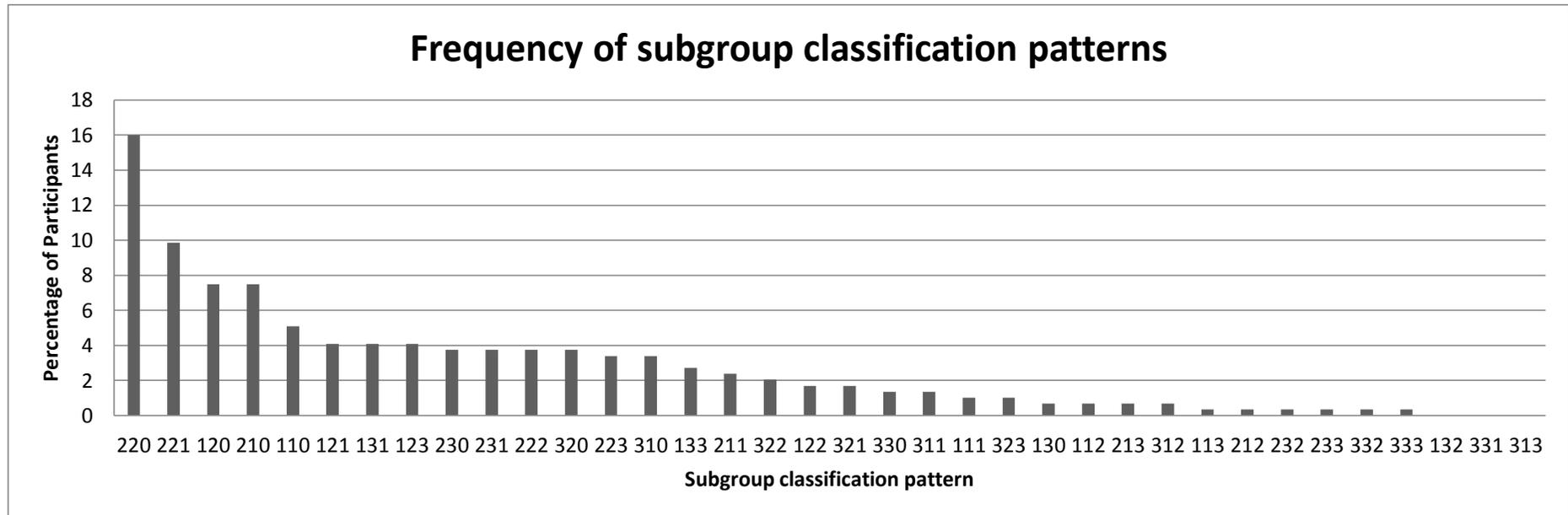
Underneath each column the three digits, reading from left to right, represent:		
1st digit: Pain sensitivity cluster	2nd digit: Psychological cluster	3rd digit: Pain responses following spinal bending
1. Average to high pressure and thermal pain sensitivity	1.Lower-scoring	0.No increase in pain (NIP)
2. Average to high average pressure pain sensitivity	2.Low affect, intermediate cognitive scores	1.Increased pain with forward bending only (FB)
3. Low pressure and thermal pain sensitivity	3.Higher-scoring	2.Increased pain with backward bending only (BB)
		3.Increased pain with forward and backward bending (FB&BB)

Chapter Seven – Study Five

7.1 Introduction To Study Five

This research has derived subgroups based upon data from three separate dimensions: pain sensitivity, psychological questionnaire scores and pain responses following repeated movements. Determining whether subgroups are prognostic of outcome in people with CLBP may be considered an important step towards validating such subgroups (Kamper et al., 2010, Kent et al., 2010). It is also important to determine whether subgroups are prognostic because CLBP has a high burden (Vos et al., 2012), and management tailored towards prognostic factors may facilitate improved treatment outcomes (Hill et al., 2011). Therefore the prognostic validity of the subgroups from each of the three subgrouping studies was examined.

While the literature as a whole has investigated multiple dimensions in prognostic studies the dimensions considered in any one study are generally limited. Reviews of prognostic studies have revealed wide variability in the variables entered into prognostic models, and conflicting evidence of the prognostic importance of individual variables (Hayden et al., 2010, Verkerk et al., 2012). Also, only one study (Anema et al., 2009) appears to have considered broad intervention groups (e.g. exercise-based or psychologically-based interventions) as potential prognostic factors. As such it was deemed important to include all baseline variables, together with subgroup membership and broad intervention groupings, to determine whether this combination may encompass the complexity of CLBP and afford multidimensional prognostic models (Hayden et al., 2009).

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7.2   Study Five.

Multidimensional Prognostic Modelling In People With Chronic Axial Low Back Pain.

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7.2.1 Abstract

Objectives.

To derive prognostic models at one-year follow-up based upon a wide range of potentially prognostic, multidimensional baseline characteristics.

Methods.

This study entered multidimensional data (demographics, pain characteristics, movement / behaviours associated with pain, pain sensitivity, psychological, social, health, lifestyle) and broad intervention groupings into prognostic models for pain intensity, disability, global rating of change (GRC) and bothersomeness in a chronic low back pain (CLBP) cohort (n=294) at one-year follow-up.

Results.

The final multivariable prognostic model for higher pain intensity (explaining 23.2% of the variance) included higher baseline pain intensity and punishing spousal interactions, and lower years in education; while participating in exercise as intervention was prognostic of lower pain intensity. The model for higher disability (explaining 33.6% of the variance) included higher baseline disability, longer time taken to complete five forward bends, scores for two psychological principal components (one reflecting fear-avoidance beliefs, pain catastrophising, pain self-efficacy; the other endurance behaviours) and punishing spousal interactions; while participating in exercise as intervention was prognostic of lower disability. In the model for GRC rated as much / very much improved, having participated in exercise as intervention, having some leg pain as well as CLBP and higher chronic pain acceptance increased the odds. The receiver operating characteristic area under the curve (ROC AUC) was .72 indicating acceptable discrimination. In the model for having CLBP rated as very / extremely bothersome, higher baseline pain intensity, longer forward bend time and receiving spinal injection(s) as intervention increased the odds; while higher age and years in education and having some leg pain decreased the odds. The ROC AUC was .80 indicating acceptable discrimination.

Discussion.

The degree of variance explained by prognostic models in this study is similar to that reported in previous studies, despite inclusion of a broad range of potentially prognostic, multidimensional baseline variables. This finding may reflect the complexity of the CLBP. Clinical implications of variables included in the multivariable prognostic models are postulated.

7.2.2 Introduction

Identifying prognostic factors in people with CLBP is important because the disorder has a high burden (Vos et al., 2012), the majority of people with CLBP have no identifiable structural cause for their symptoms (Deyo and Weinstein, 2001) and treatment outcomes are moderate at best (Burton, 2005). Furthermore, directing management towards prognostic factors may facilitate improved treatment outcomes (Hill et al., 2011).

Over 200 prognostic factors have been identified in people with LBP, categorised into 36 dimensions including demographics, pain characteristics, physical examination findings, psychological, socio-environmental, health and work-related (Hayden et al., 2010, Hayden, 2007). However, reviews of prognostic studies have revealed discrepancies in the variables entered into prognostic models, and conflicting and inconsistent evidence of the prognostic importance of individual factors (Hayden et al., 2010, Verkerk et al., 2012).

Most prognostic studies explain less than 50% of the variance in their chosen outcome measure (Hayden et al., 2010). While the literature as a whole has investigated multiple dimensions in prognostic studies, the number of dimensions in any one study is generally limited. Examples of broader, multidimensional prognostic studies are those by Campbell et al. (2013b) and Verkerk et al. (2013), which have included demographic, pain characteristics, physical, psychological and occupational factors (32 and 23 variables respectively). However, these studies still do not explain a greater proportion of the variance in pain and /or disability, possibly indicating a larger spectrum of potential factors related to the back pain experience may need to be considered in prognostic modelling (Hayden et al.,

2010). Few studies have included potential prognostic factors from the movement, tissue sensitivity or lifestyle dimensions.

Another approach to researching prognostic outcomes is to determine whether statistically derived subgroups based upon valid and reliable measures are prognostic. In one such study, subgroups based on bothersomeness, pain referral, psychological factors and disability were prognostic of differing levels of disability at six-month follow-up (Hill et al., 2008). In a similar study, subgroups based upon psychological and occupational factors, pain characteristics, disability, and sleep were prognostic for pain intensity, disability and work absenteeism at six- and twelve-month follow-up (Linton and Boersma, 2003, Boersma and Linton, 2005). While there is initial evidence that such subgroups may be prognostic they have considered a relatively limited range of dimensions associated with CLBP and disability. Consideration of a broader range of dimensions may improve prognostic modelling (Hayden et al., 2010). In our previous work we have derived subgroups based upon pain sensitivity (Rabey et al., 2015), psychological questionnaire scores and pain responses following repeated movements. To date it is not known whether these subgroups are predictive of outcome.

Also, while many studies examine factors predictive of outcome following certain interventions, few studies have considered a range of broad intervention groups (e.g. exercise or psychologically-based interventions) as potential factors in prognostic modelling alongside baseline dimensions. In a study of 2825 people off work due to low back pain (LBP) across six countries Anema et al. (2009) investigated the prognosis associated with different interventions (surgery, analgesia, passive therapies, exercise, back school) on return to work. They found that receiving analgesia or participating in exercise therapy was positively associated with return to work at one and / or two-year follow, but did not derive prognostic models for pain intensity or disability. No other studies appear to have considered a broad range of interventions as potential prognostic factors. Inclusion of such factors may facilitate prognostic modelling across other outcomes, and guide intervention.

When considering outcome measures for prognostic studies it is important to note perceived recovery from CLBP is multidimensional: dependent upon the person's perception of the impact LBP has upon their quality of life, functional capacity and psychological health, as well as their perceived pain intensity (Hush et al., 2009). Few prognostic studies include greater than one outcome measure (Verkerk et al., 2012), and are unlikely to reflect the multidimensional lived experience of a person with CLBP. Guidelines for research into chronic pain (Dworkin et al., 2005, Dworkin et al., 2008) suggest measuring pain intensity, disability, and global rating of change (GRC) as outcomes covering differing dimensions of recovery. GRC, when rated much or very much improved, has been shown to be most discriminatory of a positive treatment response (Jensen et al., 2012) and equates to the patient acceptable symptom state (Strand et al., 2011). Bothersomeness has also been proposed as an outcome measure, as it is considered a summary of patient perception of symptoms, including severity, and their physical and psychological impact (Dunn and Croft, 2005). Assessment of bothersomeness can be dichotomised to reflect clinical importance (Dunn and Croft, 2005).

The aim of this study was to derive prognostic models at one-year follow-up in a large CLBP cohort, based upon a wide range of potentially prognostic, multidimensional baseline characteristics. These include: demographics, pain characteristics, movement / behaviours associated with pain, pain sensitivity, psychological, social, health and lifestyle factors; and previously derived subgroups based upon pain sensitivity, psychological questionnaire scores and pain responses following repeated movement, as well as broad intervention groupings. The following outcomes were assessed: i) pain intensity, ii) disability levels, iii) GRC, iv) bothersomeness.

7.2.3   Methods And Materials

This research was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013). All study procedures were approved by the human research ethics committees of Curtin University, Royal Perth Hospital, and Sir Charles Gairdner Hospital in Perth, Western Australia.

Study population.

This was a longitudinal cohort study involving people with axial CLBP (n=294; 57.1% female; median age 50 years). Particiants were recruited via multi-media advertisements from metropolitan and rural Western Australia (77.6%), private metropolitan physiotherapy clinics (20.1%), public metropolitan hospitals (physiotherapy / emergency departments) (1.4%); and private metropolitan pain management and general practice clinics (1.0%).

Potential participants contacted one researcher (MR), and were sent an inclusion / exclusion criteria screening questionnaire. Ambiguous responses were clarified by telephone. Inclusion criteria were: aged 18-70 years old; LBP > 3-months duration; ≥2-points on an 11-point numeric rating scale (NRS) for pain intensity (past week); ≥5-points on the Roland Morris Disability Questionnaire (RMDQ) (Roland and Morris, 1983); ≥60% LBP on the following question (Wai et al., 2009): "Which situation describes your pain over the past 4 weeks the best? 100% of the pain in the low back; 80% of the pain in the low back and 20% in the leg(s); 60% of the pain in the low back and 40% in the leg(s); 50% of the pain in the low back and 50% in the leg(s); 40% of the pain in the low back and 60% in the leg(s). 20% of the pain in the low back and 80% in the leg(s)."

Exclusion criteria were: previous extensive spinal surgery (greater than single level fusion / instrumentation or discectomy), spinal surgery in the past six-months, serious spinal pathology (cancer, inflammatory arthropathy, acute vertebral fracture), diagnosed neurological disease, bilateral dorsal wrist / hand pain, pregnancy, inability to understand English.

Baseline data collection.

The following potentially prognostic baseline data were collected:

Demographics.

Age in years, sex.

Pain characteristics.

Average pain intensity over the past week was measured using an 11-point numeric rating scale (NRS) (Dworkin et al., 2005).

Low back pain related disability was measured using the Roland Morris Disability Questionnaire (RMDQ) (Roland and Morris, 1983).

Duration of CLBP in months.

Pain distribution was determined as 100%, 80% or 60% percent low back versus leg pain based on aforementioned question (Wai et al., 2009) used in participant screening.

The following two questions from the Standardised Evaluation of Pain were utilised to determine whether pain was evoked by activities or body positions (Scholz et al., 2009): "Is your pain caused by activity, e.g. when you are moving an arm or a leg, turning or bending your back, when you are walking, coughing or chewing? Is your pain caused by a particular position of your body, e.g. when you are sitting or lying flat?"

Bothersomeness was evaluated using a seven-point scale to answer the question, "Overall, how bothersome has your back pain been in the last 2 weeks?" (Patrick et al., 1995) Answers were dichotomised, with participants answering, "Very much," or, "Extremely," classed as having clinically-relevant levels of bothersomeness (Dunn and Croft, 2005).

Tissue sensitivity dimension.

A battery of nociceptive and non-nociceptive "bedside" and laboratory quantitative sensory tests (QST) were measured as described in Rabey et al. (2015). Pressure pain threshold (PPT), cold pain threshold (CPT), heat pain threshold (HPT) and mechanical detection threshold (MDT) were tested at both the area of maximal lumbar pain as indicated by the participant, and the dorsal wrist joint line of an asymptomatic wrist. Two-point discrimination, temporal summation to repeated nylon monofilament stimulation and pinprick hyperalgesia were tested at the lumbar region only. Conditioned pain modulation was tested using pressure at the lumbar region as the test stimulus, and noxious heat at the dorsal wrist as the conditioning stimulus

according to the protocol described by Rabey et al. (2015). This yielded two scores: baseline pressure (kPa) rated as 6/10 for pain intensity on an 11-point NRS, and mean change in pain intensity rating from three applications of the test stimulus while the conditioning stimulus was concurrent.

Movement dimension.

Participants were asked to perform two repeated movement tasks:

1. Pick up a pencil from the floor, and place it back down, for a total of 20 forward bends.

2. Complete 20 backward bends to view a marker placed on the ceiling approximately 60cm behind the participant.

Participants were able to refuse to undertake these movements, or decline to complete the full 20 repetitions should they feel that their pain became too great, or fear exacerbation of symptoms. The number of repetitions completed was recorded.

Participants received standardised instructions:

1. For the pencil task, participants were asked simply to pick up a pencil that was placed on the floor in front of them. This counted as one forward bend. They then placed the pencil back on the floor, which counted as the second forward bend. They repeated this until a total of 20 forward bends was reached. Participants were told that they could undertake this task however they wished, and at whatever speed they wished.

2. For the backward bending task, participants were instructed to take sight of the marker placed on the ceiling behind them however they wished, at whatever speed they wished, but without turning around, and then to return to neutral before repeating the task up to a total of 20 times.

These instructions were reiterated if the participant subsequently questioned whether they should perform the task in a certain manner. Participants were

instructed that there would be a brief pause every five repetitions, during both tasks, to ask them to rate their pain intensity (see below).

Video recordings were made of the repeated movement tasks using two iPads (4th Generation) (Apple, California, USA) (1080p HD video recording) mounted on tripods; one directly in front of the participant, the second repositioned to optimise a lateral view of the participant's lumbar region.

Participants were asked to rate the intensity of their pain on an 11-point NRS before commencement of each task, and then during both tasks, after every five repetitions. A change score was then determined by subtracting the score on the NRS given after the last set of repetitions completed (maximum 20) from the baseline NRS score (Sullivan et al., 2009). A four-category subgrouping variable, "pain response following repeated movement", was derived based on pain increase by the minimum clinically important difference (MCID) of two-points (Salaffi et al., 2004) in response to movement as follows.:

No increase in pain (NIP) in either direction (n=144, 49.0%).

Increased pain following forward bending only (FB) (n=83, 28.2%).

Increased pain following backward bending only (BB) (n=29, 9.9%).

Increased pain following forward and backward bending (FB&BB) (n=38, 12.9%).

A count of protective and communicative behaviours associated with pain was undertaken as previously described (Keefe and Block, 1982, Sullivan et al., 2006). Protective behaviours associated with pain included: guarding - abnormally slow or rigid movements; bracing - using a limb for extra support during movement; rubbing or holding the affected area. Communicative behaviours associated with pain included: grimacing, or other facial expressions of pain; sighing, moaning etc. As per Sullivan et al. (2006) no minimum duration of any of the aforementioned behaviours was stipulated. These behaviours were only scored during the first five bends in each direction. The time, in seconds, taken to complete the first five bends in each direction was also recorded. This commenced at the initiation of the first

bend, and was completed at the participant's return to a neutral standing position at the completion of the fifth bend.

Psychological dimension.

Depression, anxiety and stress symptomatology were measured using the short-form version of the Depression Anxiety Stress Scale (DASS-21) (Lovibond and Lovibond, 1995).

Fear-avoidance beliefs were measured using either the Fear-Avoidance Beliefs Questionnaire (FABQ) (Waddell et al., 1993) which has two subscales (physical activity (FABQ-PA) and work (FABQ-W)).

Pain catastrophising was measured using the Pain Catastrophising Scale (PCS) (Sullivan et al., 1995) which has three subscales (rumination, magnification, helplessness).

Pain self-efficacy was measured using the Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas, 2007).

Endurance behaviours were measured using the Avoidance Endurance Questionnaire (AEQ) (Hasenbring et al., 2009, Hasenbring et al., 2012). To complete the AEQ, scores are derived on two subscales: the Thought Suppression subscale (TSS), and the Behavioural Endurance subscale (BES). These scores are then used to classify participants into four subgroups exhibiting fear-avoidance, endurance behaviour (associated with eustress or distress) or adaptive coping, when combined with the degree of depressive symptoms exhibited. In this study the cut-off score for mild depressive symptoms (nine-points) from the DASS-21 (Lovibond and Lovibond, 1995) was utilised in conjunction with the AEQ scores to classify participants into AEQ classification groups as follows:

1) Fear-avoidance: ≥9 on the DASS-21 depressive sub-scale, and <3 on the TSS and BES.
2) Distress-endurance: ≥9 on the DASS-21 depressive sub-scale and ≥3 for a mean TSS and / or BES.

3) Eustress-endurance: <9 on the DASS-21 depressive sub-scale and >3 on the BES.

4) Adaptive coping: <9 on the DASS-21 depressive sub-scale, TSS and BES <3.

Chronic pain acceptance was measured using the short-form Chronic Pain Acceptance Questionnaire (CPAQ-8) (2010) which has two subscales (pain willingness, activity engagement).

Mindfulness was measured using the Mindful Attention Awareness Scale (MAAS) (Brown and Ryan, 2003).

Perceived risk of persistent pain was measured using an NRS from the Örebro Musculoskeletal Pain Questionnaire anchored at one end by, "0 - No risk," and at the other by, "10 - Very large risk," for the question, "In your view, how large is the risk that your current pain may become persistent?" (Linton and Boersma, 2003)

Distortion of perception of the low back region was measured using the Fremantle Back Awareness Questionnaire (FreBAQ) (Wand et al., 2014).

Health dimension.

The presence of differing types of comorbidities (diagnosed medical conditions (Beales et al., 2012, Dominick et al., 2012), undiagnosed symptoms (Tschudi-Madsen et al., 2011, Hagen et al., 2006a) and functional pain disorders (Mayer and Bushnell, 2009) associated with LBP were assessed. As well as a total comorbidity count ranging from a possible 0 to 22, a number of separate counts were determined: functional pain syndrome comorbidities (0 to 6), musculoskeletal pain comorbidities (0 to 3), other diagnosed medical disorders (0 to 13), and other undiagnosed symptoms (0 to 9).

To examine the presence of widespread pain participants completed a quantifiable body chart (Öhlund et al., 1996). As well as the total number of body chart squares containing pain, participants were also classified according to the Manchester definition of chronic widespread pain (Macfarlane et al., 1996) (pain in the low back

/ axial skeleton plus in two sections in two contralateral limbs) based on their areas of pain indicated on the body chart.

General health was rated on a five point scale from, "Poor," to, "Excellent," using a single item from the COOP / WONCA Charts (Van Weel et al., 2012).

Height and weight were measured, and body mass index (BMI) calculated.

Social and lifestyle dimensions.

Sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) which comprises 17 questions assessing sleep quality, quantity, disturbance and its effect on daily living. The scoring scheme described by the authors generates a final score, which if above five is suggestive of significant sleep disturbance (Buysse et al., 1989).

Smoking status was assessed by asking whether participants were currently a smoker, ex-smoker or a non-smoker.

Moderate and vigourous physical activity levels per week were measured using the short-form International Physical Activity Questionnaire (IPAQ) (IPAQ Group, 2005).

Years in formal education was measured by asking, "How many years have you spent in education (school, college, university or professional education)?"

Compensation status was examined by asking participants to rate their response, on a seven-point scale, from complete disagreement (0) to complete agreement (6) for the following single question from the FABQ (Waddell et al., 1993), "I have a claim for compensation for my pain."

Whether participants were currently working was assessed by asking, "Are you currently in work (either paid or unpaid work e.g. student, housewife)?"

Participants were asked to name their occupation, and responses were dichotomised into manual or sedentary occupations, upon consultation of the Australian and New Zealand Standard Classification of Occupations (Australian Bureau of Statistics, 2013).

Job satisfaction was measured using an NRS anchored at one end with, "0 - Not satisfied at all," and at the other with, "10 - Completely satisfied," for the question, "If you take into consideration your work routines, management, salary, promotion possibilities and work mates, how satisfied are you with your job?"(Linton and Boersma, 2003)

Stressful life events were measured using an NRS anchored at one end by, "1 - No stress," and at the other by, "6 - Extreme stress," in response to the question, "In the past year, how would you rate the amount of stress in your life (at home and at work)?" (Littman et al., 2006)

How participants perceived the response of their significant other to their pain was measured using the Social Support subscale, and subscales considering perceived solicitous, distracting and punishing spouse responses from the West Haven-Yale Multidimensional Pain Inventory (Kerns et al., 1985, McCracken, 2005). Four scores are derived: social support, punishing responses, solicitous responses, distracting responses.

Follow-up data collection.

At the end of the one-year follow-up period participants provided data on the following four outcomes:

1) Pain intensity (average over past week), measured using an 11-point NRS.
2) Disability level, measured using the RMDQ (Roland and Morris, 1983).
3) GRC, measured using a valid and reliable seven-point global rating scale from, "Very much worse," to, "Very much improved," (adapted from (Kamper et al., 2009)) based upon the question, "With respect to your low back pain how would you describe yourself now, compared to one year ago when we examined you for the research project (laboratory session at Curtin University)?" Answers to this question were dichotomised with a positive outcome defined as a rating of much or very much improved on the GRC.
4) Bothersomeness, evaluated using the same seven-point scale as at baseline. Answers to this question were dichotomised with participants rating the

bothersomeness of their CLBP as, "Very," or, "Extremely," classified as having clinically-important bothersomeness (Dunn and Croft, 2005).

Interventions.

Patients were free to undergo any intervention they wished during the follow-up period, at the end of which they were asked, "Can you describe any treatments you have had over the past year?" Interventions were combined into eight broad groupings: 1) manual therapies (offered by physiotherapists, chiropractors, osteopaths, general practitioners, massage therapists), 2) any exercise described by the participant (prescribed or self-administered), 3) psychological therapies, 4) pharmacological management, 5) any form of spinal injection, 6) spinal surgery including rhizotomy, 7) acupuncture, 8) multidisciplinary pain management. Participants were able to list as many interventions as they wished. Separate binary variables for each treatment group, indicating whether the intervention was received versus not received, were used in statistical models.

7.2.4 Statistical Analysis

All analysis was performed using Stata 13.1 (Statacorp, Texas, USA).

The number of participants with missing data for each variable is detailed in Table 1. For questionnaires, missing data management was undertaken as suggested in original manuscripts where described. Otherwise, the mean of other items was imputed in the case of one missing item, and the total score was considered missing in the case of two or more missing items.

Descriptive statistics were calculated for each outcome measure. Baseline and one-year RMDQ were log-transformed due to skewed distribution (logRMDQ).Changes from baseline were evaluated using paired t-tests (pain intensity and logRMDQ), Wilcoxon signed-rank sum tests (RMDQ) and McNemar's test (bothersomeness).

Data from the tissue sensitivity and psychological dimensions were utilised in prognostic models in three different, and separate, ways. In addition to consideration of each specific variable, correlated measures were also grouped into

broader constructs using principal component analysis (PCA), and people classified into subgroups with similar profiles on measures using latent class analysis (LCA). Analysis of 13 QST variables yielded five principal components (PCs) which explained 69% of the variance within the data (Appendix 1). These PCs can be summarised as representing: thermal pain sensitivity (PC1); pressure pain sensitivity (PC2); conditioned pain modulation, temporal summation and pinprick hyperalgesia (PC3); mechanical detection thresholds (PC4); and two-point discrimination and vibration perception (PC5). All QST PC scores were calculated using component loadings (Rabey et al., 2015). LCA of the QST PCs was used to derive three differing clusters (known as pain sensitivity clusters) within the CLBP cohort with differing pain sensitivity profiles. Cluster 1 (n=94, 31.9%) was characterised by average to high temperature and pressure pain sensitivity. Cluster 2 (n=153, 52.0%) was characterised by average to high pressure pain sensitivity. Cluster 3 (n=47, 16.0%) was characterised by low temperature and pressure pain sensitivity (Rabey et al., 2015).

Data from ten psychological questionnaires / subscales (DASS depression, anxiety and stress subscales, PSEQ, pain willingness and activity engagement subscales of the CPAQ-8, TSS and BES sub-scales of the AEQ, FABQ-PA and PCS) were utilised to derive four PC scores using PCA (known as psychological PCs) (Appendix 2). These PCs can be summarised as representing: depression, anxiety and stress (combined DASS score) (PC1); fear-avoidance beliefs, pain catastrophising and pain self-efficacy (PC2) (calculated using component loading); mean of thought suppression and behavioural endurance (PC3); and chronic pain acceptance (CPAQ-8 total score) (PC4). LCA using eight baseline psychological variables (DASS depression, anxiety and stress subscales; PSEQ; TSS; PCS rumination, magnification and helplessness subscales) resulted in three clusters of participants (known as psychological clusters). Cluster 1 (23.5%) was characterised by low scores across all indicator variables. Compared to Cluster 1, Cluster 2 (58.8%) was characterised by relatively elevated thought suppression, pain catastrophising and fear-avoidance beliefs, but lower pain self-efficacy, depression, anxiety and stress. Cluster 3 (17.7%) was characterised by higher scores across all indicator variables.

Univariable associations between each baseline variable and the four outcome measures were assessed using linear (pain intensity and logRMDQ) or logistic regression (GRC and bothersomeness). The pain intensity and disability models were adjusted for baseline pain intensity and baseline disability (logRMDQ) respectively when considering univariable associations of these outcomes with other variables, as baseline measures were strongly associated with follow-up measures. It is important to recognise that statistically this equates to identifying factors prognostic of change in pain or disability over the one-year follow-up period, rather than pain intensity or disability at one-year alone. Variables with univariable associations ($p<.1$) were considered candidate variables, and were selected for final multivariable regression models using a backwards stepwise method combined with purposeful selection of covariates approach to ensure no important confounding variables were omitted (Hosmer and Lemeshow, 2000). For the tissue sensitivity and psychological dimensions, separate models were compared using either single measures, PC scores, and clusters of participants, where candidates for the final model included more than one of these variable types. This avoided collinearity issues from having overlapping information in the variable types, for example, having DASS depression in the same model as psychological PC1, which represented depression, anxiety and stress. The same principle was used when considering the four-category subgrouping variable pain response following repeated movement and the AEQ classification groups. Each model was examined to ensure no significant interactions for gender (as it was considered possible that different factors may be important for prognosis in males versus females), absence of influential observations, and multicollinearity of variables. In addition models were examined for linearity of relationships between outcome and prognostic variables, and normality and homoscedasticity of residuals. In the linear models R^2 values were examined to determine the total variance in the outcome explained by each model as a whole, while squared semi-partial correlations were examined to determine the amount of unique variance attributable to each individual variable, in addition to r shared variance. Logistic models were also examined for goodness of fit, and the receiver operating characteristic (ROC) area under the curve (AUC) was calculated as a measure of the discrimination of the model. Probabilities of

outcome as predicted by the final models for various combinations of prognostic indicators were generated for interpretative purposes. The sample size for final models ensured at least two cases per candidate predictor variable for all outcome models (Austin and Steyerberg, 2015).

7.2.5   Results

There were 28 (9.5%) participants lost to follow-up, leaving 266 participants (90.5%) available for analysis. Those lost to follow-up had a median age of 47 years (range: 27-66) which was not significantly different from participants included at follow-up (median age 51 years, range 18-70, Wilcoxon-Mann-Whitney test, p=.29). Eleven participants lost to follow-up were female (39.3%), which was a significantly lower proportion than those participants included at follow-up (59.0%, χ^2 analysis, p=.04). Baseline pain intensity (past week) did not differ between those included at follow-up and those lost to follow-up (independent t-test, p=.64). However, baseline RMDQ score (median (IQR)) was significantly lower for those included at follow-up (8 (6-12)) than those lost to follow-up (10.5 (8-15.5), Wilcoxon-Mann-Whitney test, p=.02).

Two hundred and sixty-two participants answered the question regarding interventions, of which 47 replied they had not received any intervention, making the total number of respondents receiving an intervention 215. Of these 83 people listed a second intervention, and 12 people listed a third. The proportion of participants reporting receiving each type of intervention is reported in Table 1.

There were significant improvements at one-year follow-up for pain intensity, disability and bothersomeness across the cohort as a whole (Table 2, all p-values <.001). Mean pain intensity (past week) was 1.6-points lower at follow-up. Median disability (RMDQ) fell from eight points to four points. The proportion of participants rating CLBP as very or extremely bothersome fell from 50.4% at baseline to 19.6% one year later. Of those *without* significantly bothersome CLBP at baseline (n=132, 49.6%), 118 (89.4%) were still without significantly bothersome CLBP at follow-up, while 14 (10.6%) had developed bothersome CLBP. Of those *with* significantly bothersome CLBP at baseline (n=134, 50.4%), 96 (71.6%) improved so

their CLBP was no longer bothersome at follow-up, while 38 (28.4%) remained bothered. Overall 33.6% of participants rated their CLBP as much or very much improved on the GRC.

Table 1.

Baseline Descriptive Statistics for all Variables for all Participants with Follow-up Data (n=266)

Variable	Summary Statistic
Demographics	
Age median (IQR) (min, max)	51 (39, 60) (18, 70)
Female n (%)	157 (59.0)
Pain Characteristics	
Baseline pain intensity (NRS) mean (SD) (min, max)	5.8 (1.9) (2, 10)
Baseline disability (RMDQ) median (IQR) (min, max)	8 (6, 12) (5, 24)
Duration of CLBP (months)[4] median (IQR) (min, max)	120 (42, 240) (3, 720)
100% of pain in low back region n (%)	129 (48.5)
Aggravated by activity (StEP)[1] n (%)	226 (85.3)
Aggravated by position (StEP)[1] n (%)	215 (81.1)
Baseline bothersomeness (very / extremely bothersome) n (%)	134 (50.4)
Interventions[1]	
No intervention n (%)	47 (17.9)
Manual therapy n (%)	89 (34.0)
Exercise n (%)	115 (43.9)
Psychological n (%)	15 (5.7)
Pharmacological n (%)	42 (16.0)
Injection n (%)	25 (8.8)
Surgery n (%)	10 (3.8)
Acupuncture n (%)	14 (5.3)
Multidisciplinary rehabilitation n (%)	2 (0.8)

Variable		Summary Statistic
Pain Sensitivity		
Pain sensitivity clusters n (%)	Cluster 1	87 (32.7)
	Cluster 2	137 (51.5)
	Cluster 3	42 (15.8)
PPT (wrist), kPa median (IQR) (min,max)		262.7 (177.3, 342.7) (55.3, 1200.0)
PPT (lumbar), kPa median (IQR) (min,max)		261.2 (162.0, 444.7) (36.7, 1600.0)
CPT (wrist), °C median (IQR) (min,max)		5.6 (4.0, 13.1) (4.0, 30.6)
CPT (lumbar), °C median (IQR) (min,max)		4.3 (4.0, 24.1) (4.0, 31.2)
HPT (wrist), °C median (IQR) (min,max)		45.1 (42.5, 47.7) (32.2, 50.0)
HPT (lumbar), °C mean (SD) (min, max)		42.4 (3.9) (33.6, 50)
MDT (wrist), mN[3] median (IQR) (min, max)		3.9 (3.9, 5.9) (.1, 19.6)
MDT (lumbar), mN[3] median (IQR) (min, max)		5.9 (3.9, 13.7) (0.1, 58.8)
Two-point discrimination, cm mean (SD) (min, max)		5.7 (2.1) (.5, 10.0)
Baseline CPM pressure, kPa[11] median (IQR) (min,max)		430.5 (253.0, 655.0) (60.0, 1700.0)
CPM change score (NRS)[11] mean (SD) (min, max)		1.0 (1.2) (-3.0, 4.0)
Temporal summation[1] n (%)		51 (19.2)
Pinprick hyperalgesia n (%)		41 (15.4)
Movement Dimension		
Pain response following repeated movement subgroups n (%)	NIP	132 (49.6)
	FB	74 (27.8)
	BB	26 (9.8)
	FB&BB	34 (12.8)
Forward bend time, sec[1] median (IQR) (min, max)		18 (15, 22) (9, 186)
Backward bend time, sec[1] median (IQR) (min, max)		16 (14, 20) (9, 57)
Communicative behaviours, forward bending[1] median (IQR) (min, max)		0 (0, 0.2) (0, 3.8)
Protective behaviours, forward bending[1] median (IQR) (min, max)		1 (0.3, 1.0) (0, 4.2)
Communicative behaviours, backward bending[1] median (IQR) (min, max)		0 (0, 0.2) (0, 5.4)
Protective behaviours, backward bending[1] median (IQR) (min, max)		0 (0, 0) (0, 2)

Variable		Summary Statistic
Psychological Dimension		
Psychological clusters n (%)	Cluster 1	65 (24.4)
	Cluster 2	157 (59.0)
	Cluster 3	44 (16.5)
DASS depression median (IQR) (min, max)		6 (2, 14) (0, 42)
DASS anxiety median (IQR) (min, max)		4 (0, 8) (0, 42)
DASS stress median (IQR) (min, max)		11 (6, 18) (0, 42)
DASS combined total (also PC1) median (IQR) (min, max)		21 (12, 36) (0, 126)
FABQ-W[8] median (IQR) (min, max)		16 (7, 27) (0, 42)
FABQ-PA mean (SD) (min, max)		14.3 (5.9) (0, 24)
PCS rumination[1] median (IQR) (min, max)		6 (3, 10) (0, 16)
PCS magnification[1] median (IQR) (min, max)		3 (1, 5) (0, 12)
PCS helplessness[1] median (IQR) (min, max)		8 (4, 13) (0, 24)
PCS total[1] median (IQR) (min, max)		17 (9, 26) (0, 52)
PSEQ median (IQR) (min, max)		42.5 (32, 50) (1, 60)
AEQ classification[2] n (%)	Adaptive	75 (28.4)
	Distress endurance	73 (27.6)
	Eustress endurance	88 (33.3)
	Fear-avoidance	28 (10.6)
TSS[1] mean (SD) (min, max)		2.2 (1.7) (0, 6.0)
BES mean (SD) (min, max)		3.0 (1.0) (0, 5.9)
Psychological PC3 (TSS, BES) mean (SD) (min, max)		2.6 (1.2) (0, 5.9)
CPAQ-8 pain willingness mean (SD) (min, max)		9.1 (4.8) (0, 22)
CPAQ-8 activity engagement median (IQR) (min, max)		18 (15, 21) (0, 24)
CPAQ-8 total (also PC4) mean (SD) (min, max)		26.2 (7.7) (0, 45)
MAAS[3] mean (SD) (min, max)		4.2 (0.9) (1.3, 6.0)
Perceived risk of persistent pain[1] median (IQR) (min, max)		9 (8, 10) (3, 10)
FreBAQ (median (IQR) (min, max)		9 (5, 14) (0, 32)

Variable		Summary Statistic
Health Dimension		
Total diagnosed comorbidities median (IQR) (min, max)		2 (0, 3) (0, 11)
Musculoskeletal comorbidities median (IQR) (min, max)		0 (0, 1) (0, 3)
Functional pain comorbidities median (IQR) (min, max)		0 (0, 1) (0, 4)
Other diagnosed comorbidities median (IQR) (min, max)		1 (0, 2) (0, 8)
Other comorbid symptoms median (IQR) (min, max)		2 (1, 4) (0, 9)
Number of body chart squares filled-in median (IQR) (min, max)		13 (7, 20) (1, 68)
Manchester CWP classification n (%)		74 (27.8)
Baseline COOP/WONCA overall health score mean (SD) (min, max)		3.0 (1.0) (1.0, 5.0)
BMI, kg/m^2 median (IQR) (min, max)		26.2 (23.4, 29.3) (17.7, 50.3)
Lifestyle and Social Dimensions		
PSQI[9] mean (SD) (min, max)		9.3 (4.1) (2, 20)
Smoking status	Non-smoker	159 (59.8)
	Ex-smoker	80 (30.1)
	Smoker	27 (10.2)
Moderate and vigourous physical activity (min / week)[5] median (IQR) (min, max)		114 (0, 302.5) (0, 2100)
Years in education[10] mean (SD) (min, max)		14.9 (3.5) (7, 27)
Compensation claim[5] n (%)		42 (16.2)
Currently at work n (%)		204 (76.7)
Manual v. sedentary occupation[12] n (%)	Not working	25 (10.0)
	Sedentary	168 (67.2)
	Manual	57 (22.8)
Job satisfaction (NRS)[13] median (IQR) (min, max)		7 (5, 9) (0, 10)
Life events mean (SD) (min, max)		3.6 (1.5) (0, 6)
MPI social support[7] median (IQR) (min, max)		4 (3, 5) (0, 6)
MPI punishing[6] median (IQR) (min, max)		1.0 (0.2, 2.0) (0, 6.0)
MPI solicitous[6] mean (SD) (min, max)		2.8 (1.4) (0, 6)
MPI distracting[6] median (IQR) (min, max)		1.8 (0.8, 2.8) (0, 6.0)

Note. [1] missing in one case, [2] missing in two cases, [3] missing in three cases, [4] missing in four cases, [5] missing in six cases, [6] missing in eight cases, [7] missing in nine cases, [8] missing in 10 cases, [9] missing in 11 cases, [10] missing in 13 cases, [11] missing in 14 cases, [12] missing in 16 cases, [13] missing in 39 cases

NRS – numeric rating scale, RMDQ – Roland Morris Disability questionnaire, StEP – Standardised Evaluation of Pain, PPT – Pressure pain threshold, kPa – kilopascals, CPT – cold pain threshold, ^{o}C – degrees Centigrade, HPT - Heat pain threshold, MDT – Mechanical detection threshold, mN – millinewtons, cm – centimetres, CPM – Conditioned pain modulation, NIP – No increased pain following repeated bending, FB – Pain increased following repeated forward bending only, BB – Pain increased following repeated back bending only, FB&BB – Pain increased following repeated forward and backward bending, sec – seconds, DASS – Depression Anxiety Stress scales, PC – principal component, FABQ-W – Fear-Avoidance Beliefs questionnaire (Work subscale), FABQ-PA - Fear-Avoidance Beliefs questionnaire (Physical activity subscale), PCS – Pain Catastrophising scale, PSEQ – Pain Self-efficacy questionnaire, Psychological PC2 – principal component score derived from FABQ-PA, PCS and PSEQ scores, AEQ – Avoidance Endurance questionnaire, TSS – Thought Suppression subscale, BES – Behavioural Endurance subscale, Psychological PC3 - mean of TSS and BES scores, CPAQ-8 – Chronic Pain Acceptance questionnaire (Short form), MAAS – Mindful Attention Awareness scale, FreBAQ – Fremantle Back Awareness questionnaire, CWP – Chronic widespread pain, BMI – Body mass index, kg/m^2 – kilograms per metre squared, PSQI – Pittsburgh Sleep Quality index, min / week – minutes per week, MPI - Multidimensional Pain Inventory

Table 2.

Descriptive statistics for questionnaire data at one year follow-up for the entire cohort.

Follow-up variable	Baseline	Follow-Up	Difference (95% CI)	*p*-value
Pain Intensity (NRS) (n=266) mean (SD) (min,max)	5.8 (1.9) (2, 10)	4.2 (2.1) (0, 10)	-1.6 (-1.4 to -1.9)	**<.001**[1]
RMDQ Score (n=266) median (IQR) (min,max)	8 (6,12) (5,24)	4 (2, 8) (0, 23)		**<.001**[2]
Natural log RMDQ Score (n=266) mean (SD) (min,max)	2.30 (.38) (1.80, 3.22)	1.61 (.79) (0, 3.18)	-.68 (-0.60 to-0.77)	**<.001**[1]
Bothersomeness (very / extremely) (n=266) n (%)	134 (50.4)	52 (19.6)		**<.001**[3]
Global rating of change (-3 - +3) (n=265) mean (SD) (min,max)	n/a	0.7 (1.3) (-3, 3)		
Global rating of change (much improved / very much improved) (n=265) n (%)	n/a	89 (33.6)		

Note. [1] paired t-test; [2] Wilcoxon signed rank sum test; [3] McNemar test

n/a – not applicable

Pain at one-year follow-up.

The associations between each baseline factor with pain intensity at one-year follow-up, adjusted for baseline pain intensity, are presented in Appendix 3. Baseline pain intensity was strongly associated with pain intensity at one-year, with a one-point increase on an 11-point NRS being associated with an estimated 0.4-point increase in follow-up pain intensity (95% CI: 0.3 - 0.5, p<.001). After adjustment for baseline pain intensity variables from multiple dimensions were associated with pain at follow-up at a significance of $p<.1$, and were subsequently considered for inclusion in a multivariable model. From the intervention dimension, having no intervention or acupuncture in the interim period was associated with higher pain intensity at follow-up, whereas participating in exercise was associated with lower pain intensity. From the tissue sensitivity dimension, having higher lumbar MDT and sensory testing PC4 score (reflecting lumbar and wrist MDT) were associated with greater pain at follow-up. From the psychological dimension, membership of psychological Cluster 2 (characterised by relatively elevated thought suppression, pain catastrophising and fear-avoidance beliefs, but lower pain self-efficacy, depression, anxiety and stress) and Cluster 3 (characterised by higher scores across all psychological indicator variables) were associated with higher pain intensity at follow-up. Also associated with higher pain intensity at follow-up were higher scores on psychological PC2 (representing FABQ-PA, PCS and PSEQ) and PC3 (representing TES and BSS), and the individual PCS helplessness and TSS subscales. Higher pain self-efficacy and activity engagement were associated with lower pain intensity. From the health dimension, poorer baseline general health was associated with higher pain intensity at follow-up. From the lifestyle and social dimensions, higher sleep disturbance and more years in education were associated with lower pain intensity, while performing a manual occupation and having a relationship with a significant other involving a punishing response style were associated with higher pain intensity.

The final multivariable model included baseline pain intensity, having participated in exercise as intervention, number of years in education and MPI punishing subscale score (Table 3). The X-standardised coefficients allow the most interpretable

comparison of the strength of the continuous variables in linear regression models with a non-transformed outcome. From these it can be seen that pain intensity at baseline was the strongest independent continuous predictor, as a one SD increase in this was associated with an estimated mean increase in follow-up pain intensity of 0.6. An increase of one SD in years in education and MPI punishing subscale score were associated with a mean decrease of 0.4 and increase of 0.3 in pain intensity at one-year respectively, independently of other variables in the model. Participating in exercise as intervention was associated with an estimated 0.8 decrease in pain intensity at one-year follow-up independently of other variables in the model. This final model explained 23.2% of the variance in pain intensity at one-year follow-up, and consistent with the results from the X-standardised coefficients, this explained variance could be partitioned as follows; 6.9% shared by all four predictors, 7.6% uniquely by baseline pain intensity, 3.6% uniquely by exercise as intervention, 3.4% uniquely by years of education and 1.6% uniquely by a punishing partner response. The proportion of variance left unexplained was 76.8% (Figure 1).

Table 3.

Final multivariable regression model for pain intensity (NRS (0-10), n=245) at one-year follow-up (R^2=.23).

	Unstandardized coefficient (95% CI)				*p*-value	bStdX[1]
Pain intensity at one year follow-up						
Pain at baseline	0.32	(0.19	to	0.45)	**<.001**	.60
Exercise as intervention	-0.82	(-1.31	to	-0.34)	**.001**	NA
Years in education	-0.11	(-0.18	to	-0.04)	**.001**	-.40
MPI punishing subscale score	0.20	(0.02	to	0.38)	**.026**	.27

Note. [1]bStdX is x-standardized coefficient, represents expected change in pain intensity at one-year follow-up for a 1 standard deviation increase in continuous predictors
NRS – numeric rating scale; MPI – Multidimensional Pain inventory

Pain Intensity: Variance explained

- Shared by all variables in model (6.9%)
- Baseline NRS (7.6%)
- Exercise (3.6%)
- Years of education (3.4%)
- Punishing partner (1.6%)
- Unexplained (76.8%)
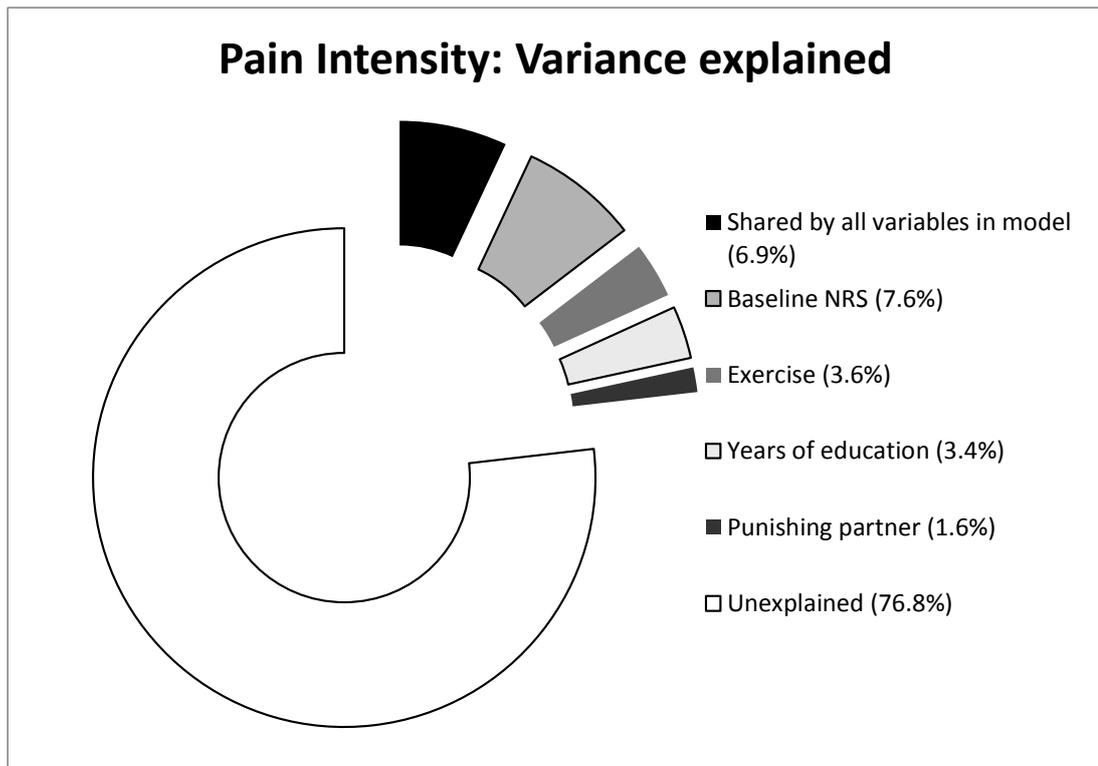
Figure 1. Graph to show proportions of variance uniquely explained by individual variables, shared variance and unexplained variance for the prognostic model for pain intensity at one-year follow-up. NRS – numeric rating scale.

Disability at one-year follow-up.

The associations between each baseline factor with the logRMDQ score at one-year follow-up are presented in Appendix 4. Baseline disability was strongly associated with disability at one year, with a one-point increase on the logRMDQ at baseline being associated with an estimated .6-point increase in follow-up logRMDQ score (95%CI: .5-.7, $p<.001$). After adjustment for baseline disability variables from multiple dimensions were associated with logRMDQ scores at follow-up at a significance of $p<.1$, and were subsequently considered for inclusion in a multivariable model. From the intervention dimension, having pharmacological or spinal injection therapies in the interim period were associated with higher logRMDQ scores at follow-up, whereas participating in exercise was associated with lower logRMDQ scores. From the tissue sensitivity dimension, having a higher lumbar MDT, sensory testing PC4 score (MDT lumbar / wrist) and lumbar CPT (more sensitive) was associated with higher logRMDQ scores at follow-up. From the

movement dimension, having a slower forward bending time and a higher number of protective behaviours during backward bending were associated with higher follow-up log RMDQ scores. From the psychological dimension, membership of psychological Cluster 3 (characterised by higher scores across all psychological indicator variables) and being classified as exhibiting distress endurance by the AEQ were associated with higher follow-up logRMDQ scores. Also associated with higher logRMDQ scores at follow-up were having higher scores on psychological PC2 (representing FABQ-PA, PCS and PSEQ) and PC3 (representing TES and BSS), pain catastrophising (PCS total and subscales), and the depression, fear-avoidance beliefs (physical activity), and thought suppression subscales. Higher pain self-efficacy was associated with lower logRMDQ scores. From the health dimension, poorer baseline general health and higher BMI were associated with higher logRMDQ scores at follow-up. From the lifestyle and social dimensions, more years in education and being currently working were associated with lower logRMDQ scores, while having a relationship with a significant other involving a punishing response style was associated with higher logRMDQ scores.

The final multivariable model included baseline disability, having participated in exercise as intervention, forward bending time, scores for psychological PC2 and PC3, and the score on the MPI punishing subscale (Table 4). The XY-standardised coefficients allow the most interpretable comparison of the strength of the continuous variables in a linear regression model with a transformed outcome. From these it can be seen that baseline disability was the strongest independent continuous predictor, as a one SD increase in this was associated with an estimated mean increase in follow-up logRMDQ scores of 0.3SD, while an increase of one SD in forward bend time, PC2, PC3 and MPI punishing subscale scores were all associated with a mean increase of 0.1SD at one year, independently of other variables in the model. Participating in exercise as intervention was associated with an estimated 0.3 decrease in logRMDQ scores at one-year follow-up independently of other variables in the model. This final model explained 33.6% of the variance in logRMDQ scores at one-year follow-up, and consistent with the results from the XY-standardised coefficients, this explained variance could be partitioned as follows;

19.0% shared by all six predictors, 6.5% uniquely by baseline disability, 2.8% uniquely by exercise as intervention, 1.5% uniquely by forward bend time, 1.4% uniquely by psychological PC2, 1.3% uniquely by psychological PC3 and 1.1% uniquely by a punishing partner response. The proportion of variance left unexplained was 66.5% (Figure 2).

Table 4.

Final multivariable regression model for disability (log-RMDQ, n=256) at one-year follow-up (R^2=.34).

	Unstandardized coefficient (95% CI)				*p*-value	bStdXY[2]
Disability at one year follow-up						
Disability at baseline[1]	0.67	(0.40	to	0.93)	**<.001**	.31
Exercise as intervention	-0.27	(-0.43	to	-0.10)	**.001**	-.34[b]
Forward bend time	0.01	(0.00	to	0.02)	**.019**	.13
Psychological PC3 (FABQ-PA, PCS, PSEQ)	0.08	(0.01	to	0.15)	**.024**	.12
Psychological PC2 (TSS, BES)	0.08	(0.01	to	0.15)	**.028**	.13
MPI punishing subscale score	0.07	(0.00	to	0.13)	**.040**	.11

Note. [1]natural logRMDQ
[2]bStdY standardised coefficient, representing expected decrease in logRMDQ in units of 1 standard deviation when exercise as intervention = yes
bStdXY is xy-standardized coefficient, representing expected change in logRMDQ in units of 1 standard deviation, for a 1 standard deviation increase in continuous predictors.
PC – principal component; FABQ-PA – Fear-avoidance beliefs questionnaire (Physical activity subscale); PCS – Pain Catastrophising scale; PSEQ – Pain Self-efficacy questionnaire; TSS – Thought Supression subscale; BES – Behavioural Endurance subscale; MPI – Multidimensional Pain inventory

Log-RMDQ score: Variance explained

Legend:
- ■ Shared by all variables in model (19.0%)
- ▨ Baseline disability (6.5%)
- ▨ Exercise (2.8%)
- □ Forward bend time (1.5%)
- ■ Punishing partner (1.1%)
- ▨ Psychological PC2 (1.4%)
- ▨ Psychological PC3 (1.3%)
- □ Unexplained (66.5%)
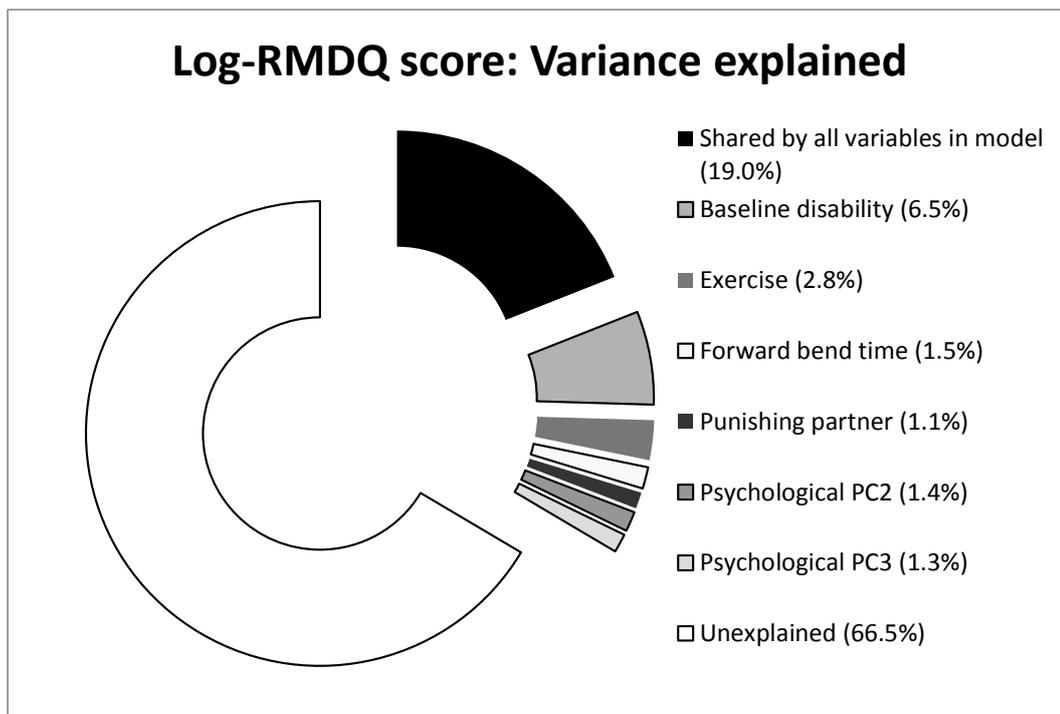
Figure 2. Graph to show proportions of variance uniquely explained by individual variables, shared variance and unexplained variance for the prognostic model for disability at one-year follow-up. Psychological PC2 – principal component score representing Fear-Avoidance Beliefs questionnaire (Physical Activity subscale), Pain Catastrophising scale and Pain Self-Efficacy questionnaire; PC3 – representing Thought Suppression and Behavioural Endurance

Global rating of change at one-year follow-up.

The associations between each baseline factor with a positive outcome on the GRC of, "much," or, "very much improved," at one-year follow-up are presented in Appendix 5. A range of variables from multiple dimensions were associated with increased or decreased odds of such improvement on the GRC at follow-up at a significance of $p<.1$, and were subsequently considered for inclusion in a multivariable model. From the demographic and pain characteristic dimensions, being male and having 100% of CLBP in the low back region (versus 80% or 60%) were associated with decreased odds of improvement on the GRC. From the intervention dimension, having no intervention or receiving pharmacotherapy were associated with decreased odds of improvement at follow-up, while participating in exercise as intervention was associated with increased odds. From the tissue

sensitivity dimension, having a higher lumbar MDT and wrist HPT (less sensitive) were associated with decreased odds for improvement, while having a higher sensory testing PC4 score (more sensitive, MDT lumbar / wrist) was associated with increased odds. From the psychological dimension, higher scores on both the activity engagement subscale and total chronic pain acceptance score were associated with increased odds of improvement. From the health dimension, poorer baseline general health was associated with decreased odds of improvement. From the lifestyle and social dimensions, being a smoker and being in a manual occupation were associated with decreased odds of improvement, while having more years in education was associated with increased odds.

The final multivariable model included having participated in exercise as intervention, having some leg pain as well as LBP and acceptance measured as the CPAQ-8 total score (Table 5). The odds ratios presented in Table 5 allow a comparison of the strength of the variables in the model, and from these it can be seen that having participated in exercise as intervention was the strongest predictor, with 3.5 times the odds of a GRC of much or very much improved. Those with some leg pain as well as back pain had approximately twice the odds of improvement, while a one SD increase in total pain acceptance score gave a 1.4% increase in odds of improvement at follow-up. This final model has a ROC AUC of .72 indicating the model has acceptable discrimination (Hosmer and Lemeshow, 2000), and the cumulative value of the AUC shows the majority of the discriminative ability of the model was achieved by participating in exercise as intervention, with small additional contributions from the presence of leg pain and chronic pain acceptance scores. The model estimated that the probability of improvement on the GRC for an individual who did not participate in exercise, did not have leg pain and had a CPAQ-8 score one SD below the mean was .12 (95%CI: 0.06 - 0.18); while for an individual who participated in exercise, had some leg pain and had a CPAQ-8 score one SD above the mean the probability of improvement was .64 (95%CI: 0.52 - 0.76).

Table 5.

Logistic regression model to predict "much" or "very much" improved at one-year follow-up on Global Rating of Change scale (n=89 of 265, 33.6%).

	Odds ratio (95% CI)				*p*-value	Cumulative ROC AUC
Exercise as intervention	3.51	(2.03	to	6.08)	**<.001**	.66
Leg pain[1]	2.02	(1.16	to	3.51)	**.013**	.70
CPAQ-8 score (1 SD change)	1.36	(1.04	to	1.80)	**.028**	.72

Note. [1]Leg pain – A rating of 80% of the pain in the low back and 20% in the leg(s) or 60% of the pain in the low back and 40% in the leg(s) on the question, "Which situation describes your pain over the past 4 weeks the best?" (Wai et al., 2009)
CPAQ-8 – Chronic Pain Acceptance questionnaire (Short form)

Bothersomeness at one-year follow-up.

The associations between each baseline factor with a participant's rating of the bothersomeness of their CLBP as "very" or "extremely" bothersome at one-year follow-up are presented in Appendix 6. Variables from multiple dimensions were associated with increased or decreased odds of such significant bothersomeness at follow-up at a significance of *p*<.1, and were subsequently considered for inclusion in a multivariable model. From the demographic and pain characteristic dimensions, being older was associated with decreased odds of bothersome CLBP at follow-up, while having higher baseline pain intensity, disability and bothersomeness, and having 100% of their pain in the low back region were associated with increased odds. From the intervention dimension, having exercise as intervention was associated with decreased odds, while receiving spinal injection(s) or acupuncture were associated with increased odds of significant bothersomeness at follow-up. From the tissue sensitivity dimension, having a higher lumbar MDT (less sensitive) was associated with increased odds of significant bothersomeness, while a higher sensory testing PC4 score (more sensitive, MDT lumbar / wrist) was associated with decreased odds. From the movement dimension, higher forward bend time and a

greater number of protective behaviours during backward bending were associated with increased odds of bothersome CLBP at follow-up. From the psychological dimension, membership of psychological Cluster 3 (characterised by higher scores across all psychological variables) was associated with increased odds of significant bothersomeness. Higher stress, fear-avoidance beliefs (work) and rumination and helplessness PCS subscale scores were all associated with increased odds of significant bothersomeness at follow-up. Also associated with increased odds of bothersome CLBP at follow-up were psychological PC2 (reflecting fear-avoidance beliefs, pain catastrophising and pain self-efficacy) and PC3 (reflecting thought suppression and behavioural endurance). Higher scores for pain self-efficacy were associated with decreased odds of significant bothersomeness. From the health dimension, poorer baseline general health and a higher number of squares filled in on the body chart were associated with increased odds of significant bothersomeness at follow-up, while having a higher number of other diagnosed comorbidities was associated with decreased odds. From the lifestyle and social dimensions, being a non-smoker, having more years in education and being not working or in a sedentary occupation were associated with decreased odds of significant bothersomeness.

The final multivariable model included baseline pain intensity, having received spinal injection(s) as intervention, age, forward bend time, years in education and having some leg pain as well as LBP (Table 6). The odds ratios presented in Table 6 show that baseline pain and having received injection(s) as intervention were the strongest predictors, with a one SD increase in baseline pain intensity associated with 2.3 times the odds of having significantly bothersome CLBP at follow-up and receiving injection(s) as intervention with 6.2 times the odds, although the confidence intervals for this estimate were wide due to the small number of participants receiving spinal injection(s) (n=23, 8.7%). A one SD increase in forward bend time gave a 66% increase in odds of significant bothersomeness. Those with some leg pain as well as LBP had a 58% decrease in the odds of having bothersome CLBP at follow-up. A one SD increase in years in education gave a 40% decrease, and a one SD increase in age gave a 49% decrease in odds of significant bothersomeness

at follow-up. This final model has a ROC AUC of .80 indicating the model meets the lower limit of the criteria for excellent discrimination (Hosmer and Lemeshow, 2000), and the cumulative value of the AUC shows that the majority of the discriminative ability of the model was achieved by baseline pain intensity, with small additional contributions from the other five variables. The model estimated the probability of having bothersome CBLP for an individual with a "worst case" scenario who had baseline pain intensity and forward bend time one SD above the mean, and age and years in education one SD below the mean, received spinal injection(s) and had no leg pain as .95 (95%CI: 0.87 - 1.0); while an individual with baseline pain intensity and forward bend time one SD below the mean, and age and years in education one SD above the mean, not receiving spinal injection(s) and having leg pain as .01 (95%CI: 0.00 - 0.02).

Table 6.

Logistic regression model to predict, "very," or, "extremely bothersome," chronic low back pain at one-year follow-up (n=52 of 266, 19.6%).

	Odds ratio (95% CI)				Xstd OR[2]	*p*-value	Cumulative ROC AUC
Baseline pain (NRS 0-10)	1.54	(1.22	to	1.95)	2.28	**<.001**	.67
Injection as intervention	6.20	(2.17	to	17.7)	n/a	**.001**	.72
Age (yrs)	0.95	(0.93	to	0.98)	0.51	**<.001**	.74
Forward bend time (sec)	1.07	(1.02	to	1.11)	1.66	**.004**	.75
Years in education	0.86	(0.77	to	0.97)	0.60	**.011**	.78
[1]Leg pain	0.42	(0.20	to	0.86)	n/a	**.018**	.80

Note. [1]Leg pain – A rating of 80% of the pain in the low back and 20% in the leg(s) or 60% of the pain in the low back and 40% in the leg(s) on the question, "Which situation describes your pain over the past 4 weeks the best?" (Wai et al., 2009) [2]X-standardised odds ratio: change in odds for SD increase in continuous variables
NRS – numeric rating scale; n/a – not applicable

7.2.6 Discussion

This cohort demonstrated significant improvements in pain intensity, disability and bothersomeness over the follow-up period (Costa et al., 2012) with 33.6% of participants rating themselves much / very much improved. This is consistent with a meta-analysis showing improved pain and disability in people with CBLP over time (Costa et al., 2012), possibly reflecting the natural history of the disorder, regression to the mean, or the Hawthorne effect.

Most previous prognostic studies in CLBP cohorts have examined a limited range of prognostic variables, and commonly only have one outcome measure (Verkerk et al., 2012). In contrast, this study utilised individual, component and subgrouped multidimensional data and broad intervention groupings to derive prognostic models for pain intensity, disability, GRC and bothersomeness. Despite inclusion of a broad range of multidimensional variables with potential to be prognostic, the variance in pain intensity and disability explained by our models (23.2% and 33.6% respectively) appears similar to previous research (Hayden et al., 2010), leaving approximately 70% of the variance unexplained. Some variables (e.g. baseline pain intensity, baseline disability) in our models are similar to previous models (Hayden et al., 2009, Verkerk et al., 2012). While variation in the variables across models is common (Verkerk et al., 2012, Hayden et al., 2009), some variables consistently prognostic of poor outcome in people with CLBP, such as sex, poor general health, occupational factors, (Hayden et al., 2009, Verkerk et al., 2012) were not included in our final prognostic models. Conversely other novel variables such as forward bending time and the MPI punishing subscale were prognostic. QST, which offers a "window" to explore pain mechanisms (Baron et al., 2012), was a novel inclusion for prognostic modelling. However, no QST measure remained in the final models. Since signs and symptoms, such as those possibly provoked by QST, cannot be directly translated into pain mechanisms (Woolf and Mannion, 1999), this does not exclude the possibility that pain mechanisms may be associated with certain prognoses.

Previous reports suggest that the relatively low variance explained by prior models may be a result of limited inclusion of potential prognostic variables (Hayden et al.,

2010). In response to this, this study utilised 108 variables from multiple dimensions, but was only able to explain a similar variance. This study limited variables to clinically-applicable measures to facilitate translation into practice, and limit participant burden. Examination of genetics / epigenetics, participant interactions with healthcare systems / practitioners, cultural or broader social influences, other positive psychological factors (i.e. resilience), underlying pathophysiology and pain mechanisms may explain a greater proportion of variance, but were excluded for the above reasons. Furthermore some clinically-applicable measures chosen may not be gold standard measurements (i.e. PSQI scores versus polysomnography). Gold standards may have led to different models explaining greater variance.

This research also utilised subgroups based upon pain sensitivity, psychological questionnaire scores and pain responses following repeated movements in order to determine their prognostic value. Examination of univariable associations between the derived subgroups and the four outcome measures reveals that the pain sensitivity clusters and subgroups derived from pain responses following repeated movements were not prognostic. However, membership of psychological Cluster 3 (high scores across all indicator variables) had a significant univariable association with greater pain intensity, disability and bothersomeness at one-year follow-up, suggesting that those with a poorer psychological profile may warrant targeted management of this dimension. This is consistent with previous LBP prognostic studies involving subgrouping that incorporated psychological data, pain intensity and disability (Hill et al., 2008, Boersma and Linton, 2005). Interestingly psychological subgroups were not retained in the final multivariable prognostic models. One reason for this finding may relate to the complex multidimensional nature of CLBP (Simons et al., 2014), where subgroups derived from a single dimension fail to capture the complexity of the disorder. This is supported by the finding that factors from other dimensions such as educational status, spousal interactions and forward bend time were shown to be important in the final multidimensional prognostic models for this cohort. However, psychological PC scores did contribute weakly to the final multivariable model for disability. It may

therefore be that psychological subgroups were not retained in the final models because of reduced power for detecting categorical associations, when compared to the continuous PC scores.

Given CLBP is a complex disorder involving multiple interacting dimensions (Kucyi and Davis, 2015, Simons et al., 2014) statistical models such as those used in this study only account for prognostic factors common across the whole sample and at one time point rather than important, heterogeneous, fluctuating interactions at an individual level (Brown, 2009). Even with extremely large samples, these statistical models may not capture this complexity, suggesting that other frameworks and methods need to be explored. One alternate approach to understanding CLBP is complexity theory, which posits that a person's presentation may be the product of non-linear, emergent interactions across multiple dimensions, where summation of constituent dimensions cannot account for the entire being. Examination of this process would necessitate analysis of interactions of multiple dimensions over time, using more sophisticated statistical techniques with very large samples, such as cluster analysis repeated at multiple time points (Griffiths and Byrne, 1998) or alternatively, data-rich single case experiments that track change at multiple time-points (Linton et al., 2002, Vlaeyen et al., 2001).

Prognostic baseline variables.

The pain intensity and disability models were adjusted for baseline pain intensity and disability respectively, consistent with other prognostic studies involving CLBP cohorts (Verkerk et al., 2013, Grotle et al., 2010, Costa et al., 2009). People with LBP are known to have differing trajectories with some having stable low levels of pain, while others have permanently high pain and disability with associated poor psychosocial status (Dunn et al., 2006). Psychological factors are known to mediate the relationship between pain and disability in people with LBP (Lee et al., 2015), possibly via altered HPA axis function (Gatchel et al., 2007), allostasis (McEwen and Gianaros, 2010), descending pain modulation (Zusman, 2002) and altered movement and behaviours (Hodges and Smeets, 2015, Sullivan et al., 2009, Sullivan et al., 2006). Baseline pain intensity was also a prognostic variable in the

bothersomeness model. Rarely considered as an outcome measure, bothersomeness may be a summary of patient perception of symptoms, and correlates with pain intensity and disability (Dunn and Croft, 2005).

Lower years in education was prognostic of higher pain intensity and bothersomeness. Previous studies have associated lower educational level with persistent low back-related disability (Dionne et al., 2001, Costa et al., 2009, Verkerk et al., 2013). Lower years in education, as a measure of lower socio-economic status (Liberatos et al., 1988), may reflect a surrogate measure for a number of factors previously reported to adversely influence CLBP prognosis. These include manual occupations involving greater physical strain (Lacey et al., 2013, Hagen et al., 2006b, Leclerc et al., 2009), greater psychological stress and more negative health behaviours (e.g. smoking) (Dionne et al., 2001), poorer general health (Chou R, 2010, Hayden et al., 2009, van der Heide et al., 2013),and possibly poorer health literacy (Briggs et al., 2010, Camerini and Schulz, 2015) and healthcare access (Meghani, 2011).

Greater participant-reported punishing spousal responses contributed to prognostic models for higher pain and disability, consistent with findings from an earlier cross-sectional study (Boothby et al., 2004). Punishing spousal responses may influence pain via altered central pain modulation secondary to higher psychological distress (Zusman, 2002), and disability via greater dependent and support seeking behaviours (Quartana et al., 2009).

Slower forward bend time was prognostic of greater disability and bothersomeness. People with CLBP are reported to move slower than healthy controls (Laird et al., 2014) possibly due to altered movement patterns or kinesiophobia (McGregor et al., 1997), suggesting those having a slower forward bend time may attach greater perceived threat value to the movement, perpetuating disability (Vlaeyen et al., 1995) and bothersomeness. In line with our findings a slower "up-and-go" test was previously found to be prognostic for poorer perceived recovery in people >55 years old with acute LBP (Scheele et al., 2013).

Higher psychological PC2 scores, reflecting higher levels of fear-avoidance beliefs, pain catastrophising and poorer pain self-efficacy were prognostic of greater disability. The derivation of PC2 is consistent with a recent study suggesting conceptual overlap of these factors (Campbell et al., 2013a). These findings are consistent with previous research showing that higher pain catastrophising and fear-avoidance beliefs, and lower pain self-efficacy are prognostic of greater disability (Wertli et al., 2014, Leeuw et al., 2007, Jackson et al., 2014).

A higher psychological PC3 score, indicating endurance behaviours (Hasenbring et al., 2009) postulated to maintain symptoms through persistent physical overload of tissues (Hasenbring et al., 2012), was also prognostic of greater disability. This finding is consistent with a study of 177 people with subacute LBP in primary care, showing that endurance behaviours were prognostic of greater disability at six-month follow-up (Hasenbring et al., 2012).

Having some leg pain contributed to prognostic models for improved GRC and lower bothersomeness, inconsistent with a review of prognostic studies highlighting worse outcomes for those with leg pain compared to LBP only (Konstantinou et al., 2013). While one previous study (Scheele et al., 2013) also included leg pain in their prognostic model, there is no clear explanation for this finding. We postulate that if leg pain at baseline has improved at follow-up, greater improvement may be perceived, however, we were unable to determine whether pain distribution had changed over time. It is also important to note that participants with dominant leg pain were excluded from our cohort.

Chronic pain acceptance was associated with improved GRC, and has previously been shown to be prognostic of less disability, better emotional and social functioning (McCracken and Eccleston, 2005) and quality of life, and lower pain intensity, depression and anxiety (McCracken and Eccleston, 2003, Mason et al., 2008) in people with chronic musculoskeletal pain. This is consistent with GRC being regarded as a composite measure of perceived improvement (Kamper et al., 2009).

Significant bothersomeness was associated with younger age. While this association does not appear to have been reported in people with CLBP, it appears inconsistent

with some reports that older age is associated with greater disability (Verkerk et al., 2012, Hayden et al., 2009) and pain intensity (Verkerk et al., 2015). While speculative it may be that with increasing age the proportion of people with disability perceived to be due to CLBP may reduce as other health problems are perceived to cause greater disability (Australian Bureau of Statistics, 2010), possibly influencing levels of bothersomeness.

Prognostic intervention variables.

Novel to this research was inclusion of broadly grouped intervention types as prognostic variables. While more specific interventions may be more strongly associated with certain prognoses, this was not accounted for.

Exercise contributed towards positive outcomes for pain intensity, disability and GRC supporting previous reports that exercise improves pain and disability in people with CLBP (van Middelkoop et al., 2010), and reduces symptom recurrence (Choi et al., 2010). Potential hypoalgesic effects of exercise involve centrally-mediated opioid and non-opioid mechanisms, but are incompletely understood (Ellingson and Cook, 2013). Exercise is also reported to positively impact on an individual's self-efficacy, general health, level of catastrophising, activity engagement (Hodges and Smeets, 2015) and overall perceived improvement (Kamper et al., 2009).

Conversely, those receiving spinal injection(s) (n=23) had high odds of significantly bothersome CLBP at follow-up. It may be that they perceived symptoms as more bothersome throughout the study, or injection has a negative effect. There is no strong evidence for or against injection therapy in people with CLBP (Staal et al., 2008) and no clear indications, in terms of patient characteristics, for or against injecting. Future research should consider factors prognostic of outcomes of injection therapy to provide further guidance for clinical management.

Strengths and limitations.

Most participants were recruited via advertisements, facilitating generalizability to the wider community. Only participants with dominant CLBP (Wai et al., 2009) were included, minimizing the likelihood of participants having radiculopathy.

Although only 9.5% of participants were lost to follow-up they reported significantly higher baseline disability than those responding at follow-up, so the follow-up sample might not be representative of the entire spectrum of disability. Prognostic factors identified are highly variable across longitudinal studies of LBP and the results of this study are consistent with this variability, where multiple candidate variables from all dimensions demonstrated associations with all outcomes considered. The specific set of variables retained in each final model may be sample specific, and it is likely that replication in other samples may identify different sets of these candidate variables. Ideally, these prognostic models should be externally validated in independent samples.

Clinical implications.

This study supports that baseline pain and disability, pain catastrophising, pain self-efficacy, chronic pain acceptance, fear-avoidance beliefs, punishing interactions with a significant other, speed of movement and endurance behaviours should be considered in the management of CLBP disorders. This is in line with a previous intervention study targeting psychological factors in combination with movement and behavioural factors demonstrating improved outcomes at twelve-month follow-up (Vibe Fersum et al., 2013). However, it must be noted that these factors only explain a small proportion of the variance in this cohort, and are unlikely to capture the multiple interacting dimensions relevant to an individual presentation (Brown, 2009, Simons et al., 2014).

This study also supports the important role of exercise for the management of CLBP in line with clinical guidelines (Airaksinen et al., 2006). To date there is little evidence that one form of exercise is more effective than others (van Middelkoop et al., 2010), and adherence is a major barrier to uptake of this intervention (Jordan et al., 2010).

Overall, one third of this cohort rated their CLBP as much or very much improved over the one-year follow-up period. Broad multidimensional data was entered into prognostic models, however, the variance explained was similar to previous research. Such modelling is unlikely to capture the complexity of the fluctuating multidimensional interactions influencing the lived experience of individuals with CLBP.

7.2.7 References

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7.2.8 Appendices

Appendix 1.

Rotated (Varimax) components for sensory testing variables included in principal component analysis.

Variable	Component 1	Component 2	Component 3	Component 4	Component 5
PPT w		**.64**			
PPT lx		**.66**			
HPT w	**.39**				
HPT lx	**.48**				
CPT w	**.48**				
CPT lx	**.54**				
MDT w				**.71**	
MDT lx				**.64**	
Conditioned pain modulation change score			**.54**		
Temporal summation			**.51**		
Pinprick hyperalgesia			**-.66**		
Vibration detection					**.71**
Two-point discrimination					**-.68**

Note. PPT – pressure pain threshold; w – wrist; lx – lumbar; HPT – heat pain threshold; CPT – cold pain threshold; MDT – mechanical detection threshold

Appendix 2.

Rotated (Varimax) components for psychological variables included in principal component analysis.

Variable	Component 1	Component 2	Component 3	Component 4
DASS depression subscale	.52			
DASS anxiety subscale	.58			
DASS stress subscale	.56			
FABQ-PA		.72		
PCS		.40		
PSEQ		-.46		
CPAQ-8 pain willingness subscale				.70
CPAQ-8 activity engagement subscale				.70
TSS			.65	
BES			.73	

Note. DASS – Depression, anxiety, stress scales; FABQ-PA – Fear-avoidance Beliefs questionnaire (Physical activity subscale); PCS – Pain Catastrophising scale; PSEQ – Pain Self-efficacy questionnaire; CPAQ-8 – Chronic Pain Acceptance questionnaire (Short form); TSS – Thought Suppression subscale; BES – Behavioural Endurance subscale

Appendix 3.

Regression analysis separately for each potential baseline predictor with pain intensity at one-year follow-up as the dependent variable, adjusting for baseline pain intensity (n=266).

Variable	Co-efficient	(95% CI)			*p* value
Baseline pain intensity (NRS)	0.40	(0.27	to	0.53)	**<.001**
Demographics					
Age	-0.01	(-0.02	to	0.01)	.54
Sex	0.16	(-0.34	to	0.66)	.52
Pain Characteristics					
Baseline disability (RMDQ)	0.04	(-0.02	to	0.11)	.17
Duration of CLBP (months)[4]	0.00	(0.00	to	0.00)	.94
100% of pain in low back region	0.34	(-0.14	to	0.83)	.16
Aggravated by activity (StEP)[1]	-0.17	(-0.86	to	0.51)	.62
Aggravated by position (StEP)[1]	-0.14	(-0.76	to	0.48)	.66
Baseline bothersomeness	0.26	(-0.26	to	0.79)	.32
Interventions					
No intervention[4]	0.61	(-0.02	to	1.25)	**.06**
Manual therapy[4]	-0.03	(-0.54	to	0.49)	.91
Exercise[4]	-0.88	(-1.37	to	-0.40)	**<.001**
Psychological[4]	0.35	(-0.70	to	1.41)	.51
Pharmacological[4]	0.36	(-0.31	to	1.03)	.29
Injection[4]	0.65	(-0.22	to	1.51)	.14
Surgery[4]	-1.04	(-2.33	to	0.24)	.11
Acupuncture[4]	1.45	(0.37	to	2.52)	**.01**
Multidisciplinary rehabilitation[4]	-0.45	(-3.27	to	2.37)	.75

Variable		Co-efficient	(95% CI)			p value
		Pain Sensitivity				
Pain sensitivity clusters	Cluster 1	Reference				.59
	Cluster 2	0.08	(-0.46	to	0.62)	.77
	Cluster 3	-0.29	(-1.03	to	0.46)	.45
Sensory testing PCs[12]	PC1	-0.00	(-0.02	to	0.02)	.86
	PC2	0.00	(-0.00	to	0.00)	.92
	PC3	-0.06	(-0.23	to	0.11)	.51
	PC4	-0.03	(-0.06	to	-0.00)	**.04**
	PC5	-0.01	(-0.04	to	0.03)	.68
PPT (wrist)		0.00	(0.00	to	0.00)	.67
PPT (lumbar)		0.00	(0.00	to	0.00)	.95
CPT (wrist)		-0.01	(-0.05	to	0.02)	.44
CPT (lumbar)		0.00	(-0.02	to	0.03)	.92
HPT (wrist)		0.01	(-0.05	to	0.07)	.77
HPT (lumbar)		-0.01	(-0.08	to	0.05)	.68
MDT (wrist)[3]		0.03	(-0.03	to	0.08)	.36
MDT (lumbar)[3]		0.04	(0.01	to	0.07)	**.01**
Two-point discrimination		-0.05	(-0.17	to	0.07)	.40
Baseline CPM presure[11]		0.00	(0.00	to	0.00)	.70
CPM change score[11]		-0.16	(-0.36	to	0.05)	.13
Temporal summation[1]		-0.28	(-0.90	to	0.34)	.37
Pinprick hyperalgesia		0.42	(-0.25	to	1.09)	.22
		Movement Dimension				
Pain response following repeated movement subgroups	NIP	Reference				.84
	FB	0.04	(-0.54	to	0.62)	.89
	BB	-0.37	(-1.22	to	0.49)	.40
	FB&BB	0.02	(-0.75	to	0.80)	.95
Forward bending time[1]		0.02	(-0.01	to	0.05)	.19
Backward bending time[1]		-0.02	(-0.06	to	0.02)	.30
Communicative behaviours, forward bending		0.08	(-0.36	to	0.51)	.73
Protective behaviours, forward bending		-0.04	(-0.11	to	0.02)	.19
Communicative behaviours, backward bending		0.09	(-0.76	to	0.94)	.84
Protective behaviours, backward bending		0.05	(-0.05	to	0.15)	.31

Variable		Co-efficient	(95% CI)			p value
Psychological Dimension						
Psychological clusters	Cluster 1	Reference				**.03**
	Cluster 2	0.73	(0.14	to	1.32)	**.02**
	Cluster 3	0.87	(0.08	to	1.65)	**.03**
DASS depression		0.01	(-0.01	to	0.04)	.25
DASS anxiety		-0.01	(-0.04	to	0.03)	.67
DASS stress		0.01	(-0.02	to	0.03)	.55
DASS combined total (also PC1)		0.00	(-0.01	to	0.01)	.56
FABQ-W[8]		0.01	(-0.01	to	0.03)	.54
FABQ-PA		0.00	(-0.04	to	0.04)	.88
PCS rumination[1]		0.03	(-0.03	to	0.08)	.30
PCS magnification[1]		0.05	(-0.04	to	0.13)	.29
PCS helplessness[1]		0.04	(0.00	to	0.09)	**.05**
PCS total[1]		0.02	(0.00	to	0.04)	.10
PSEQ		-0.03	(-0.05	to	-0.01)	**.01**
Psychological PC2[1]		0.20	(0.01	to	0.39)	**.04**
AEQ classification[2]	Adaptive	Reference				.44
	Distress endurance	0.50	(-0.17	to	1.18)	.14
	Eustress endurance	0.20	(-0.45	to	0.84)	.55
	Fear-avoidance	-0.06	(-0.94	to	0.82)	.89
TSS[1]		0.21	(0.06	to	0.35)	**.01**
BES		0.15	(-0.09	to	0.39)	.22
Psychological PC3		0.26	(0.06	to	0.47)	**.01**
CPAQ-8 pain willingness		0.01	(-0.05	to	0.06)	.84
CPAQ-8 activity engagement		-0.05	(-0.10	to	0.01)	**.08**
CPAQ-8 total (also PC4)		-0.02	(-0.05	to	0.02)	.33
MAAS[3]		-0.15	(-0.43	to	0.14)	.31
Perceived risk of persistent pain[1]		0.06	(-0.09	to	0.21)	.43
FreBAQ		0.01	(-0.03	to	0.05)	.64
Health Dimension						
Total diagnosed comorbidities		-0.02	(-0.14	to	0.10)	.74
Musculoskeletal comorbidities		-0.05	(-0.51	to	0.40)	.82
Functional pain comorbidities		-0.01	(-0.30	to	0.29)	.97
Other diagnosed comorbidities		-0.03	(-0.21	to	0.14)	.71
Other comorbid symptoms		-0.07	(-0.19	to	0.04)	.21
Number of body chart squares filled-in		0.01	(-0.01	to	0.03)	.29
Manchester CWP classification		0.33	(-0.22	to	0.87)	.24
Baseline COOP/WONCA overall health rating		0.35	(0.10	to	0.61)	**.01**
BMI		0.00	(-0.05	to	0.05)	.94

Variable		Co-efficient	(95% CI)			*p* value
Lifestyle and Social Dimensions						
PSQI[9]		-0.06	(-0.12	to	0.00)	**.07**
Smoking status	Non-smoker	Reference				.38
	Ex-smoker	0.16	(-0.38	to	0.70)	.56
	Smoker	0.57	(-0.25	to	1.40)	.17
Moderate and vigourous physical activity per week[5]		0.00	(0.00	to	0.00)	.52
Years in education[10]		-0.14	(-0.21	to	-0.07)	**<.001**
Compensation status[5]		0.10	(-0.56	to	0.77)	.76
Currently at work		-0.22	(-0.80	to	0.37)	.47
Manual v. sedentary occupation[12]	Not working	Reference				**.09**
	Sedentary	0.01	(-0.85	to	0.86)	.99
	Manual	0.67	(-0.28	to	1.62)	.16
Job satisfaction[13]		-0.04	(-0.13	to	0.06)	.44
Life events		0.01	(-0.16	to	0.17)	.93
MPI social support[7]		0.01	(-0.15	to	0.17)	.88
MPI punishing[6]		0.26	(0.08	to	0.44)	**.005**
MPI solicitous[6]		-0.01	(-0.18	to	0.17)	.94
MPI distracting[6]		0.08	(-0.12	to	0.27)	.45

[1] missing in one case, [2] missing in two cases, [3] missing in three cases, [4] missing in four cases, [5] missing in six cases, [6] missing in eight cases, [7] missing in nine cases, [8] missing in 10 cases, [9] missing in 11 cases, [10] missing in 13 cases, [11] missing in 14 cases, [12] missing in 16 cases, [13] missing in 39 cases

NRS – numeric rating scale, RMDQ – Roland Morris Disability questionnaire, StEP – Standardised Evaluation of Pain, PC – principal component, Sensory testing PC1 - principal component score derived from thermal pain sensitivity, PC2 - principal component score derived from pressure pain sensitivity, PC3 - principal component score derived from conditioned pain modulation change score, temporal summation and pinprick hyperalgesia, PC4 - principal component score derived from mechanical detection thresholds, PC5 - principal component score derived from two-point discrimination and vibration perception, PPT – Pressure pain threshold, CPT – cold pain threshold, HPT - Heat pain threshold, MDT – Mechanical detection threshold, CPM – Conditioned pain modulation, NIP – No increased pain following repeated bending, FB – Pain increased following repeated forward bending only, BB – Pain increased following repeated back bending only, FB&BB – Pain increased following repeated forward and backward bending, DASS – Depression Anxiety Stress scales, FABQ-W – Fear-Avoidance Beliefs questionnaire (Work subscale), FABQ-PA - Fear-Avoidance Beliefs questionnaire (Physical activity subscale), PCS – Pain Catastrophising scale, PSEQ – Pain Self-efficacy questionnaire, Psychological PC2 – principal component score derived from FABQ-PA, PCS and PSEQ scores, AEQ – Avoidance Endurance questionnaire, TSS – Thought Suppression subscale, BES – Behavioural Endurance subscale, Psychological PC3 - mean of TSS and BES scores, CPAQ-8 – Chronic Pain Acceptance questionnaire (Short form), MAAS – Mindful Attention Awareness scale, FreBAQ – Fremantle Back Awareness questionnaire, CWP – Chronic widespread pain, BMI – Body mass index, PSQI – Pittsburgh Sleep Quality index, MPI - Multidimensional Pain Inventory

Appendix 4.

Regression analysis separately for each potential baseline predictor with disability at one-year follow-up as the dependent variable, adjusting for baseline disability (n=266).

Variable	Co-efficient	(95% CI)			*p* value
Baseline disability (RMDQ)	0.59	(0.47	to	0.72)	**<.001**
Demographics					
Age	0.03	(-0.01	to	0.07)	.13
Sex	0.24	(-0.80	to	1.28)	.65
Pain Characteristics					
Baseline pain intensity (NRS)	0.16	(-0.13	to	0.44)	.28
Duration of CLBP (months)[4]	0.00	(0.00	to	0.00)	.49
100% of pain in low back region	0.69	(-0.34	to	1.71)	.19
Aggravated by activity (StEP)[1]	0.90	(-0.56	to	2.35)	.23
Aggravated by position (StEP)[1]	0.78	(-0.52	to	2.09)	.24
Baseline bothersomeness	0.66	(-0.39	to	1.70)	.22
Interventions					
No intervention[4]	0.50	(-0.84	to	1.84)	.46
Manual therapy[4]	-0.11	(-1.19	to	0.98)	.84
Exercise[4]	-0.10	(-3.10	to	-1.10)	**<.001**
Psychological[4]	0.04	(-2.18	to	2.27)	.97
Pharmacological[4]	1.32	(-0.07	to	2.71)	**.06**
Injection[4]	1.94	(0.13	to	3.75)	**.04**
Surgery[4]	1.15	(-1.60	to	3.90)	.41
Acupuncture[4]	1.78	(-0.50	to	4.05)	.13
Multidisciplinary rehabilitation[4]	-0.92	(-6.88	to	5.04)	.76

Variable		Co-efficient	(95% CI)			p value
Pain Sensitivity						
Pain sensitivity clusters	Cluster 1	Reference				.25
	Cluster 2	-0.96	(-2.10	to	0.18)	.10
	Cluster 3	-0.52	(-2.08	to	1.04)	.52
Sensory testing PCs[12]	PC1	0.03	(-0.02	to	0.08)	.20
	PC2	0.00	(-0.00	to	0.00)	.56
	PC3	-0.13	(-0.50	to	0.24)	.48
	PC4	0.06	(-0.13	to	-0.00)	**.05**
	PC5	-0.04	(-0.11	to	0.03)	.29
PPT (wrist)		0.00	(0.00	to	0.00)	.90
PPT (lumbar)		0.00	(0.00	to	0.00)	.86
CPT (wrist)		0.03	(-0.04	to	0.10)	.36
CPT (lumbar)		0.05	(0.00	to	0.10)	**.05**
HPT (wrist)		0.03	(-0.10	to	0.16)	.66
HPT (lumbar)		0.03	(-0.10	to	0.16)	.69
MDT (wrist)[3]		0.05	(-0.07	to	0.17)	.42
MDT (lumbar)[3]		0.08	(0.02	to	0.14)	**.01**
Two-point discrimination		0.01	(-0.23	to	0.26)	.90
Baseline CPM presure[11]		0.00	(0.00	to	0.00)	.84
CPM change score[11]		-0.27	(-0.70	to	0.17)	.22
Temporal summation[1]		0.29	(-1.01	to	1.58)	.66
Pinprick hyperalgesia		0.03	(-1.38	to	1.44)	.96
Movement Dimension						
Pain response following repeated movement subgroups	NIP	Reference				.50
	FB	-0.19	(-1.43	to	1.04)	.76
	BB	-1.37	(-3.15	to	0.42)	.13
	FB&BB	-0.46	(-2.07	to	1.14)	.57
Forward bending time[1]		0.13	(0.06	to	0.19)	**<.001**
Backward bending time[1]		0.01	(-0.08	to	0.09)	.89
Communicative behaviours, forward bending		0.21	(-0.70	to	1.12)	.65
Protective behaviours, forward bending		0.05	(-0.09	to	0.19)	.48
Communicative behaviours, backward bending		0.87	(-0.96	to	2.69)	.35
Protective behaviours, backward bending		0.22	(0.01	to	0.43)	**.04**

Variable		Co-efficient	(95% CI)			p value
Psychological Dimension						
	Cluster 1	Reference				**.02**
Psychological clusters	Cluster 2	1.06	(-0.19	to	2.30)	.10
	Cluster 3	2.53	(0.80	to	4.26)	**.004**
DASS depression		0.06	(0.00	to	0.12)	**.04**
DASS anxiety		0.02	(-0.05	to	0.09)	.60
DASS stress		0.02	(-0.04	to	0.08)	.50
DASS combined total (also PC1)		0.02	(-0.01	to	0.04)	.19
FABQ-W[8]		0.02	(-0.02	to	0.06)	.36
FABQ-PA		0.08	(-0.01	to	0.17)	**.07**
PCS rumination[1]		0.12	(0.01	to	0.23)	**.04**
PCS magnification[1]		0.16	(-0.02	to	0.35)	**.08**
PCS helplessness[1]		0.14	(0.05	to	0.23)	**.003**
PCS total[1]		0.06	(0.01	to	0.10)	**.01**
PSEQ		-0.06	(-0.11	to	-0.01)	**.03**
Psychological PC2[1]		0.70	(0.27	to	1.13)	**.002**
	Adaptive	Reference				**.09**
AEQ	Distress endurance	1.47	(0.03	to	2.91)	**.04**
classification[2]	Eustress endurance	-0.17	(-1.47	to	1.13)	.79
	Fear-avoidance	0.07	(-1.77	to	1.91)	.94
TSS[1]		0.73	(0.42	to	1.03)	**<.001**
BES		0.37	(-0.13	to	0.86)	.15
Psychological PC3		0.85	(0.42	to	1.28)	**<.001**
CPAQ-8 pain willingness		0.04	(-0.07	to	0.14)	.51
CPAQ-8 activity engagement		-0.01	(-0.12	to	0.10)	.84
CPAQ-8 total (also PC4)		0.01	(-0.06	to	0.08)	.78
MAAS[3]		-0.25	(-0.85	to	0.35)	.41
Perceived risk of persistent pain[1]		0.26	(-0.05	to	0.58)	.10
FreBAQ		0.00	(-0.08	to	0.08)	.98
Health Dimension						
Total diagnosed comorbidities		0.20	(-0.05	to	0.45)	.12
Musculoskeletal comorbidities		0.38	(-0.59	to	1.34)	.44
Functional pain comorbidities		0.23	(-0.39	to	0.85))	.46
Other diagnosed comorbidities		0.29	(-0.08	to	0.66)	.12
Other comorbid symptoms		0.05	(-0.20	to	0.29)	.72
Number of body chart squares filled-in		0.02	(-0.02	to	0.07)	.32
Manchester CWP classification		0.77	(-0.41	to	1.96)	.20
Baseline COOP/WONCA overall health rating		0.59	(0.03	to	1.15)	**.04**
BMI		0.09	(-0.01	to	0.20)	**.08**

Variable		Co-efficient	(95% CI)			p value
Lifestyle and Social Dimensions						
PSQI[9]		-0.02	(-0.15	to	0.10)	.71
Smoking status	Non-smoker	Reference				
	Ex-smoker	0.16	(-0.38	to	0.70)	.56
	Smoker	0.57	(-0.25	to	1.40)	.17
Moderate and vigourous physical activity per week[5]		0.00	(0.00	to	0.00)	.52
Years in education[10]		-0.17	(-0.32	to	-0.03)	**.02**
Compensation status5		0.67	(-0.74	to	2.07)	.35
Currently at work		-1.68	(-2.88	to	-0.47)	**.01**
Manual v. sedentary occupation[12]	Not working	Reference				
	Sedentary	-0.42	(-2.16	to	1.33)	.64
	Manual	0.91	(-1.05	to	2.87)	.36
Job satisfaction[13]		-0.01	(-0.21	to	0.20)	.95
Life events		0.02	(-0.32	to	0.37)	.90
MPI social support[7]		0.11	(-0.22	to	0.44)	.52
MPI punishing[6]		0.43	(0.03	to	0.82)	**.04**
MPI solicitous[6]		0.07	(-0.30	to	0.44)	.71
MPI distracting[6]		0.04	(-0.37	to	0.44)	.86

Note. [1] missing in one case, [2] missing in two cases, [3] missing in three cases, [4] missing in four cases, [5] missing in six cases, [6] missing in eight cases, [7] missing in nine cases, [8] missing in 10 cases, [9] missing in 11 cases, [10] missing in 13 cases, [11] missing in 14 cases, [12] missing in 16 cases, [13] missing in 39 cases

NRS – numeric rating scale, RMDQ – Roland Morris Disability questionnaire, StEP – Standardised Evaluation of Pain, PC – principal component, Sensory testing PC1 - principal component score derived from thermal pain sensitivity, PC2 - principal component score derived from pressure pain sensitivity, PC3 - principal component score derived from conditioned pain modulation change score, temporal summation and pinprick hyperalgesia, PC4 - principal component score derived from mechanical detection thresholds, PC5 - principal component score derived from two-point discrimination and vibration perception, PPT – Pressure pain threshold, CPT – cold pain threshold, HPT - Heat pain threshold, MDT – Mechanical detection threshold, CPM – Conditioned pain modulation, NIP – No increased pain following repeated bending, FB – Pain increased following repeated forward bending only, BB – Pain increased following repeated back bending only, FB&BB – Pain increased following repeated forward and backward bending, DASS – Depression Anxiety Stress scales, FABQ-W – Fear-Avoidance Beliefs questionnaire (Work subscale), FABQ-PA - Fear-Avoidance Beliefs questionnaire (Physical activity subscale), PCS – Pain Catastrophising scale, PSEQ – Pain Self-efficacy questionnaire, Psychological PC2 – principal component score derived from FABQ-PA, PCS and PSEQ scores, AEQ – Avoidance Endurance questionnaire, TSS – Thought Suppression subscale, BES – Behavioural Endurance subscale, Psychological PC3 - mean of TSS and BES scores, CPAQ-8 – Chronic Pain Acceptance questionnaire (Short form), MAAS – Mindful Attention Awareness scale, FreBAQ – Fremantle Back Awareness questionnaire, CWP – Chronic widespread pain, BMI – Body mass index, PSQI – Pittsburgh Sleep Quality index, MPI - Multidimensional Pain Inventory

Appendix 5.

Regression analysis separately for each potential baseline predictor with global rating of change at one-year follow-up as the dependent variable (n=265).

Variable	R^2	Co-efficient	(95% CI)			*p* value
Demographics						
Age	.00	0.99	(0.97	to	1.01)	.47
Sex	.01	0.58	(0.34	to	0.99)	**.04**
Pain Characteristics						
Baseline pain intensity (NRS)	.00	0.95	(0.83	to	1.08)	.43
Baseline disability (RMDQ)	.00	1.00	(0.94	to	1.06)	1.00
Duration of CLBP (months)[4]	.01	1.00	(1.00	to	1.00)	.11
100% of pain in low back region	.03	0.46	(0.27	to	0.77)	**.003**
Aggravated by activity (StEP)[1]	.00	1.00	(0.49	to	2.06)	1.00
Aggravated by position (StEP)[1]	.00	1.21	(0.62	to	2.36)	.58
Baseline bothersomeness	.00	1.00	(0.60	to	1.66)	1.00
Interventions						
No intervention[4]	.04	0.25	(0.10	to	0.60)	**.002**
Manual therapy[4]	.00	1.09	(0.64	to	1.86)	.76
Exercise[4]	.07	3.62	(2.12	to	6.19)	**<.001**
Psychological[4]	.00	1.79	(0.63	to	5.11)	.28
Pharmacological[4]	.02	0.41	(0.18	to	0.93)	**.03**
Injection[4]	.00	0.85	(0.34	to	2.16)	.74
Surgery[4]	.00	2.04	(0.57	to	7.23)	.27
Acupuncture[4]	.01	0.31	(0.07	to	1.44)	.14
Multidisciplinary rehabilitation[4]	.00	1.99	(0.12	to	32.20)	.63

Variable		R²	Co-efficient	(95% CI)			p value
Pain Sensitivity							
Pain sensitivity clusters	Cluster 1	.00	Reference		to		.86
	Cluster 2		0.89	(0.51	to	1.57)	.70
	Cluster 3		0.81	(0.37	to	1.78)	.60
Sensory testing PCs[11]	PC1	.00	1.01	(0.99	to	1.04)	.34
	PC2	.00	1.00	(1.00	to	1.00)	.54
	PC3	.00	1.06	(0.89	to	1.27)	.50
	PC4	.02	1.04	(1.00	to	1.08)	**.03**
	PC5	.00	0.99	(0.96	to	1.03)	.69
PPT (wrist)		.00	1.00	(1.00	to	1.00)	.56
PPT (lumbar)		.00	1.00	(1.00	to	1.00)	.85
CPT (wrist)		.00	1.01	(0.98	to	1.05)	.49
CPT (lumbar)		.00	1.00	(0.98	to	1.03)	.89
HPT (wrist)		.01	0.93	(0.87	to	0.99)	**.03**
HPT (lumbar)		.00	1.00	(0.93	to	1.06)	.93
MDT (wrist)[3]		.01	0.95	(0.89	to	1.01)	.11
MDT (lumbar)[3]		.01	0.96	(0.92	to	1.00)	**.05**
Two-point discrimination		.00	1.06	(0.94	to	1.20)	.33
Baseline CPM pressure[10]		.00	1.00	(1.00	to	1.00)	.29
CPM change score[10]		.00	1.13	(0.91	to	1.40)	.27
Temporal summation[1]		.00	1.35	(0.72	to	2.53)	.36
Pinprick hyperalgesia		.01	0.59	(0.30	to	1.17)	.13
Movement Dimension							
Pain response following repeated movement subgroups	NIP	.01	Reference				.18
	FB		0.97	(0.52	to	1.81)	.93
	BB		1.97	(0.84	to	4.64)	.12
	FB&BB		1.92	(0.88	to	4.18)	.10
Forward bending time[1]		.01	0.97	(0.94	to	1.01)	.11
Backward bending time[1]		.01	1.03	(0.99	to	1.07)	.18
Communicative behaviours, forward bending		.00	0.88	(0.51	to	1.51)	.64
Protective behaviours, forward bending		.00	1.05	(0.98	to	1.12)	.20
Communicative behaviours, backward bending		.01	0.43	(0.12	to	1.57)	.20
Protective behaviours, backward bending		.00	1.03	(0.93	to	1.14)	.56

Variable		R²	Co-efficient	(95% CI)			p value
Psychological Dimension							
Psychological clusters	Cluster 1	.01	Reference				.37
	Cluster 2		1.17	(0.63	to	2.16)	.62
	Cluster 3		0.68	(0.29	to	1.61)	.38
DASS depression		.00	0.98	(0.96	to	1.01)	.26
DASS anxiety		.00	1.00	(0.96	to	1.03)	.86
DASS stress		.00	1.00	(0.97	to	1.02)	.82
DASS combined total (also PC1)		.00	1.00	(0.99	to	1.01)	.54
FABQ-W[8]		.00	1.00	(0.98	to	1.02)	.80
FABQ-PA		.01	0.97	(0.93	to	1.01)	.14
PCS rumination[1]		.00	1.00	(0.95	to	1.06)	.91
PCS magnification[1]		.00	0.96	(0.88	to	1.05)	.37
PCS helplessness[1]		.00	0.98	(0.93	to	1.02)	.29
PCS total[1]		.00	0.99	(0.97	to	1.01)	.49
PSEQ		.00	1.00	(0.98	to	1.02)	.86
Psychological PC2[1]		.00	0.91	(0.74	to	1.10)	.32
AEQ classification[2]	Adaptive	.01	Reference				.42
	Distress endurance		0.88	(0.45	to	1.71)	.70
	Eustress endurance		0.75	(0.39	to	1.44)	.39
	Fear-avoidance		0.43	(0.16	to	1.19)	.11
TSS[1]		.00	0.93	(0.79	to	1.08)	.34
BES		.00	1.08	(0.84	to	1.38)	.55
Psychological PC3		.00	0.96	(0.77	to	1.18)	.68
CPAQ-8 pain willingness		.01	1.04	(0.99	to	1.10)	.14
CPAQ-8 activity engagement		.01	1.06	(1.00	to	1.12)	**.05**
CPAQ-8 total (also PC4)		.01	1.04	(1.00	to	1.07)	**.03**
MAAS[3]		.00	1.13	(0.84	to	1.52)	.44
Perceived risk of persistent pain[1]		.01	0.89	(0.76	to	1.04)	.14
FreBAQ		.00	0.97	(0.94	to	1.01)	.20

Variable	R²	Co-efficient	(95% CI)			p value
Health Dimension						
Total diagnosed comorbidities	.00	1.01	(0.89	to	1.14)	.92
Musculoskeletal comorbidities	.00	0.93	(0.58	to	1.50)	.77
Functional pain comorbidities	.00	1.09	(0.81	to	1.49)	.56
Other diagnosed comorbidities	.00	0.99	(0.83	to	1.19)	.94
Other comorbid symptoms	.00	1.08	(0.96	to	1.22)	.21
Number of body chart squares filled-in	.01	1.02	(1.00	to	1.04)	.12
Manchester CWP classification	.00	0.93	(0.53	to	1.65)	.80
Baseline COOP/WONCA overall health rating	.01	0.74	(0.56	to	0.98)	**.03**
BMI	.00	0.99	(0.94	to	1.04)	.73

Variable		R²	Co-efficient	(95% CI)			p value
Lifestyle and Social Dimensions							
PSQI[5]		.00	1.03	(0.97	to	1.10)	.35
	Non-smoker	.02	Reference				**.07**
Smoking status	Ex-smoker		0.76	(0.43	to	1.35)	.35
	Smoker		0.29	(0.09	to	0.87)	**.03**
Moderate and vigourous physical activity per week[5]		.00	1.00	(1.00	to	1.00)	.43
Years in education[9]		.02	1.11	(1.02	to	1.19)	**.01**
Compensation status[5]		.00	0.85	(0.42	to	1.73)	.65
Currently at work		.00	1.31	(0.71	to	2.44)	.39
Manual v. sedentary occupation[11]	Not working	.02	Reference				**.05**
	Sedentary		1.60	(0.63	to	4.04)	.32
	Manual		0.69	(0.23	to	2.02)	.49
Job satisfaction[12]		.00	1.04	(0.94	to	1.16)	.42
Life events		.01	1.13	(0.95	to	1.35)	.16
MPI social support[7]		.00	0.94	(0.79	to	1.11)	.46
MPI punishing[6]		.00	0.93	(0.76	to	1.14)	.48
MPI solicitous[6]		.00	0.90	(0.75	to	1.09)	.28
MPI distracting[6]		.00	0.99	(0.80	to	1.21)	.90

Note. [1] missing in one case, [2] missing in two cases, [3] missing in three cases, [4] missing in four cases, [5] missing in six cases, [6] missing in eight cases, [7] missing in nine cases, [8] missing in 10 cases, [9] missing in 13 cases, [10] missing in 14 cases, [11] missing in 16 cases, [12] missing in 39 cases

NRS – numeric rating scale, RMDQ – Roland Morris Disability questionnaire, StEP – Standardised Evaluation of Pain, PC – principal component, Sensory testing PC1 - principal component score derived from thermal pain sensitivity, PC2 - principal component score derived from pressure pain sensitivity, PC3 - principal component score derived from conditioned pain modulation change score, temporal summation and pinprick hyperalgesia, PC4 - principal component score derived from mechanical detection thresholds, PC5 - principal component score derived from two-point discrimination and vibration perception, PPT – Pressure pain threshold, CPT – cold pain threshold, HPT - Heat pain threshold, MDT – Mechanical detection threshold, CPM – Conditioned pain modulation, NIP – No increased pain following repeated bending, FB – Pain increased following repeated forward bending only, BB – Pain increased following repeated back bending only, FB&BB – Pain increased following repeated forward and backward bending, DASS – Depression Anxiety Stress scales, FABQ-W – Fear-Avoidance Beliefs questionnaire (Work subscale), FABQ-PA - Fear-Avoidance Beliefs questionnaire (Physical activity subscale), PCS – Pain Catastrophising scale, PSEQ – Pain Self-efficacy questionnaire, Psychological PC2 – principal component score derived from FABQ-PA, PCS and PSEQ scores, AEQ – Avoidance Endurance questionnaire, TSS – Thought Suppression subscale, BES – Behavioural Endurance subscale, Psychological PC3 - mean of TSS and BES scores, CPAQ-8 – Chronic Pain Acceptance questionnaire (Short form), MAAS – Mindful Attention Awareness scale, FreBAQ – Fremantle Back Awareness questionnaire, CWP – Chronic widespread pain, BMI – Body mass index, PSQI – Pittsburgh Sleep Quality index, MPI - Multidimensional Pain Inventory

Appendix 6.

Regression analysis separately for each potential baseline predictor with

bothersomeness at one-year follow-up as the dependent variable.

Variable	R²	Co-efficient	(95% CI)			*p* value
Demographics						
Age	.02	0.98	(0.96	to	1.00)	**.03**
Sex	.00	0.97	(0.52	to	1.80)	.92
Pain Characteristics						
Baseline pain intensity (NRS)	.07	1.46	(1.21	to	1.77)	**<.001**
Baseline disability (RMDQ)	.01	1.07	(1.00	to	1.15)	**.05**
Duration of CLBP (months)[4]	.00	1.00	(1.00	to	1.00)	.28
100% of pain in low back region	.01	1.75	(0.94	to	3.23)	**.08**
Aggravated by activity (StEP)[1]	.01	2.36	(0.80	to	6.97)	.12
Aggravated by position (StEP)[1]	.01	1.63	(0.69	to	3.86)	.27
Baseline bothersomeness	.05	3.34	(1.71	to	6.52)	**<.001**
Interventions						
No intervention[4]	.00	1.53	(0.73	to	3.22)	.26
Manual therapy[4]	.00	0.68	(0.35	to	1.34)	.27
Exercise[4]	.03	0.37	(0.18	to	0.72)	**.004**
Psychological[4]	.00	1.03	(0.28	to	3.79)	.96
Pharmacological[4]	.00	1.35	(0.62	to	2.97)	.45
Injection[4]	.03	3.68	(1.51	to	8.96)	**.004**
Surgery[4]	.00	1.81	(0.45	to	7.25)	.40
Acupuncture[4]	.02	3.36	(1.11	to	10.20)	**.03**
Multidisciplinary rehabilitation[4]			Collinear			

Variable		R²	Co-efficient	(95% CI)			*p* value
			Pain Sensitivity				
Pain sensitivity clusters	Cluster 1	.01	Reference				.39
	Cluster 2		0.92	(0.48	to	1.77)	.80
	Cluster 3		0.48	(0.17	to	1.40)	.18
	PC1	.00	1.01	(0.98	to	1.04)	.56
	PC2	.00	1.00	(1.00	to	1.00)	.49
Sensory testing PCs[12]	PC3	.00	1.08	(0.88	to	1.33)	.46
	PC4	.02	0.96	(0.92	to	0.99)	**.01**
	PC5	.00	0.98	(0.93	to	1.02)	.28
PPT (wrist)		.00	1.00	(1.00	to	1.00)	.51
PPT (lumbar)		.00	1.00	(1.00	to	1.00)	.32
CPT (wrist)		.00	1.01	(0.97	to	1.05)	.64
CPT (lumbar)		.00	1.01	(0.99	to	1.04)	.34
HPT (wrist)		.00	1.00	(0.92	to	1.08)	.94
HPT (lumbar)		.00	0.98	(0.90	to	1.05)	.52
MDT (wrist)[3]		.01	1.04	(0.97	to	1.11)	.24
MDT (lumbar)[3]		.04	1.05	(1.02	to	1.08)	**.002**
Two-point discrimination		.00	0.98	(0.85	to	1.14)	.82
Baseline CPM pressure[11]		.00	1.00	(1.00	to	1.00)	.94
CPM change score[11]		.00	1.02	(0.79	to	1.32)	.88
Temporal summation[1]		.00	1.38	(0.66	to	2.88)	.39
Pinprick hyperalgesia		.01	0.61	(0.28	to	1.31)	.20
			Movement Dimension				
Pain response following repeated movement subgroups	NIP	.00	Reference				.99
	FB		1.04	(0.51	to	2.11)	.92
	BB		0.97	(0.33	to	2.82)	.96
	FB& BB		0.87	(0.33	to	2.33)	.79
Forward bending time[1]		.02	1.05	(1.01	to	1.08)	**.01**
Backward bending time[1]		.01	1.03	(0.98	to	1.07)	.24
Communicative behaviours, forward bending		.01	1.32	(0.84	to	2.06)	.22
Protective behaviours, forward bending		.00	1.02	(0.94	to	1.11)	.58
Communicative behaviours, backward bending		.01	1.98	(0.84	to	4.67)	.12
Protective behaviours, backward bending		.04	1.20	(1.07	to	1.35)	**.002**

Variable		R²	Co-efficient	(95% CI)			*p* value
			Psychological Dimension				
Psychological clusters	Cluster 1	.02	Reference				.69
	Cluster 2		1.82	(0.79	to	4.21)	.16
	Cluster 3		2.67	(0.99	to	7.22)	**.05**
DASS depression		.00	1.02	(0.99	to	1.05)	.26
DASS anxiety		.00	1.01	(0.97	to	1.05)	.78
DASS stress		.01	1.03	(1.00	to	1.06)	**.09**
DASS combined total (also PC1)		.01	1.01	(1.00	to	1.02)	.22
FABQ-W[8]		.01	1.02	(1.00	to	1.05)	**.07**
FABQ-PA		.00	0.99	(0.94	to	1.05)	.82
PCS rumination[1]		.02	1.09	(1.02	to	1.16)	**.01**
PCS magnification[1]		.00	1.04	(0.93	to	1.15)	.51
PCS helplessness[1]		.02	1.06	(1.00	to	1.11)	**.04**
PCS total[1]		.02	1.03	(1.00	to	1.05)	**.03**
PSEQ		.03	0.97	(0.94	to	0.99)	**.01**
Psychological PC2[1]		.02	1.31	(1.04	to	1.65)	**.02**
AEQ classification[2]	Adaptive	.01	Reference				.51
	Distress endurance		1.72	(0.76	to	3.88)	.19
	Eustress endurance		1.35	(0.60	to	3.02)	.46
	Fear-avoidance		0.88	(0.26	to	2.98)	.83
TSS[1]		.03	1.32	(1.10	to	1.59)	**.003**
BES		.02	1.42	(1.05	to	1.93)	**.02**
Psychological PC3		.04	1.50	(1.15	to	1.94)	**.002**
CPAQ-8 pain willingness		.00	1.02	(0.95	to	1.08)	.63
CPAQ-8 activity engagement		.00	0.98	(0.92	to	1.05)	.61
CPAQ-8 total (also PC4)		.00	1.00	(0.96	to	1.04)	.98
MAAS[3]		.00	0.85	(0.60	to	1.21)	.38
Perceived risk of persistent pain[1]		.00	1.11	(0.91	to	1.35)	.31
FreBAQ		.00	1.01	(0.96	to	1.06)	.70

Variable	R²	Co-efficient	(95% CI)			*p* value
Health Dimension						
Total diagnosed comorbidities	.01	0.89	(0.75	to	1.05)	.17
Musculoskeletal comorbidities	.00	0.74	(0.40	to	1.36)	.33
Functional pain comorbidities	.00	1.01	(0.70	to	1.45)	.97
Other diagnosed comorbidities	.01	0.80	(0.62	to	1.04)	**.09**
Other comorbid symptoms	.00	0.94	(0.81	to	1.09)	.41
Number of body chart squares filled-in	.03	1.03	(1.01	to	1.06)	**.01**
Manchester CWP classification	.01	1.49	(0.78	to	2.85)	.22
Baseline COOP/WONCA overall health rating	.03	1.54	(1.12	to	2.13)	**.01**
BMI	.01	0.95	(0.89	to	1.01)	.12

Variable		R²	Co-efficient	(95% CI)			p value
Lifestyle and Social Dimensions							
PSQI[9]		.01	0.95	(0.88	to	1.03)	.19
Smoking status	Non-smoker	.02	Reference				**.06**
	Ex-smoker		0.55	(0.25	to	1.17)	.12
	Smoker		1.91	(0.79	to	4.64)	.15
Moderate and vigourous physical activity per week[5]		.00	1.00	(1.00	to	1.00)	.53
Years in education[10]		.03	0.88	(0.80	to	0.97)	**.01**
Compensation status[5]		.00	1.43	(0.65	to	3.16)	.37
Currently at work		.01	0.62	(0.31	to	1.21)	.16
Manual v. sedentary occupation[12]	Not working	.03	Reference				**.01**
	Sedentary		0.30	(0.12	to	0.75)	**.01**
	Manual		0.63	(0.23	to	1.74)	.38
Job satisfaction[13]		.01	0.92	(0.82	to	1.04)	.18
Life events		.01	1.14	(0.92	to	1.41)	.23
MPI social support[7]		.01	1.19	(0.96	to	1.48)	.12
MPI punishing[6]		.01	1.18	(0.94	to	1.47)	.15
MPI solicitous[6]		.01	1.19	(0.95	to	1.49)	.13
MPI distracting[6]		.01	1.17	(0.91	to	1.49)	.22

Note. [1] missing in one case, [2] missing in two cases, [3] missing in three cases, [4] missing in four cases, [5] missing in six cases, [6] missing in eight cases, [7] missing in nine cases, [8] missing in 10 cases, [9] missing in 11 cases, [10] missing in 13 cases, [11] missing in 14 cases, [12] missing in 39 cases

NRS – numeric rating scale, RMDQ – Roland Morris Disability questionnaire, StEP – Standardised Evaluation of Pain, PC – principal component, Sensory testing PC1 - principal component score derived from thermal pain sensitivity, PC2 - principal component score derived from pressure pain sensitivity, PC3 - principal component score derived from conditioned pain modulation change score, temporal summation and pinprick hyperalgesia, PC4 - principal component score derived from mechanical detection thresholds, PC5 - principal component score derived from two-point discrimination and vibration perception, PPT – Pressure pain threshold, CPT – cold pain threshold, HPT - Heat pain threshold, MDT – Mechanical detection threshold, CPM – Conditioned pain modulation, NIP – No increased pain following repeated bending, FB – Pain increased following repeated forward bending only, BB – Pain increased following repeated back bending only, FB&BB – Pain increased following repeated forward and backward bending, DASS – Depression Anxiety Stress scales, FABQ-W – Fear-Avoidance Beliefs questionnaire (Work subscale), FABQ-PA - Fear-Avoidance Beliefs questionnaire (Physical activity subscale), PCS – Pain Catastrophising scale, PSEQ – Pain Self-efficacy questionnaire, Psychological PC2 – principal component score derived from FABQ-PA, PCS and PSEQ scores, AEQ – Avoidance Endurance questionnaire, TSS – Thought Suppression subscale, BES – Behavioural Endurance subscale, Psychological PC3 - mean of TSS and BES scores, CPAQ-8 – Chronic Pain Acceptance questionnaire (Short form), MAAS – Mindful Attention Awareness scale, FreBAQ – Fremantle Back Awareness questionnaire, CWP – Chronic widespread pain, BMI – Body mass index, PSQI – Pittsburgh Sleep Quality index, MPI - Multidimensional Pain Inventory

Chapter Eight – Discussion

This thesis represents the most extensive attempt at multidimensional subgrouping and profiling of people with CLBP in the literature to date. As they relate to the initial aims of the thesis, each of the studies will be summarised in turn, highlighting novel contributions to the literature made by each. Discussion of the varied individual patterns of subgroup membership across all subgrouping studies, and the clinical implications of this research, will follow.

8.1 Summary Of Studies Included In This Thesis

8.1.1 Study 1: Multidimensional pain profiles in four cases of chronic non-specific axial low back pain: An examination of the limitations of contemporary classification systems.

Prior to attempting to determine the existence of any subgroups within our CLBP cohort, the first aim of this thesis was to examine four individual clinical cases of people with axial CLBP with contrasting multidimensional profiles determined using data from valid and reliable clinical measures.

The first study in this thesis (Rabey et al., 2015a) described these four cases (P1-4). Their presentations were considered within a framework incorporating multiple dimensions associated with CLBP (pain characteristics, tissue sensitivity, psychological, social, health, lifestyle, movement), and allowing consideration of individual variability of the relative contributions of each dimension (O'Sullivan et al., 2015, Vibe Fersum et al., 2013, O'Sullivan, 2012). P1 presented with localised, heightened lumbar pain sensitivity, a directional pain response following repeated movement and elevated pain catastrophising. This profile was deemed consistent with dominantly peripheral nociception. P2 had a "mixed" profile characterised by localised, heightened lumbar pain sensitivity, and a directional pain response following repeated movement associated with elevated fear-avoidance beliefs. These findings combined with the presence of functional pain comorbidities and elevated stressful life events, are suggestive of centrally-mediated facilitation of nociception. P3 showed widespread heightened pain sensitivity, possibly reflective

of dominant centrally-mediated pain mechanisms, combined with multidirectional pain responses following movement, elevated scores for multiple affective and cognitive factors and multiple comorbidities. P4 had normal pain sensitivity and no increase in pain following movement, but had dominant cognitive and affective factors and comorbidities associated with greater pain and disability, possibly via centrally-mediated pain faciltation (Nater et al., 2011, McEwen and Gianaros, 2010, Zusman, 2002). Rather than clearly fitting into subgroups based on existing LBP CS, these four complex cases highlighted the multidimensional variability that exists in people with CLBP. The limitations of contemporary CS in relation to these cases was outlined, as no unidimensional CS could effectively classify all four cases. The need for a flexible CS that considers the relative contributions and interactions of all relevant dimensions, was discussed. The CS described by O'Sullivan et al. (2015) has been reported to be the most all-encompassing multidimensional CS for LBP (Karayannis et al., 2012). However, that CS relies largely on clinical judgement leaving it open to bias, and currently lacks adequate non-judgemental validation across a number of dimensions.

The subsequent aims of this thesis were to determine the existence and number of subgroups of people with CLBP using non-judgemental methods, utilising valid and reliable, clinically-applicable measures from multiple dimensions. Multidimensional profiling of the derived subgroups was conducted in order to gain a deeper clinical insight into the subgroups. The original intention of this thesis was to identify subgroups in a large CLBP cohort using LCA of data from multiple dimensions associated with CLBP. However, due to the complexity of the data there were difficulties in converging upon an optimal cluster solution. It was therefore deemed appropriate to examine the data set by deriving subgroups of people based on three different dimensions (QST data, psychological questionnaire scores and pain responses following repeated spinal bending).

8.1.2 Study 2: Somatosensory nociceptive characteristics differentiate subgroups in people with chronic low back pain: A cluster analysis.

In Study 2 (Rabey et al., 2015b) LCA was used to derive subgroups in a cohort with axial CLBP (n=294), based upon results of multimodal QST, and profiled subgroups on multidimensional data. QST findings were chosen because they have rarely been utilised to derive subgroups in people with CLBP, they offer a "window" to explore nociceptive and non-nociceptive processes underlying CLBP (Baron et al., 2012), and may also influence treatment outcomes (Coronado et al., 2014). Bedside (two-point discrimination; brush / vibration / pinprick perception; temporal summation) and laboratory (MDT, PPT, HPT, CPT, CPM) sensory testing were examined at wrist / lumbar sites. These sensory tests are increasingly used in clinical practice (Backonja et al., 2013), facilitating translation of the results of this study. Data were reduced using principal component analysis, and the resultant five prinicipal component scores were utilised as indicator variables in LCA.

Three clusters were derived:

- Cluster 1 (31.9%) - average to high temperature and pressure pain sensitivity, both locally and remotely, likely reflecting involvement of central pain mechanisms (Woolf, 2011).
- Cluster 2 (52.0%) - average to high pressure pain sensitivity, mechanisms for which remain unclear (Basbaum et al., 2009) in people with CLBP.
- Cluster 3 (16.0%) - low temperature and pressure pain sensitivity, the relevance of which also remains unclear Neziri et al. (2011).

Clusters 1 and 2 had a significantly greater proportion of female participants, and higher depression and sleep disturbance scores than Cluster 3. The proportion of participants undertaking <300 minutes / week of moderate activity was significantly greater in Cluster 1 than Clusters 2 and 3. Interestingly, the subgroups did not differ in regard to pain or disability.

While comparison with other sensory subgrouping studies is limited by use of differing QST and sample characteristics, the results from this research support that

pain sensitivity is not homogeneous in people with CLBP. Being the first study to derive subgroups in a large CLBP cohort using multimodal sensory testing, and to profile the subgroups across a broad range of multidimensional data, allowed postulation regarding the possible pain mechanisms underlying the cluster profiles. The findings support the understanding of CLBP as multidimensional in nature, where the pain sensitivity clusters are associated with different profiles based on sex, depression, sleep disturbance and activity levels.

8.1.3 Study 3: Differing psychologically-derived clusters in people with chronic low back pain are associated with different multidimensional profiles.

In Study 3, LCA was used to derive subgroups in the same CLBP cohort based upon data from multiple psychological questionnaires. These subgroups were then profiled on multidimensional data. The psychological dimension was chosen for subgrouping because many psychological factors are prognostic of pain and disability in people with chronic low back pain (CLBP) (Hayden et al., 2010). While cluster analysis has been used many times to derive subgroups based upon one or multiple psychological factors, it was unclear which psychological factors, or combinations thereof, may be most important for determining subgroups in people with CLBP. Previous subgrouping studies have only considered a limited range of factors when profiling their subgroups. Therefore, this study entered a broad range of psychological questionnaire scores into LCA (Depression, Anxiety, Stress scales, Thought Suppression and Behavioural Endurance subscales (Avoidance Endurance questionnaire), Chronic Pain Acceptance questionnaire, Pain Catastrophising scale, Pain Self-Efficacy questionnaire, Fear-Avoidance Beliefs questionnaire).

Three clusters were derived:

- Cluster 1 (23.5%) - lower scores across all retained indicator variables (depression, anxiety, stress; thought supression; pain catastrophising rumination, magnification and helplessness subscales; pain self-efficacy).

- Cluster 2 (58.8%) - comparatively elevated thought suppression and pain catastrophising; lower pain self-efficacy, depression, anxiety and stress.

- Cluster 3 (17.7%) - highest scores across all retained indicator variables.

Cluster 1 reported significantly lower pain intensity and bothersomeness than other clusters. Disability, stressful life events and low back perceptual distortion increased progressively from Cluster 1 to Cluster 3 while mindfulness progressively decreased. Clusters 2 and 3 had more people with increased pain following repeated spinal bending than Cluster 1. Cluster 3 had significantly greater lumbar pressure pain sensitivity, more undiagnosed comorbid symptoms and more widespread pain than other clusters.

Both the range of psychological indicator variables entered into LCA, and the broad multidimensional profiling of derived subgroups are novel to this study. However, while comparison with previous studies is limited by use of differing questionnaires, the results from this research add support to the existence of lower and higher-scoring psychologically-derived clusters in people with CLBP (Viniol et al., 2013, Strong et al., 1995), and possibly an intermediate cluster scoring relatively low for affect and higher on cognitive factors (Boersma and Linton, 2005, Barons et al., 2014, Hirsch et al., 2014). The findings support the view of CLBP as a multidimensional disorder, where psychological subgroups are associated with different profiles based on pain intensity, distribution and bothersomeness, disability, stressful life events, perceptual distortion, mindfulness, pain responses following repeated spinal bending, pressure pain sensitivity, and comorbid symptoms.

8.1.4   Study 4: Pain provocation following repeated movements in people with chronic low back pain: subgrouping and multidimensional profiles.

Subgroups were derived in the same cohort based upon pain responses following a standardised protocol involving repeated forward and backward spinal bending, and profiled across multidimensional data. Pain responses following repeated movements were chosen for the derivation of subgroups because they are

commonly examined clinically (May and Aina, 2012) and appear to vary across people with LBP (Hidalgo et al., 2014, Rabey et al., 2015a). Furthermore, there had been no attempts to determine whether different subgroups exist in a large CLBP cohort, based upon differing pain responses to repeated movement using statistical methods.

Four subgroups were derived:

- No clinically important increase in pain with bending in either direction (49.0%).
- Increased pain with repeated forward bending only (28.2%).
- Increased pain with repeated backward bending only (9.9%).
- Increased pain bending in both directions (12.9%).

Subgroup 1 has not been previously described. They showed the fastest movement in both directions and normal pain sensitivity, but had elevated fear-avoidance beliefs and distorted body perception compared to published normative data. Subgroup 2 had elevated disability and pain catastrophising, slower movement speed, and low pain self-efficacy compared to other subgroups; and elevated depression and fear-avoidance beliefs, and distorted body perception compared to published normative data, possibly suggesting enhanced central nociceptive facilitation (Simons et al., 2014, Zusman, 2002, Hodges and Smeets, 2015). Subgroup 3 had a similar profile to subgroup 1. Approximately 20% of participants in subgroups 2 and 3 had a clinically-important amelioration of pain intensity with repeated movements in the opposite direction to that which was provocative. This proportion appears lower than previously reported (60-74%) (Long et al., 2004, Werneke et al., 2011), possibly reflecting the manner by which the subgrouping was determined (two-point change on an NRS in response to a standardised protocol). While amelioration of pain intensity in people demonstrating a directional preference or centralisation phenomenon is implied in studies of the McKenzie CS, actual changes in pain intensity immediately following repeated movements have not been reported. This limits comparison between studies (Long et al., 2004, Werneke et al., 2011). Subgroup 4 had higher pain intensity, pain catastrophising

and lower pain self-efficacy than other subgroups; and elevated lumbar pressure and cold pain sensitivity, depression and fear-avoidance beliefs, and distortion of body perception compared to published normative data, suggesting involvement of peripheral sensitisation and / or centrally-mediated pain faciltation (Nater et al., 2011, McEwen and Gianaros, 2010, Zusman, 2002, Sullivan et al., 2009, Cruz-Almeida and Fillingim, 2014, Graven-Nielsen and Arendt-Nielsen, 2010, Curatolo and Arendt-Nielsen, 2015).These findings support the complex nature of CLBP, where directional pain responses to movement are associated with different multidimensional profiles based on disability, speed of movement, depression, fear-avoidance beliefs, pain catastrophising, pain self-efficacy, distorted body perception and pressure and cold pain sensitivity.

These three subgrouping studies have drawn together factors considered independently in previous cross-sectional, subgrouping or prognostic studies, and added previously unconsidered factors. This broad approach has facilitated an understanding of the complexity of CLBP. Involvement of a sample predominantly recruited from the general community with dominant axial CLBP, facilitates interpretation of these findings and increases their generalisability.

8.1.5   Individual patterns of subgroup membership across all subgrouping studies.

Examination of individual patterns of subgroup membership across all subgrouping studies revealed participants displayed 33 out of the 36 possible patterns (Afterword to Chapters Four to Six, Figure 1). The most common pattern occurred in only 16.0% of the sample. No particular pattern was dominant, with all other response patterns occuring in less than 10% of the sample. This finding supports that the presentations of people with CLBP are highly variable when considering these three dimensions (Brown, 2009). This high degree of variability between participants questions the likelihood that clinically meaningful subgroups that consider the multidimensional nature of CLBP can be identified for the purpose of developing treatments which are targeted to subgroups.

While speculative, consideration of the uni-dimensional subgroups together with their multidimensional profiles could be hypothesised to offer clinicians some guidance for tailored interventions. However, the highly varied individual patterns of subgroup membership across all subgrouping studies suggests uni-dimensional subgrouping is likely to reflect an overly simplistic view of CLBP. This is also supported by the high degree of variability reflected in the four case studies. Examination of the patterns of subgroup membership across all subgrouping studies for each of the cases was broadly accurate, revealing minor inconsistencies, due to the utilisation of non-judgemental subgrouping methods. This suggests that the assessment of people with CLBP, when guided by a multidimensional framework may approximate data-driven, statistical subgrouping. However, even within one particular subgroup, participant's multidimensional profiles vary considerably. This supports the need to adopt a flexible, multidimensional framework which allows clinicians to consider the relative contributions of multiple interacting dimensions associated with CLBP (O'Sullivan et al., 2015, O'Sullivan, 2012, Vibe Fersum et al., 2013) in order to individualise care.

8.1.6 Study 5: Multidimensional prognostic modelling in people with chronic low back pain.

While the subgroups derived in the three cross-sectional studies appear to have face validity, it was also important to examine their prognostic validity. Therefore the fourth aim of this thesis was to determine whether multidimensional baseline data, including subgroup membership from the three studies and broad intervention groupings, were prognostic of a range of clinical outcomes. Previous prognostic studies in CLBP cohorts have examined limited ranges of prognostic variables and commonly have not considered a range of broad treatment groupings (e.g. exercise- or psychologically-based treatments) as potential prognostic factors. Furthermore, they have tended to only consider one outcome measure (Verkerk et al., 2012). In Study 5 baseline multidimensional data and broad intervention groupings were utilised to derive prognostic models for pain intensity, disability, GRC and bothersomeness in this cohort at one-year follow-up. This appears to be the most comprehensive prognostic study in people with CLBP to date.

Factors prognostic for higher pain intensity (explaining 23.2% of the variance) included higher baseline pain intensity and punishing interactions with a significant other, and lower years in education; while participating in exercise as treatment was prognostic of lower pain intensity. Factors prognostic for greater disability (explaining 33.6% of the variance) included higher baseline disability, time taken to complete five forward bends, fear-avoidance beliefs, pain catastrophising, pain self-efficacy, endurance behaviours and punishing interactions with a significant other; while participating in exercise as treatment was prognostic of lower disability. The odds of reporting GRC of much / very much improved, were increased where participants reported participating in exercise as treatment, having some leg pain and having higher chronic pain acceptance. The ROC AUC indicated acceptable discrimination for this model. The odds of rating CLBP as very / extremely bothersome, were increased where participants reported higher baseline pain intensity and forward bend time, and receiving spinal injection(s) as treatment; while they were decreased where participants reported higher age and years in education, and having some leg pain (acceptable discrimination). While some variables consistently prognostic of poor outcome in CLBP (sex, poor general health, occupational factors) (Hayden et al., 2009, Verkerk et al., 2012) were not included in our final prognostic models, other novel variables (forward bending time, punishing interactions with a significant other) were included.

While this study demonstrated that prognostic factors in people with CLBP are multidimensional, and differ based on what outcome variable is considered, only approximately 30% of the variance in any single outcome was explained. These findings suggest that consideration of a broader range of potentially prognostic variables may not improve prognosis. Prognostic models in people with CLBP only capture factors that are common to the cohort at one time point, rather than factors unique to individuals which may fluctuate over time. This suggests differing approaches such as consideration of complexity theory, or data-rich single case experiments tracking change at multiple time-points, may be more appropriate to improve our understanding of multidimensional interactions in people with CLBP.

Of particular note, none of the subgroups from the three subgrouping studies were retained in final prognostic models, possibly because while unidimensional subgroup membership may have been important for prognosis in some individuals it may not have been commonly prognostic across the whole sample. Membership of psychological Cluster 3 (higher scores across all indicator variables) had a significant univariable association with greater pain intensity, disability and bothersomeness at one-year follow-up, suggesting those with a poorer psychological profile may warrant targeted management of this dimension. For pain sensitivity clusters it has been proposed that with increasing chronicity the neurophysiological processes underlying such somatosensory manifestations become self-sustaining and potentially more difficult to change (Simons et al., 2014, Borsook and Kalso, 2013), making them less likely to be prognostic of any change in outcomes. While the different subgroups were not prognostic, whether they would be predictive if treatments were targeted towards these factors requires further investigation.

8.2   The Role Of Pain Sensitivity In CLBP

Understanding pain mechanisms underlying differing pain presentations has been proposed as a way to guide targeted interventions (Woolf and Mannion, 1999, Baron et al., 2012). QST, which is increasingly used in clinical practice (Backonja et al., 2013), allows examination of tissue sensitivity, and may afford a "window" through which to postulate underlying pain mechanisms (Baron et al., 2012). Numerous cross-sectional studies have examined differing QST measures in people with CLBP (Chapter 2, Table 3), and shown varying results compared to control subjects, from no significant difference between groups (Meeus et al., 2010), or heightened, localised lumbar pressure pain sensitivity (Blumenstiel et al., 2011), to widespread heightened pressure and thermal pain sensitivity (Neziri et al., 2012). This highlights the variability in tissue sensitivity in people with CLBP.

The derivation of subgroups with differing tissue sensitivity profiles may be a means of making sense of this heterogeneity, and allow the development of more targeted interventions (Baron et al., 2012). However, only two studies to date appear to have

derived subgroups in people with LBP based upon differing pain sensitivity profiles (Scholz et al., 2009, Coronado et al., 2014). Both studies utilised hierarchical cluster analysis, which has numerous disadvantages compared to probabilistic clustering procedures such as LCA. While these studies did derive heterogeneous subgroups, they have a number of limitations. Scholz et al. (2009) derived two small subgroups (n=18, n=32) using only a limited range of bedside sensory tests, and did not undertake any broader multidimensional profiling of the subgroups. Coronado et al. (2014) examined a mixed neck pain / LBP cohort (LBP: n=110; neck pain: n=47) using static pressure, and static and dynamic heat pain stimuli, but excluded participants if they had chronic conditions unrelated to LBP, and considered only fear-avoidance beliefs and pain catastrophising as broader profiling variables. In contrast, this thesis supports the existence of heterogeneous pain sensitivity clusters with differing multidimensional profiles in this large cohort of people with CLBP. Due to the complexity of CLBP it would appear appropriate to consider both the pain sensitivity, and broader multidimensional profiles, in the clinical reasoning process rather than attempting to develop interventions based upon pain sensitivity alone (Elvey and O'Sullivan, 2004).

In this research, additional multidimensional profiling revealed between cluster differences for sex, depression, sleep disturbance and physical activity levels, all of which have been previously shown to influence nociceptive processing (Racine et al., 2012, Lautenbacher et al., 1999, Klauenberg et al., 2008, Kundermann et al., 2004, Ellingson et al., 2012). This lends support to the validity of the subgroups derived (Kent et al., 2010, McCarthy et al., 2004), and to the view of CLBP as an emergent disorder involving multiple interacting dimensions (Simons et al., 2014, Hush et al., 2013). Despite the differing profiling variables possibly influencing pain sensitivity, the exact mechanisms and clinical relevance underlying these differences remain unclear (Basbaum et al., 2009), Neziri et al. (2011). These subgroups may represent different underlying mechanisms and / or somatosensory phenotypes, but it should be acknowledged that pain sensitivity clusters may also have been influenced by factors that were not measured in this cohort, such as genetics (Simons et al., 2014). Examination of the multidimensional profiles, and

individual patterns of subgroup membership across all subgrouping studies again highlights significant heterogeneity between individuals. These findings are also consistent with the four case reports described in Study 1.

Given the cross-sectional nature of this reseach it is not possible to conclude whether these sensory changes preceeded the pain disorder, or developed subsequent to it. However, clusters with differing pain sensitivity profiles have been derived in healthy controls (Hastie et al., 2005) suggesting differing pain sensitivity subgroups may exist before the onset of a pain disorder.

A recent systematic review and meta-analysis (Hübscher et al., 2013) found low correlations between pain thresholds and pain intensity and disability. The authors suggested that a limitation of the included studies was that samples were assumed to be homogeneous, and that subgroups of people with LBP may exist where pain sensitivity has a greater association with these outcomes. However, subgroups of people with CLBP with differing pain sensitivity were derived in this cohort, and the levels of pain and disability still did not differ between subgroups. This is in contrast to two small to moderate sized studies involving clinically derived subgroups where differences in pain intensity and disability have been related to differing levels of pain sensitivity (O'Sullivan et al., 2014, Tesarz et al., 2015). However, subgrouping in both of these studies involved clinical judgement. In the study by O'Sullivan et al. (2014) subgroups were partly based upon pain responses to movement, possibly consistent with the subgroup demonstrating pain provocation following both repeated forward and backward bending in Study 4, which also demonstrated the highest pain intensity and pressure and cold pain sensitivity. These findings suggest that while pain sensitivity may not be related to baseline pain and disability, it may be related to pain responses following movement. The results of the meta-analysis by Hübscher et al. (2013) also differ from a recent study where people with localised CLBP had significantly lower pain intensity, but not disability, from those with more widespread CLBP. These two subgroups differed across thermal and pressure pain sensitivity compared to each other and to healthy control participants (Gerhardt et al., 2015). Self-reported pain and disability levels may therefore be influenced by dimensions other than pain sensitivity alone.

The pain sensitivity clusters were not prognostic of any outcomes (pain intensity, disability, bothersomeness, GRC) at one-year follow-up. This may either reflect that the outcome measures are not driven by pain sensitivity, or that the chronic nature of the CLBP in this study rendered these pain sensitivity profiles resistant to change. The prognoses associated with previously derived pain sensitivity clusters have not been examined (Scholz et al., 2009, Coronado et al., 2014). The exclusion of pain sensitivity measures from the prognostic models derived in this study is consistent with a recent study which excluded PPT at the second toe and CPM from a prognostic model for pain intensity at one-year follow-up, in a mixed cohort of people with chronic pain (CLBP n=113, chronic neck pain n=56) (Mlekusch et al., 2013). However, the exclusion of QST from prognostic models in this thesis contrasts with people with whiplash associated disorder. In this context those with the highest pain levels also have the highest pressure and thermal pain sensitivity at one and six-months following their motor vehicle accident (Sterling et al., 2011, Sterling et al., 2003). This suggests that self-report pain intensity and tissue sensitivity may be more closely linked in acute disorders such as whiplash, possibly due to time-dependent pain mechanisms that emerge early after pain onset. While alterations in pain sensitivity may be present in people with acute LBP (Marcuzzi et al., 2015), whether such findings may be similarly prognostic requires further investigation. Previous studies have reported pain sensitivity to be modifiable following nerve root injection for lumbar radiculopathy (Mehta et al., 2013), radiofrequency neurotomy for whiplash associated disorder (Smith et al., 2014), joint arthroplasty for knee osteoarthritis (Graven-Nielsen et al., 2012), and pain neurophysiology education for fibromyalgia (Van Oosterwijck et al., 2013) supporting that pain sensitivity profiles may be modifiable. However, the causal pathways for these outcomes is unclear and likely varies across interventions, time and cohorts.

While ongoing pain and disability levels did not differ across the pain sensitivity clusters this research suggests that the presence of pressure or thermal pain sensitivity in people with CLBP may trigger clinicians to consider broadening their examination to include, and possibly tailoring their management towards,

modifiable associated factors from other dimensions, such as psychological, lifestyle and movement factors. These clusters might also provide an opportunity for targeted pharmacological interventions directed towards these different pain sensitivity clusters (Baron et al., 2015, Schwittay et al., 2014). To date no research has investigated the targeting of sensitivity clusters in CLBP.

8.3   The Role Of The Psychological Dimension In CLBP

Psychological factors are known to be associated with pain and disability in people with CLBP (Hayden et al., 2010). The heterogeneous nature of psychological factors in those with CLBP has been examined using subgrouping techniques for nearly four decades (Bradley et al., 1978). Ongoing research has supported the existence of psychologically-derived subgroups in people with CLBP based upon specific psychological factors (e.g. fear-avoidance beliefs (Beneciuk et al., 2011)) or combinations of factors (e.g. fear-avoidance beliefs, pain self-efficacy, anxiety, depression and troublesomeness (Barons et al., 2014)).

The cross-sectional findings of this thesis are consistent with the existence of heterogeneous psychologically-derived subgroups in people with CLBP, including subgroups scoring relatively low or high across cognitive and affective measures, and an intermediate subgroup scoring relatively low for affect and high on cognitive factors (Boersma and Linton, 2005, Barons et al., 2014, Hirsch et al., 2014, Viniol et al., 2013, Strong et al., 1995).

A strength of this thesis was the broad multidimensional profiling of clusters. Interactions between the psychological dimension and the other profiling factors, provide a unique understanding of the multidimensional factors associated with different psychological profiles. Clusters differed across pain intensity, disability, bothersomeness, age, distortion of perception of the lumbar region, and the movement, tissue sensitivity, and health and lifestyle dimensions, lending validity to the subgroups (Kent et al., 2010, McCarthy et al., 2004). The psychological dimension (unlike the tissue sensitivity dimension in this cohort) had a significant association with the burden of CLBP. This may be consistent with the definition of pain as an, "unpleasant sensory and emotional experience" (IASP Taxonomy

Working Group, 2011). The multidimensional profiles suggest that while psychologically-derived clusters exist there is likely to be significant heterogeneity at the level of the individual. This is consistent with the differing patterns of subgroup membership across all subgrouping studies, the differences between psychological factors across both the pain sensitivity clusters and movement subgroups, as well as the four case reports. Consistent with previous studies (Viniol et al., 2013, Strong et al., 1995) Cluster 3, with the highest psychological scores, appeared to have the highest burden, with higher disability levels compared to the lowest-scoring Cluster 1.

As this study was cross-sectional, it is not possible to determine whether these psychological differences existed prior to the onset of CLBP, or developed subsequently. From previous research, there is some suggestion that some psychological factors may have a premorbid contribution to such presentations (Simons et al., 2014, Fernandez and Kerns, 2012).

In univariable prognostic models membership of Cluster 3 was associated with greater pain intensity, disability and bothersomeness at one-year follow-up. Studies involving similar high scoring psychologically-derived subgroups in people with CLBP have not examined their prognostic validity (Viniol et al., 2013, Strong et al., 1995). However, two studies of people with LBP attending primare care, with subgroups derived in full or in part by higher psychological scores have shown such subgroups to be prognostic of greater disability (Barons et al., 2014, Hill et al., 2008). This suggests it may be important for early interventions to specifically target those with high psychological scores to attempt to improve their prognosis.

Membership of Cluster 3 was not retained in the final multivariable prognostic models. This may reflect the small size of this subgroup (18% of the cohort). It may also be that the psychologically-derived clusters in this research were less prognostic of poor outcomes than subgroups derived in primary care because participants already had chronic symptoms, and were therefore less likely to have significant changes in their pain and disability levels (Dunn and Croft, 2006). This is supported by the pain and disability levels in this research not changing by the

established MCIDs of two-points for pain intensity and five-points for disability (Stratford et al., 1996, Salaffi et al., 2004). However, while psychologically-derived clusters were not independently prognostic of any outcome in this research, two psychologically-derived PCs (derived from: i) FABQ-PA, PCS and PSEQ scores, ii) TSS and BES scores) were retained in the multivariable prognostic model for disability. This is consistent with previous research showing that greater pain catastrophising, fear-avoidance beliefs and endurance behaviours, and lower pain self-efficacy are prognostic of greater disability (Wertli et al., 2014, Leeuw et al., 2007, Jackson et al., 2014, Hasenbring et al., 2012).

It is unknown whether membership of the psychologically-derived clusters may predict treatment outcomes. Both the psychological profiles of the different clusters and their multidimensional profiles may, in future, give clinicians direction for matching interventions to each cluster. For example, a matched intervention for (intermediate) Cluster 2 may involve targeting cognitive factors (pain catastrophising and pain-self efficacy in particular), sensorimotor disturbances and building stress resilience. While psychologically-derived clusters may have been influenced by factors that were not measured in this cohort, such as genetics / epigenetics (Pinheiro et al., 2014), many of the psychological indicator variables may be modifiable with differing interventions (Cooney et al., 2013 , Arroll et al., 2009 , Coventry et al., 2014, Cross, 2009, Altmaier et al., 1993, Nicholas et al., 1992).

Apart from age, the multidimensional profiling variables that differed between clusters may also all be modifiable. Where subgroups, based in part upon the psychological dimension, have received matched treatments, long-term outcomes have been similar to control or unmatched treatments (Vollenbroek-Hutten M et al., 2004, Hill et al., 2011, Bergbom et al., 2014, Verra et al., 2015). This may be because interventions have not considered all relevant dimensions associated with the presentations of the different subgroups. The broad multidimensional profiling of the psychologically-derived clusters in this research may provide greater direction for targeted care (Rusu et al., 2012).

Overall this research suggests that clinicians should consider the complex interactions between the psychological dimension, and pain intensity, disability, bothersomeness, body perception, and the movement, tissue sensitivity, health and lifestyle dimensions in people with CLBP. It appears to be clinically important to recognise people with CLBP and high scores across a number of psychological factors because of the greater associated burden. However, when tailoring interventions clinicians should consider potential differing contributions from cognitive and affective factors. When considering cognitions, clinicians may focus on fear-avoidance beliefs, pain catastrophising, pain self-efficacy and endurance behaviours as they are prognostic of poor outcomes. To attempt to improve treatment outcomes tailored management should also take into account modifiable factors from the broader multidimensional profiles associated with the different psychologically-derived clusters.

8.4 The Role Of Pain Responses Following Repeated Spinal Bending In CLBP

Clinicians commonly evaluate pain responses to repeated forward and backward spinal bending in people with CLBP. Directional patterns of pain amelioration and provocation with repeated spinal bending have been reported (May and Aina, 2012, Hidalgo et al., 2014). Such pain responses following repeated movement have long been utilised to determine clinically-derived subgroups of people with CLBP (McKenzie, 1981), however, they have not previously been based upon valid and reliable, clinically important self-report changes in pain intensity in response to a standardised testing protocol. Validation of this subgrouping approach, based upon pain responses following repeated spinal bending, should be undertaken by repeating this study in an independent sample.

Using a statistical subgrouping approach this study identified four subgroups with differing pain responses to repeated spinal bending, showing that such responses are not homogeneous in people with CLBP. Forty-nine percent of participants had no significant increase in pain following movement in either direction. However, it is acknowledged that this proportion may reflect the two-point subgrouping cut-off score, the possible adoption of movement strategies effective in reducing pain

provocation, the experience of increased pain *during* movement that was unrecorded, and that the examination of tasks involving external loads may have been more provocative. For the remainder of participants provocative pain responses following repeated spinal bending were more common than ameliorative responses, with thirty-eight percent having a unidirectional increase in pain and 13% having an increase in pain following movement in both directions.

The different subgroups demonstrated differences across pain intensity and duration, disability, body perception and the psychological, movement and tissue sensitivity dimensions, supporting the validity of these subgroups (Kent et al., 2010, McCarthy et al., 2004) and the view of CLBP as a multidimensional disorder (Simons et al., 2014, Hush et al., 2013). These multidimensional profiles are broader than those previously considered in a study reporting that profiles of people with CLBP with disproportionate pain responses to movement reflected elevated pain intensity, disability, sleep disturbance, pain sensitivity and psychological distress (O'Sullivan et al., 2014). Pain responses following repeated movements may have been influenced by factors that were not measured in this cohort, such as participant's previous interactions with other healthcare practitioners. Combined with consideration of the individual patterns of subgroup membership across all subgrouping studies, the multidimensional profiles of these subgroups highlight the significant heterogeneity at the level of the individual, again consistent with the four case reports.

As this study was cross-sectional, the nature of these multidimensional associations is unknown. However, pain responses following repeated movements are more likely to be ameliorative in people with acute LBP than CLBP (May and Aina, 2012), consistent with a contemporary view that adaptations to movement associated with pain involve complex multidimensional interactions at the level of the individual, that vary across time (Hodges and Smeets, 2015).

Participants with increased pain following repeated forward bending had the highest levels of disability, possibly reflecting the percieved importance of this movement during activities of daily living (Reneman et al., 2002, Fujiwara et al.,

2010). In contrast those with increased pain following repeated movements in both directions had the highest pain intensity, linked to lower pressure and high cold pain thresholds, possibly reflecting centrally-mediated pain mechanisms (Sullivan et al., 2009).

Interestingly, subgroups based upon pain responses following repeated movements were not prognostic of outcome at one-year follow-up, suggesting the outcome measures are not driven by pain responses following repeated movements, or that the chronic nature of the CLBP in this study rendered these pain / movement interactions resistant to change. The prognostic capacity of subgroups based upon pain responses following repeated movements does not appear to have been examined in other studies. However, one specific variable from the movement dimension, slower forward bend time, was prognostic of greater disability and bothersomeness. This variable is novel for prognostic studies in people with CLBP, and is in line with previous reports that people with CLBP have consistently slower movements than healthy controls (Laird et al., 2014). While forward bend time only uniquely explained 1.5% of the variance in logRMDQ scores, a one SD increase in forward bend time gave a 66% increase in odds of significantly bothersome CLBP at one-year follow-up. Slower movement has been previously associated with greater fear of movement, and altered movement patterns (McGregor et al., 1997), reducing capacity to undertake daily activities (Crombez et al., 1999) and increasing pain related distress (Campbell et al., 2013, Crombez et al., 1999).

It is unknown whether membership of these different subgroups derived from pain responses following repeated bending may predict treatment outcomes. However, previous research has revealed that worsening (non-centralisation) of LBP +/- leg pain with repeated movements is predictive of greater pain and disability following interventions matched to the presence or absence of a directional preference in people with acute LBP (Werneke and Hart, 2001), but not those with sub-acute LBP (Schmidt et al., 2008). However, multidimensional profiles were not considered in these previous intervention studies. Further research is necessary to determine whether the CLBP subgroups in this research might be predictive of treatment outcomes matched to their multidimensional profiles, rather than pain responses to

movement alone. All of the profiling variables which differ between these subgroups may be modifiable, suggesting they may be appropriate targets for tailored interventions.

This subgrouping process would be easily incorporated into clinical assessments, and may motivate consideration of other interacting dimensions in their multidimensional profiles. For those with no increase in pain following repeated spinal bending, clinicians should consider assessing spinal loading individually-matched to the person's reported aggravating activities. Consideration of directional responses to movement, in combination with dominant factors from a multidimensional assessment have been used previously to guide rehabilitation in people with CLBP with promising early results (Vibe Fersum et al., 2013). Slower speed of movement may be considered by clinicians as prognostic of greater bothersomeness in people with CLBP, and may suggest that clinicians consider potential multidimensional influences upon the quality of the movement of an individual with CLBP (Hodges and Smeets, 2015). Maladaptive movement patterns, characterised by the adoption of postures and movements which may provoke and therefore maintain LBP, have been described and validated (O'Sullivan, 2005, Dankaerts and O'Sullivan, 2011). Consideration of such movement patterns may be appropriate additional factor when tailoring interventions.

8.5   Clinical Implications Of Multidimensional Profiling Variables From Other Dimensions

The clinical implications of multidimensional profiling variables from dimensions other than the tissue sensitivity, psychological and movement dimensions, which differed between subgroups in at least two of the subgrouping studies will now be considered.

8.5.1   Baseline pain intensity.

Pain intensity was significantly higher in the highest-scoring psychologically-derived cluster, consistent with previous cluster analyses (Viniol et al., 2013, Strong et al., 1995), and in the subgroup with increased pain following repeated forward and

backward spinal bending. This is similar to a clinically derived subgroup described by O'Sullivan et al. (2014) as having "disproportionate" pain responses to provocative movements and postures. However, differences in pain intensity between subgroups derived from either psychological questionnaire scores or pain responses following repeated movements did not reach the MCID of two-points (Salaffi et al., 2004).

Commonly adjusted for in prognostic modelling (Verkerk et al., 2013, Grotle et al., 2010, Costa et al., 2009), pain intensity at baseline was the strongest independent predictor of pain intensity. Baseline pain intensity was also in the final prognostic model for bothersomeness which may be a considered a summary of patient perception of symptoms, and correlates with pain intensity and disability (Dunn and Croft, 2005). As such a strong predictor, pain intensity may be an important interventional target, which contrasts with many intervention studies in which disability is the primary outcome (Hill et al., 2011, Bergbom et al., 2014, Verra et al., 2015). Subgroups with differing levels of pain intensity over time have been determined in people with CLBP (Macedo et al., 2014), but have not been the subject of tailored interventions. Pain may be a reflection of multiple, interacting mechanisms (Woolf and Mannion, 1999). Pharmacological interventions arguably target specific pain mechanisms. However, different forms of pharmacological analgesia generally have small treatment effects in homogeneous samples of people with CLBP (Chaparro et al., 2013, Urquhart et al., 2008, Roelofs et al., 2008), and have not been examined in subgroups with differing levels of pain intensity. Some interventions tailored towards CLBP subgroups derived from other dimensions have targeted mechanisms hypothesised to maintain higher pain intensity. For example, where altered movement patterns have been proposed to maintain ongoing pain possibly secondary to altered tissue loading (Hodges and Smeets, 2015), interventions have been tailored towards those movement patterns to attempt to reduce reported pain intensity (Sheeran et al., 2013, Kent et al., 2015, Vibe Fersum et al., 2013, Van Dillen et al., 2013, Henry et al., 2014).

8.5.2 Baseline disability.

Disability levels differed across psychologically-derived clusters, with a progressive increase in disability from psychologically-derived Cluster 1 (lower scores across all indicator variables) to Cluster 3 (higher scores across all indicator variables). The difference in disability levels between Clusters 1 and 3 is likely to be clinically important (Stratford et al., 1996), consistent with a previous cluster analysis (Strong et al., 1995). For subgroups with differing pain responses following repeated movements, statistically higher disability levels were seen in the FB and FB&BB subgroups, however, the differences between subgroups did not reach the MCID of five-points (Stratford et al., 1996). Baseline disability was also the strongest independent predictor of disability at one-year follow-up, consistent with a previous large (n=1760) prognostic study in prople with CLBP (Verkerk et al., 2013).

As a strong predictor, disability warrants targeted intervention. Once again, interventions tailored towards CLBP subgroups derived from other dimensions, for example fear-avoidance beliefs (Bergbom et al., 2014) or movement patterns (Sheeran et al., 2013), have targeted mechanisms hypothesised to maintain high levels of disability, generally with modest outcomes (Vollenbroek-Hutten M et al., 2004, Hill et al., 2011, Verra et al., 2015, Kent et al., 2015, Van Dillen et al., 2013, Henry et al., 2014).

The results of this thesis suggest higher psychological questionnaire scores and bidirectional pain responses following repeated spinal bending may be associated with higher baseline self-reported disability. Distorted perception of the low back region was also significantly different across both the psychologically-derived clusters and subgroups based upon pain responses following repeated movement, but not pain sensitivity clusters. This suggests perceptual distortion may influence disability in people with CLBP, possibly through alterations in motor behaviours (Hodges and Smeets, 2015).

While the cross-sectional nature of this research does not allow determination of whether these interactions are causative, premorbid negative psychological factors in particular may influence levels of disability (Simons et al., 2014).

8.5.3 Distorted body perception.

Distorted body perception in people with CLBP is a relatively recent consideration (Moseley, 2008, Flor et al., 1997), and has been proposed to influence pain perception through altered sensorimotor interactions (Hodges and Smeets, 2015)

The FreBAQ (Wand et al., 2014) questionnaire was used to assess altered low back perception in people with LBP. FreBAQ scores differed between the psychologically-derived clusters and subgroups based upon differing pain responses following repeated spinal bending, suggesting a relationship between body perception and psychological distress and pain responses to movement.

While FreBAQ scores differed in the psychological and movement subgroups, they were not prognostic of any outcome. The timeline for development of such perceptual changes is currently unknown. It may be that distorted perception occuring in the early stages of a disorder would be prognostic of poor outcomes, but this requires further investigation.

There have not been any studies examining whether FreBAQ scores, or other measures of distorted perception in people with CLBP, are predictive of treatment outcome. However, a recent systematic review highlighted limited evidence for treatments directed towards disturbances in perception, such as sensory discrimination training, graded motor imagery and mirror visual feedback (Daffada et al., 2015). Since the literature search for this review was completed, a number of small studies (n=25-30) (Wand et al., 2013, Trapp et al., 2015, Wälti et al., 2015), have suggested that sensory retraining may decrease pain intensity in people with CLBP, although in two of these studies this intervention was also combined with specific movement retraining. Visual feedback was also incorporated into the movement retraining interventions studied by Vibe Fersum et al. (2013) and Sheeran et al. (2013), both of which demonstrated significant improvements in pain and disability. Further investigation is therefore required to determine whether specific targeting of subjective disturbances in body perception may facilitate improved treatment outcomes.

8.6   Clinical Implications Of Prognostic Variables From Other Dimensions

Finally, prognostic variables from dimensions other than tissue sensitivity, psychological and movement, which were included in at least two of the final multivariable prognostic models will be considered.

8.6.1   Level of education.

Lower years in education was prognostic of higher pain intensity and bothersomeness. This is consistent with a previous study of people with acute LBP which showed lower educational levels were prognostic of greater pain and disability at 12-month follow-up (Costa et al., 2009). Educational status has not been previously examined as a prognostic variable for bothersomeness. Level of education only uniquely explained 3.4% of the variance in change in pain intensity at one-year follow-up. However, a one SD increase in years in education gave a 40% decrease in odds of significantly bothersome CLBP at this timepoint.

Lower years in education, may be associated with a number of factors which may adversely influence pain and bothersomeness in people with CLBP. These include manual occupations involving greater physical strain (Lacey et al., 2013, Hagen et al., 2006, Leclerc et al., 2009), higher psychological stress and more negative health behaviours (e.g. smoking) (Dionne et al., 2001), poorer general health (Chou R, 2010, Hayden et al., 2009, van der Heide et al., 2013); and possibly poorer health literacy (Briggs et al., 2010, Camerini and Schulz, 2015) and healthcare access (Meghani, 2011). Whether lower educational status is predictive of poor treatment outcomes has been inadequately examined (Dionne et al., 2001). While educational status is largely non-modifiable, it may be important for clinicians to consider an individual's health literacy when delivering an intervention (Briggs et al., 2010), and modify the intervention appropriately.

8.6.2   Punishing interactions with a significant other.

Greater punishing interactions with a significant other contributed to prognostic models for higher pain and disability. Such responses do not appear to have been

considered in prognostic models for people with CLBP previously. These findings are consistent with an earlier cross-sectional study showing greater pain and disability in those with punishing significant relationships (Boothby et al., 2004). Such punishing interactions may increase pain through altered central pain modulation, and associated increases in dependent and support seeking behaviours (Quartana et al., 2009) may increase disability. However, punishing interactions with a significant other only uniquely explained 1.6% of the variance in change in pain intensity, and 1.1% of the variance in change in logRMDQ scores at one-year follow-up. Whether punishing interactions with a significant other are predictive of outcome following specific treatments, is unclear. However, a narrative review of highly varied, predominantly behavioural, complex behavioural interventions targeting interactions with family members of chronic pain sufferers reveals that while they may improve psychological distress, they did not improve pain-related outcomes (Kerns and Otis, 2003).

8.6.3   The presence of leg pain.

Having some leg pain contributed signiificantly to prognostic models for improved GRC and lower bothersomeness. In contrast, a recent systematic review suggests that the presence of leg pain is consistently prognostic of worse outcomes compared to axial LBP only (Konstantinou et al., 2013). Those with some leg pain had approximately twice the odds of rating their GRC much or very much improved, and had a 58% decrease in the odds of having bothersome CLBP at follow-up. One previous study (Scheele et al., 2013) has included the presence leg pain in their prognostic model for participants rating themselves as strongly improved or completely recovered, in a cohort of over 55-year-olds with new onset LBP. It may be that if leg pain at baseline has improved at follow-up, greater improvement may be perceived, however, whether pain distribution had changed over the follow-up period was not assessed in this cohort.

8.6.4   Participating in exercise as an intervention.

Systematic reviews show that exercise improves pain and disability in people with CLBP (van Middelkoop et al., 2010), and reduces symptom recurrence (Choi et al.,

2010). This is consistent with reporting having participated in exercise as treatment being prognostic in this study of lower pain intensity and disability, and a GRC of much or very much improved. However, participating in exercise only uniquely explained 3.6% of the variance in change in pain intensity, and 2.8% of the variance in change in logRMDQ scores at one-year follow-up. Conversely, having participated in exercise gave 3.5 times the odds, and was the strongest predictor of a GRC of much or very much improved. This treatment grouping included all types of exercise, whether prescribed or self-directed, consistent with a review suggesting that no particular exercise type is superior to another (van Middelkoop et al., 2010). The prognosis associated with participating in exercise may therefore relate to general centrally-mediated opioid and non-opioid hypoalgesic mechanisms of exercise (Ellingson and Cook, 2013) and the positive impact of exercise upon self-efficacy, general health, pain catastrophising and activity engagement (Hodges and Smeets, 2015).

8.7   Dealing With The Complexity Of CLBP

Clinicians are faced with having to make sense of multiple interacting dimensions collected during the clinical examination. The differing multidimensional profiles in each of the subgrouping studies, prognostic factors and individual patterns of subgroup membership across all subgrouping studies revealed in this research highlight the complexity of CLBP faced by the clinician.

While many factors from multiple dimensions were included in the multidimensional profiling of subgroups and prognostic study, the results of the subgrouping studies and prognostic models suggest that the examination of certain factors may be more important for clinicians to incorporate into their overall decision-making processes, and possibly consider for the purposes of tailoring interventions. From the tissue sensitivity dimension, the presence of heightened pressure and / or thermal pain sensitivity may trigger clinicians to examine psychological, lifestyle, movement factors associated with this pain sensitivity. Screening and specific enquiry of the psychological dimension is likely to be important for determination of prognosis, particularly high scores for fear-

avoidance beliefs, pain catastrophising and endurance behaviours; and low scores for pain self-efficacy. Pain responses following repeated forward, or forward and backward bending may also act as a trigger for clinicians to examine time taken to complete movements, pain sensitivity, distorted body perception and psychological factors associated with these pain responses. Other prognostic factors for clinicians to consider, and potentially tailor interventions towards, include punishing interactions with a significant other, lower levels of education and high baseline pain and disability. Prognostic modelling also suggests that interventions should include exercise therapy. However, the high level of variability of the presentations in this research suggests that tailored interventions should consider the relative contributions of all relevant dimensions in any one individual.

Because of the high variability in individual patterns of subgroup membership across all subgrouping studies, it is unlikely that further examination of unidimensional subgrouping will capture the full complexity of CLBP, even if multidimensional profiling is conducted subsequently. Alternative methods for examining the multiple dimensions interacting in people with CLBP will be discussed below (see Future Research below).

High variability in CLBP presentations may also account for the generally poor outcomes in studies to date that have examined the effects of treatments matched to specific subgroups. No difference between matched and unmatched or control interventions have been found for subgroups based on the psychological dimension (Verra et al., 2015, Bergbom et al., 2014, Vollenbroek-Hutten M et al., 2004) and movement dimension (Petersen et al., 2002, Miller et al., 2005, Van Dillen et al., 2013, Henry et al., 2014), or treatment-based subgroups (Apeldoorn et al., 2012). One small study (n=49), using movement retraining based upon the methods described by O'Sullivan (2000), showed significant improvements in pain and disability compared to a general postural intervention (Sheeran et al., 2013), however, participants were only followed-up at the end of a four-week home programme. A larger study (n=112) compared movement retraining with biofeedback to usual medical / physiotherapy care , and showed significant improvements for the intervention group in pain and disability (Kent et al., 2015),

however, the difference in pain intensity levels did not reach the MCID of two-points (Salaffi et al., 2004).

Overall these studies suggest that unidimenional subgrouping, with the possible exception of those based upon the movement dimension, has not afforded improved treatment outcomes for people with CLBP to date. This may reflect that interventions based upon these CS do not consider the relative contributions of the multiple dimensions associated with CLBP, and do not therefore afford appropriately individualised care.

The high level of variability in the presentations of people with CLBP shown by this research may facilitate a reconceptualisation of the disorder for both clinicians and sufferers, from a simplistic, linear, cause-effect hypothesis, to a complex, emergent disorder where relative contributions of multiple different dimensions influence an individual's presentation, likely to be in constant flux. This may facilitate an understanding of how diverse factors such as stressful life events, fear-avoidance beliefs, activity levels, comorbidities or pain sensitivity can interact in a person's presentation. This is consistent with the concept of allostasis - involving the individual's attempts at adapt to such multidimensional, real or perceived stressors. Increasing allostatic load may subsequently influence chronic pain via altered cortical structure and function, neuroendocrine, inflammatory / immune, and autonomic responses (Kozlowska, 2013, Gatchel et al., 2007, McEwen and Kalia, 2010, McEwen and Gianaros, 2010). This may subsequently allow both clinicians and patients to consider multiple dimensions important to management of the condition.

This variability highlights the need for a flexible multidimensional framework (O'Sullivan et al., 2015, O'Sullivan, 2012, Vibe Fersum et al., 2013) such as that outlined in the case reports. Certain aspects of this framework have been previously validated (Vibe Fersum et al., 2009, Dankaerts and O'Sullivan, 2011), including profiling of two subgroups clinically-derived from such a flexible multidimensional framework allowing clinicians to consider relative contributions from multiple interacting dimensions associated with CLBP (O'Sullivan et al., 2014). However, in

each of these studies subgroups were derived-based upon clinician judgement, rather than the statistical subgrouping methods undertaken in this thesis. The studies in this thesis lend further support for this flexible multidimensional framework approach.

As a possible overarching intervention study, the randomised controlled trial by Vibe Fersum et al. (2013) (n=121) allowed treatment in the intervention group to be directed by findings from each individual's multidimensional assessment. The intervention targeted psychological, movement and lifestyle dimensions in an individualised manner, while considering tissue sensitivity. As well as showing significantly greater improvements in pain and disability compared to a group receiving manual therapy and exercise, participants receiving the targeted intervention showed improvements in fear-avoidance beliefs, depression and anxiety. However, the mediators of the positive outcome in this study are unknown and require further examination, and these findings have yet to be replicated.

8.8   Strengths And Limitations

8.8.1   Strengths.

This research involved a large cohort of people with CLBP with a wide range of pain intensity and disability levels, mostly recruited from the local community, facilitating generalisability to the broader population. The range of multidimensional, clinically-applicable data collected is the broadest to date in any one cohort. This data was used to statistically derive subgroups and their multidimensional profiles, allowing hypothesis generation regarding clinical implications and underlying pain mechanisms. This is one of the largest published subgrouping studies in people with CLBP, and the only study to have derived subgroups in the same cohort based upon three different dimensions. This approach, and examination of subsequent individual patterns of subgroup membership across all subgrouping studies is novel, highlights the variability of presentations within the cohort, and facilitates an understanding of the complexity of CLBP.

8.8.2 Limitations.

This study involved a cohort with CLBP and as such results cannot be extrapolated to people with acute / subacute LBP. Although larger than many previous subgrouping studies, the sample size may be considered the most notable limitation of this research. The original intention of this thesis was to identify subgroups, using LCA, from a range of multidimensional indicator variables. However, despite achieving a minimum acceptable sample size (Nylund et al., 2007, Swanson et al., 2012) LCA was unsuccessful in identifying a global solution, possibly due to the complexity of the data set. Having a significantly larger sample size would have afforded greater power which may have allowed this approach to derive an overarching multidimensional model. However, this was not feasible within the timescale and budget available, and the exact size of the sample necessary for determining models of such complexity is unknown. It was therefore deemed appropriate to examine the data set by deriving subgroups of people with different profiles on three different dimensions separately, and then profile these subgroups on broader multidimensional data. It is acknowledged that the selection of these three dimensions, based upon the potential to facilitate targeted interventions and clinical modifiability, involved a level of judgement. However, examining the data in this manner afforded a different viewpoint on this cohort, highlighting the high level of variability in individual patterns of subgroup membership across all subgrouping studies within the same cohort.

Clinical measures utilised in this study were not necessarily gold standards (e.g. IPAQ rather than actigraphy). Use of a battery of gold standard measurements may have led to the capture of even greater complexity within the presentations of our CLBP cohort. This may have further reduced the likelihood of derivation of multidimensional subgroups, as per the initial intent of the latent class analyses. However, it may have afforded greater detail to multidimensional profiling of the derived unidimensional subgroups. It is unlikely that such broad multidimensional data could have been collected had gold standard measurements been utilised throughout, as costs and participant burden would have become prohibitive. Ideally subgroup derivation may also have included examination of genetics / epigenetics,

brain imaging, electromyography and / or motion analysis, participant interactions with healthcare systems / practitioners, cultural or broader social influences, underlying pathophysiology and other helpful psychological factors (e.g. resilience). This may have led to derivation of different subgroups and multidimensional profiles, possibly explaining a greater proportion of variance in prognosis. However, such investigations were excluded for the aforementioned pragmatic reasons.

A single question (Wai et al., 2009) determined the presence of dominant axial CLBP. This minimised the likelihood of inclusion of participants who primarily had radiculopathy. However, it is acknowledged there was potential, that people with some degree of radiculopathy may have been present in those 11.9% of participants who rated their pain as 60% CLBP (40% leg pain).

One inclusion criterion was that participants must score ≥ five-points on the RMDQ. There may be people with significant levels of pain intensity, but disability levels which fell below this inclusion criterion, who were subsequently excluded. Their inclusion may have influenced subgroup membership and prognostic modelling. At one-year follow-up 9.5% of participants did not respond. These participants reported significantly higher baseline disability than those responding at follow-up, so the follow-up sample might not be representative of the entire spectrum of disability.

During profiling of the different subgroups the multiple comparisons undertaken in this research increase the possibility of type I error (Armstrong, 2014). However, the subgrouping and multidimensional profiling in this research was exploratory in nature. It was therefore deemed more appropriate to maintain p-values such that there may be a greater chance of a type I error, but less chance of a type II error (Armstrong, 2014). As such, no correction for multiple comparisons was undertaken.

8.9   Future Research

The overall results of this thesis suggest that continued attempts to determine uni-dimensional subgroups may be futile for the assessment and management of

people with CLBP, only ever offering a limited reflection of the disorder. Had subgrouping been performed on data from a fourth dimension, and individual patterns of subgroup membership across four subgrouping studies been examined, even greater variability may have been revealed. Also, measurement of data for the multiple dimensions associated with CLBP was only undertaken at a single time-point. Alternate methodologies may allow determination of how CLBP emerges as a disorder through the relative contributions of multiple interacting dimensions over time. Firstly, a number of individual cases could be examined in a similar manner to the four cases presented in Chapter 3 across repeated time-points. Ideally this would commence shortly after pain onset and be repeated at four- to six-week, three-month, six-month and one-year follow-up periods to capture the potential variation in rates of change in people with LBP (Axén and Leboeuf-Yde, 2013, Costa et al., 2012). It may also be appropriate to add a further examination at a later time-point, e.g. three-year follow-up, in consideration of the potential long-term physiological changes associated with chronic pain states (Simons et al., 2014, Borsook and Kalso, 2013). An alternative would be to use cluster analysis at multiple time-points within the same cohort, and subsequently use log linear analysis to examine the changing interactions over time (Griffiths and Byrne, 1998). Finally, examination of big data (very large data sets with complex structures) may be used to determine causality and associations between multidimensional data and outcomes. However, such analyses are currently likely to be beyond the expertise, equipment and financial capacity of most research institutions (Wang and Krishnan, 2014) without pooling of data.

The ultimate goal of this research was to offer some guidance for targeted intervention for people with CLBP, to facilitate improved treatment outcomes. The individual patterns of subgroup membership across all subgrouping studies suggest the relative contributions of each dimension may be highly variable. This highlights the need for consideration of individualised models of care. While there is early evidence that management of people with CLBP guided by a multidimensional examination framework is more effective than usual physiotherapy care (manual therapy and exercise) (Vibe Fersum et al., 2013), this requires further replication.

8.10   Conclusion

The series of studies presented within this thesis, further the understanding of CLBP as a complex, multidimensional disorder.

The initial aim was achieved by examining four individual clinical cases of people with axial CLBP with contrasting multidimensional profiles, which highlighted the multidimensional complexity of the disorder and the limitations of existing CLBP CS.

The second aim was to use statistical subgrouping techniques and standardised clinically-applicable measures from multiple dimensions to explore the existence of subgroups within a large cohort with axial CLBP. Initial attempts to derive subgroups using combined measures from all dimensions failed due to statistical estimation problems. Subsequently this research derived subgroups of people with different clinical profiles on three different dimensions: pain sensitivity, psychological questionnaire scores and pain responses following repeated spinal bending.

The third aim of profiling the different subgroups across multiple dimensions was achieved, highlighting the heterogeneity of CLBP, and allowing postulation of the clinical implications and pain mechanisms underlying the different profiles.

Examination of individual patterns of subgroup membership across all three subgrouping studies revealed high levels of variability, suggesting that current subgrouping approaches may only offer a limited reflection of the complexity of CLBP and limit the use of subgrouping to target treatment.

The final aim of determining whether multidimensional baseline data, including subgroup membership, were prognostic of outcome at one year follow-up was also achieved. Multivariable prognostic models were derived for pain intensity, disability, global rating of change and bothersomeness. The derived subgroups were not retained in any of the prognostic models suggesting subgroups derived from a single dimension fail to capture the complexity of CLBP. This is supported by the finding that factors from multiple dimensions (pain intensity, disability, age, presence of leg pain, years in education, cognitive factors, endurance behaviours, forward bend time, punishing interactions with a significant other, exercise or injection(s) as

treatment) were retained in the final multivariable prognostic models for this cohort.

Together these studies suggest that the examination of an individual with CLBP needs to be flexible, allowing for consideration of the relative contributions of multiple interacting dimensions associated with the disorder. With further examination of the multidimensional interactions in people with CLBP, and development of strategies for affording them targeted, individualised care, further improvements in treatment outcomes may be possible.

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Chapter Nine - Appendices

9.1 Appendix 1 - Ethical Procedures, Including Human Research Ethics Committee Approval Letters, Participant Information Sheet And Consent Sheet

This research was conducted in accordance with the NHMRC National Statement on Ethical Conduct in Research Involving Humans (National Health and Medical Research Council, 2007), and the Declaration of Helsinki (World Medical Association, 2013).

All study procedures were approved by the following ethics committees:

Curtin University Human Research Ethics Committee (Approval number: HR112 / 2012)

Royal Perth Hospital Human Research Ethics Committee (Approval number: EC 2012 / 148)

Fremantle Hospital Human Research Ethics Committee (Approval number: AR / 13 / 1)

Sir Charles Gairdner Hospital Human Research Ethics Committee (Approval number: 2012-197) (See appended copies of approval letters).

For each of the Human Research Ethics Committees different headed paper was utilised for the participant information sheets and consent forms (Copies appended).

All participants received a participant information sheet, written in plain English, detailing the purpose of the research, the methods, the participant burden (including time, risks, inconveniences, discomforts and possible outcomes (including likelihood and form of publication of results)).

Validated short-form questionnaires and individual questions were used where possible. Care was taken not to unduly duplicate information assessed by

questionnaires. Participants completed the questionnaires at their own convenience at home.

Participants were advised that they may experience short-lived discomfort during some physical tests, similar to that experienced during attendance for a routine clinical physiotherapy examination. As it was anticipated that some participants may halt the movement task prematurely due to pain, all participants were instructed before starting this movement that they may stop at any time.

The Depression Anxiety Stress scales (Lovibond and Lovibond, 1995) collect information regarding depressive and anxious symptoms. For participants whose score was rated as moderate or higher (depression subscale 14, anxiety subscale 10), a discussion took take place between the investigator and the participant to ascertain whether referral to the participant's general practitioner (with their consent), was appropriate, for assessment of their mental health status.

Participants gave written informed consent prior to physical testing and were made aware that they may withdraw consent at any time without prejudice.

After testing, participants were provided with verbal feedback of their results compared to published normative data or questionnaire cut-off scores where available, and were given the opportunity to ask questions. After finalisation of analysis of subgroups and prognostic models participants were sent a written summary of the research, and invited to attend a short presentation of the results at Curtin University.

Subjects received free parking at the University for the duration of their attendance.

9.1.1   References.

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National Health And Medical Research Council 2007. *National Statement on Ethical Conduct in Human Research.* Canberra: National Health and Medical Research Council.

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Memorandum

To	Professor Peter O'Sullivan, School of Physiotherapy
From	Professor Stephan Millett, Chair, Human Research Ethics Committee
Subject	Protocol Approval HR 112/2012
Date	24 October 2012
Copy	Mr Martin Rabey School of Physiotherapy Dr. Darren Beales School of Physiotherapy Dr. Anne Smith School of Physiotherapy Assoc. Prof. Helen Slater School of Physiotherapy

Thank you for providing the additional information for the project titled *"Multidimensional patient profiles in chronic non-specific axial low back pain - classification and predictors of outcome"*. The information you have provided has satisfactorily addressed the queries raised by the Committee. Your application is now **approved**.

- You have ethics clearance to undertake the research as stated in your proposal.
- The approval number for your project is HR **112/2012**. *Please quote this number in any future correspondence.*
- Approval of this project is for a period of twelve months **23-10-2012** to **23-10-2013**. To renew this approval a completed Form B (attached) must be submitted before the expiry date **23-10-2013**.
- Please amend the following before commencing research:
    i) Amend the third line of Participant Information Consent Form, change 'in' to 'is' (*"...is not clear"*).

It is your responsibility, as the researcher, to meet the conditions outlined above and to retain the necessary records demonstrating that these have been completed.

Applicants should note the following:

It is the policy of the HREC to conduct random audits on a percentage of approved projects. These audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.

The attached FORM B should be completed and returned to the Secretary, HREC, C/- Office of Research & Development:
When the project has finished, or
- If at any time during the twelve months changes/amendments occur, or
- If a serious or unexpected adverse event occurs, or
- 14 days prior to the expiry date if renewal is required.
- An application for renewal may be made with a Form B three years running, after which a new application form (Form A), providing comprehensive details, must be submitted.

Yours sincerely

Professor Stephan Millett
Chair Human Research Ethics Committee

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HUMAN RESEARCH ETHICS COMMITTEE

Ref: EC 2012-148   12 December 2012
(This number must be quoted on all correspondence)

Martin Rabey
Physiotherapy Department
Royal Perth Hospital

Dear Martin

**EC 2012/148 Multidimensional Patient Profiles in Chronic Non-Specific Axial Low Back Pain –
Classification and Predictors of Outcome**

Thank you for submitting the above application which was considered at the 26 September 2012 meeting of the
Ethics Committee. I am pleased to advise that the above study is now **APPROVED**.

The following general conditions apply to all approvals by this Committee, and starting a trial or research project
following the issue of ethics approval will be deemed to be an acceptance of them by all investigators:

1. The submission of an application for Ethics Committee approval will be deemed to indicate that the
   investigator and any sponsor recognises the Committee as a registered (with AHEC) Health Research Ethics
   Committee and that it complies in all respects with the National Statement on Ethical Conduct Research
   Involving Humans and all other national and international ethical requirements. **The Committee will not
   enter into further correspondence on this point.**

2. All income arising from the study must be lodged in a hospital special purposes account. Performance of a
   clinical trial for a sponsor is a service for tax purposes and all GST obligations must be met.

3. The investigator will report adverse events accompanied by a statement as to whether or not the trial should
   continue. The Committee reserves the right to not receive reports whose complexity or level of detail
   requires the expenditure of unreasonable time and effort. The Committee receives voluminous paperwork
   relating to adverse event reporting. From time to time the Committee chairman may require these reports
   to be summarised and approval is granted subject to the agreement of the investigator that he or she will
   prepare such a summary on request.

4. The Committee has decided that, as the responsibility for the conduct of trials lies with the investigator, all
   correspondence should be signed by the investigator.

5. All trial drugs must be dispensed by the Pharmacy Department. A fee is levied for this service and
   investigators must regard this fee as an item requiring a budget allocation. Alternatively, if a sponsor
   agrees, separate direct funding of pharmacy services may be undertaken. There are provisions for this fee
   to be waived for locally-inspired unfunded studies not having an external sponsor.

6. Though state institutions are outside the jurisdiction of the Privacy Act and related legislation, the
   Committee will assume that the privacy provisions of that Act will be the minimum standards applying
   during the conduct of a trial at Royal Perth Hospital. Traditional standards of patient confidentiality will
   apply.

7. The Committee will not acknowledge trial communications as a matter of course, unless they relate to a
   matter requiring Committee approval. Evidence of dispatch of a letter will be deemed to be evidence of
   receipt. This rule may be waived at the Committee's discretion on provision of a *pro forma* receipt by the
   investigator for the Chairman's signature and return. However, trivial correspondence (as judged by the
   Committee) will not be acknowledged even if a *pro forma* receipt is provided. Where an investigator
   requests written approval or written record of a matter for special purposes (say at the request of a
   sponsor), the investigator should prepare the required letter for the chairman's signature rather than expect
   the Committee secretary to prepare it. This mechanism increases the probability that the trial details in the
   letter are correct.

8. The Committee will provide the names and representative affiliation of members on request, but will not
   provide personal details or voting records.

9. A brief annual report on each project approved will be required at the end of each fiscal year, in default of
   which approval for the study may be suspended. Ethics approvals at RPH do not carry an expiry date so the
   annual report is an important part of Ethics Committee procedure.

The RPH Human Research Ethics Committee (HREC) is constituted and operates in accordance with NH&MRC Guidelines.

Ethics Office Level 5 Colonial House, Royal Perth Hospital, GPO Box X2213 Perth WA 6001
Tel (08) 9224 2292 | Fax (08) 9224 3668 | Email rph.hrec@health.wa.gov.au   Page 1 of 2

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10. The Committee has the authority to audit the conduct of any trial without notice. Exercise of this authority will only be considered if there are grounds to believe that some irregularity has occurred or if a complaint is received from a third party, or the Committee wishes to undertake an audit for QA purposes.

11. Complaints relating to the conduct of a clinical trial should be directed to the Chairman and will be promptly investigated. Complaints about the Ethics Committee decisions or policies that cannot be resolved by discussion with the Chairman or about any actions of a particular member including the Chairman, should be directed to the Director of Clinical Services. Only written complaints (not e-mail) will be accepted for investigation.

Investigators of sponsored studies are advised to draw the above conditions to the attention of the sponsor. Investigators are reminded that records of consent or authorisation for participation in special studies (including clinical trials) form part of the Acute Hospital Patient Record and should be stored with that record in accordance with the WA Health *Patient Information Retention and Disposal Schedule (Version 2) 2000*. A copy of the 'Patient Information Sheet' should also be included in the medical records as part of informed consent documentation.

Yours sincerely

PROF FRANK M VAN BOCKXMEER
Chairman, Royal Perth Hospital Ethics Committee

The RPH Human Research Ethics Committee (HREC) is constituted and operates in accordance with NH&MRC Guidelines.

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Government of Western Australia
Department of Health

South Metropolitan Area Health Service

7 January 2013

Mr Martin Rabey
Physiotherapy Department
Royal Perth Hospital

Dear Martin,

Re: Multidimensional Patient Profiles In Chronic Non-Specific Axial Low Back Pain – Classification And Predictors Of Outcome

I am writing with reference to your letter dated 7 December 2012, enclosing an application to ask practitioners within the physiotherapy departments at Fremantle and Bentley Hospitals, to assist with recruitment of the above study access. I understand that this will require staff identifying potential participants according to the inclusion and exclusion criteria, following which clinicians would simply give the pre-printed contact details of the principle investigator to the subjects. I note that the study has been approved by Royal Perth Hospital Human Research Ethics Committee (HREC) and that the relevant Directors of Clinical Services have given approval at both health sites.

I have perused the Access Request Form and I am happy to approve access for you to advertise for recruitment for of the above study.

This project will not be registered on the SMHS database, however, you will be allocated a reference number for this study, which will be forwarded to you by the HREC Office following the next HREC meeting (5 February 2013). You will be required to quote this reference number should it be necessary for you to correspond with the Hospital regarding the study in the future.

Yours sincerely

DR DAVID BLYTHE
EXECUTIVE DIRECTOR
FREMANTLE HOSPITAL & HEALTH SERVICE

Human Research Ethics Committee
c/- Fremantle Hospital and Health Service
Alma Street Fremantle Western Australia 6160
Postal Address: PO Box 480 Fremantle Western Australia 6959
Telephone (08) 9431 2929 Fax (08) 9431 3930
wa.gov.au

457_ARF.doc

Government of Western Australia
Department of Health

Ethics Ref: 2012-197 approval SCGOPHCG
Ext 2999

Sir Ch.
Gairdner Y.

9 April 2013

Dr Martin Rabey
36/8 Currie Street
JOLIMONT WA 6014

Dear Dr Rabey

APPLICATION TO CONDUCT HUMAN RESEARCH AT SCGOPHCG:
TRIAL No: 2012-197
TRIAL TITLE: Multidimensional Patient Profiles In Chronic Non-Specific Axial Low Back Pain – Classification And Predictors Of Outcome.

On behalf of the Sir Charles Gairdner and Osborne Park Health Care Group Executive (SCGOPHCG) I give approval to conduct your research project at Sir Charles Gairdner Hospital based on the favourable reviews provided to me by Research Governance and the Sir Charles Gairdner Group Human Research Ethics Committee. This approval is granted until 9 April 2016, and on the basis of compliance with all requirements laid out in your application and with the provision of reports as required by the Research Governance and the approving HREC in giving their favourable opinion (attached).

The responsibility for the conduct of this study remains with you as the Principal Site Investigator. You must notify the HREC Office of any relevant issues arising during the conduct of the study that may affect continued favourable opinions by the hospital or by an HREC.

Please quote Study number 2012-197 on all correspondence associated with this study.

Yours sincerely

Dr Robyn Lawrence
EXECUTIVE DIRECTOR
SIR CHARLES GAIRDNER AND
OSBORNE PARK HEALTH CARE GROUP

Sir Charles Gairdner Group Human Research Ethics Committee, Level 2 A Block, Hospital Ave, Nedlands, WA 6009
Telephone (08) 9346 2999 Fax (08) 9346 3307 ABN: 13 993 250 709
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Sir Charles Gairdner Group (SCGG)
Human Research Ethics Committee (HREC) Approval Sir Charles Gairdner Hospital

DETAILS OF STUDY

SCGG HREC No:	2012-197
Site Investigator:	Dr Martin Rabey
Title:	Multidimensional Patient Profiles In Chronic Non-Specific Axial Low Back Pain – Classification And Predictors Of Outcome.
Lead HREC:	Royal Perth Hospital Ethics Committee
Lead HREC No:	2012/148
Meeting Date:	HREC 18 April 2013

This trial will be tabled at the Human Research Ethic Committee Meeting on the above date

OUTCOME

The following documents are endorsed:

- Protocol
- Participant Information Sheet and Consent Form, version 1 dated 4 April 2013

This trial has been approved under the Reciprocal Agreement with Royal Perth Hospital Ethics Committee (the Lead HREC) in accordance with the Committee's Terms of Reference and Standard Operating Procedures. These documents outline the delegated authority I hold to review and approve this submission.

JENNY WESTGARTH-TAYLOR	Westgorth Taylor	9-4-13
Name	Signature	Date

The SCGG HREC is registered with the Australian Health Ethics Committee and operated according to the NHMRC National Statement on Ethical Conduct in Human Research

It is the responsibility and obligation of the researcher to advise the HREC of any departure from the original protocol that could impact on the ethical approval of the study. Please note that the attachments entitled 'Adverse Event Reporting for Clinical Trials' and 'Terms of Approval' forms part of this approval. Under these reporting guidelines you are required to submit formal notice of any changes to documentation, relevant information arising out of ongoing safety monitoring and annual reports on the ethical aspects of your study as well as the approval from the approving Lead HREC. An annual report form for your study will be posted to you several weeks in advance of the anniversary of the project's approval date.

As the responsibility for the conduct of the trial lies with you as the investigator, you should sign all communications to the committee.

Institutional approval must be obtained before the above trial can commence at any site within WA Health.

Sir Charles Gairdner Group Human Research Ethics Committee, Level 2 A Block, Hospital Ave, Nedlands, WA 6009
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email HREC.SCGH@health.wa.gov.au Website www.scgh.health.wa.gov.au

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PARTICIPANT INFORMATION SHEET

Low Back Pain: Identifying Factors Associated With Persistent Low Back Pain

Principal Investigator: Martin Rabey

Project Supervisor: Professor Peter O'Sullivan

Co-Supervisors: Dr. Darren Beales, Dr. Anne Smith, Associate Professor Helen Slater

Purpose of Research: Back pain can come from strained muscles or sprained joints. These usually heal and then the pain gets better. However, in some people back pain can carry on. This is called persistent or chronic back pain. It is a difficult problem and why some people have ongoing pain is not clear. There is not a strong link between what we see on x-rays or scans and the pain people feel. People with persistent pain often have other problems like low mood, fear of moving in certain ways, or worries about work.

This research is to try to increase what we know about the complex mix of factors involved in persistent back pain. We need to study people with persistent low back pain and see how these factors interact. If we study a lot of people with back pain, we may be able to identify different groups. We will measure many different factors in 300 people and then look at this information. We are also interested in any treatment people have for their back pain in the year after you join the study. So one year later we will contact you to see if your pain has changed, and find out what treatments you had. You can have any treatment you like during this time.

Your role: We would like you to be a participant in our research. We need to measure different factors to do with your pain. The study has 3 parts:

Part 1 involves you completing some questions at home. It takes 30-40 minutes.

Part 2 involves a visit to Curtin University for some tests of different sensations (pressure, touch, heat and cold). This takes 60-90 minutes.

Part 3 involves completing some more questions one year later. This takes 10 minutes.

Part 1: We will give you some questions to complete in your own time. They ask about your pain, how it makes you feel, and how it affects your work and hobbies. If you lose concentration you can take a break and finish the questions later. Some questions ask if you feel "low or down" or anxious. Depending on your response, we might send a letter to your doctor to make sure you get the best care for your pain problem. We will inform you if we send a letter.

Part 2: We will arrange for you to come to the School of Physiotherapy at Curtin University, Bentley. We will conduct some sensory (e.g.; touch, pressure) tests with you. We will ask you to lie on your tummy to test these sensations on your back and your wrist. We test the wrist because you have no pain there.

These are the sensation tests:

1)   Touch: We lightly touch the skin in one place or two places. We ask you how many places you felt.

2)   Touch: Using plastic "hairs" we touch your skin and ask if you can feel it. We will also repeatedly touch your skin with the "hairs" and see if you feel any pain.

3)   Pressure: Using a pencil, a make-up brush, a toothpick, and a tuning fork, we will see if you can feel the pencil, the brushing, the toothpick and the fork's vibrations. We will ask whether these cause any pain.

4)   Pressure: Using a special device we will find the point at which pressure changes to pain. The test stops the moment you feel pain.

5)   Heat/cold: Using another device we will find the point at which hot and cold becomes painful. Each test stops the moment you feel pain.

6)   Body's own pain control: Tests 4 and 5 are combined to see how effective your body's own pain control is. We will put the warm probe on your wrist. Then we measure how much discomfort you feel when we put pressure to your back. This lasts about one minute.

7)   We will then ask you to lie still and focus your attention on your back pain for one minute. We will measure if focusing changes your pain.

You may feel some discomfort during these last two tests. This should not last long. You can stop any time you wish.

Finally we will ask you to do some movements. You will be asked to try 20 forward bends and 20 backward bends. If your pain gets too strong you may stop at any time. During the movements video cameras will record how you move. We will ask you if your pain changes as you move.

Part 3: One year later we will send you a few questions in the mail. You complete them and mail them back to us. The questions ask about your pain and the treatments you have had.

Risks and Discomforts: You may feel some discomfort or pain during some tests. This is similar to what you might feel if you went to see your doctor or physiotherapist for your back pain, and they asked you to move your back and pressed to see where it hurts. Any increase in pain should settle down quickly once we have finished. If any tests are too painful you can tell the researcher and stop the tests. We will ask you some questions about your mood or your feelings.

Benefits: After your visit to the School of Physiotherapy we will tell you about your results. When we have all of the results we will telling you about the outcomes. We will hold a talk, which you can attend, where we discuss the results. The aim of the research is to improve our understanding of back pain. This may help find better treatments for back pain in time.

Confidentiality: We keep your details confidential by giving you an identification number. Your name will not be on any questionnaires or record sheets. It will only be on the consent form. All forms and video tapes will be stored in a locked cabinet in the School of Physiotherapy. Information on computer will be protected by a password. Only the researchers will have access to the information. Information will be kept for seven years after we have published the results.

Refusal or Withdrawal: We ask you to sign a consent form. This says that you agree to take part in the research. Whether you take part in the research or not is up to you. You may refuse to ever be involved in the research. You may withdraw your consent whenever you like, without prejudice. Please ask any questions before signing the consent form.

Further Information: If you would like more information please contact Martin Rabey at: School of Physiotherapy, Curtin University, Kent St., Bentley, Western Australia 6102; Tel: 0487007116; e-mail: martin.rabey@postgrad.curtin.edu.au.

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR112/2012). The Committee is composed of members of the public, academics, lawyers, doctors and pastoral carers. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University, GPO Box U1987, Perth 6845, or by telephoning 9266 9223 or by e-mailing hrec@curtin.edu.au.

CONSENT SHEET

This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number 112/2012).

• I understand the purpose and procedures of the study.

• I have been provided with the participant information sheet.

• I understand that the procedure itself may not benefit me.

• I understand that my involvement is voluntary and I can withdraw at any time without problem.

• I understand that a letter will be sent to my family doctor if I score highly on the questionnaire concerned with anxiety or depression.

• I understand that no personal identifying information like my name and address will be used and that all information will be securely stored for 7 years before being destroyed.

• I have been given the opportunity to ask questions.

• I agree to participate in the study outlined to me.

Signature   Date

Witness Signature   Date

9.2 Appendix 2 – Participant Recruitment, Missing Data Management And Baseline Descriptive Statistics

9.2.1 Participant recruitment.

The flow of participants through this research is described in Figure 1.
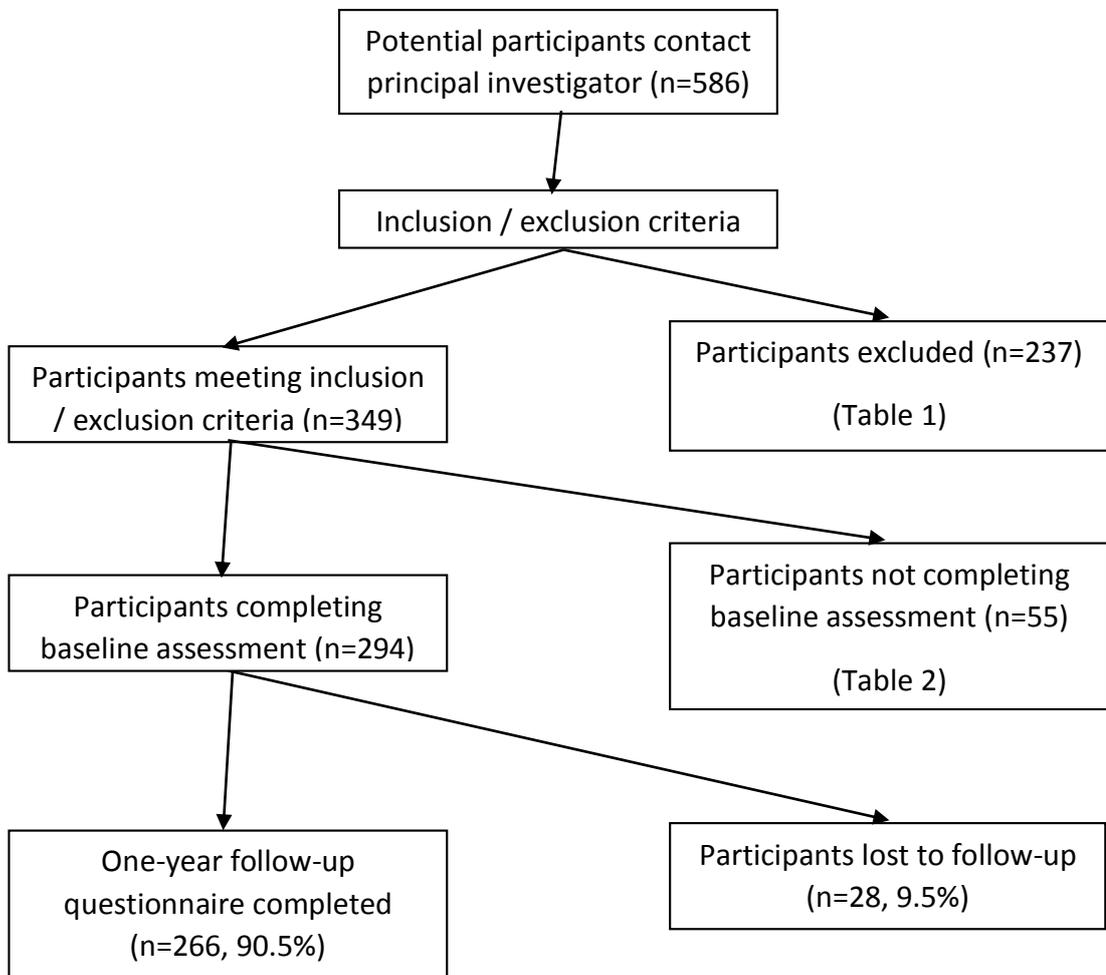
Figure 1. Participant Flowchart

9.2.2 Descriptive statistics.

Descriptive statistics for excluded participants (n=237), eligible participants who did not complete the baseline assessment (n=55), and all participants for whom full baseline data was collected (n=294) are detailed in Tables 1-3.

All data analysis was undertaken using Stata 13.1 (Statacorp, Texas, USA).

Table 1.

Baseline Descriptive Statistics for Demographic Data for Excluded Participants (n=237)

Demographic Variable	Summary Statistic (n=237)
Age, years	
median (IQR)	51 (34,65)
(min, max)	(19,88)
Female	
n (%)[1]	126 (55.5)
Reason for Exclusion	
n (%)	
Low RMDQ Score	130 (54.9)
Age >70 Years	42 (17.7)
Leg Pain > Back Pain	28 (11.8)
Bilateral Wrist Pain	23 (9.7)
Serious Spinal	
Pathology	8 (3.4)
Low Pain Intensity	6 (2.5)

Note. [1] missing in 10 cases

Table 2.

Baseline Descriptive Statistics for Demographic Data for Eligible Participants who did not Complete Baseline Assessment (n=55)

Demographic Variable	Summary Statistic (n=55)
Age, years	
median (IQR)	48 (31,63)
(min, max)	(19,70)
Female	
n (%)[1]	29 (61.7)
Pain Intensity (NRS)	
mean (SD)	6.1 (1.8)
(min, max)	(2,10)
RMDQ Score	
median (IQR)	9 (7,15)
(min, max)	(5,22)
Percentage LBP (versus Low Back Related Leg Pain)	
n (%)	
100%	26 (47.3)
80%	24 (43.6)
60%	5 (9.1)
Stage Completed	
n (%)	
Inclusion Checklist	50 (90.9)
Questionnaire	5 (9.1)

Note. [1] missing in eight cases

9.2.3   Missing data management.

Management of missing data will be described for those participants who completed all baseline data collection. The number of participants coded a missing is given in Table 3 showing baseline descriptive statistics. The following protocol was followed:

1) Determine whether the original manuscript describing the questionnaire / examination procedure detailed methods for managing missing data. If the original paper did describe the management of missing data this was undertaken as suggested in the original manuscript (e.g. IPAQ). If there was no detailed information as to how to deal with missing data the following steps were undertaken.

2) Participants with two or more missing values in a particular questionnaire were coded as missing.

3) For participants with one missing value:

   i)   If the questionnaire (or subscale) score is reported as a mean of all values (e.g. MAAS), the mean was calculated with one less value entered.

   ii) If the questionnaire (or subscale) score is reported as a total score (e.g. FreBAQ), the mean of the completed values was imputed to give the total score

4) If answers to single questions were missing these were coded as missing.

Exceptions to this protocol were as follows:

Pittsburgh Sleep Quality Index.
Five participants had two missing values and were coded as missing. Twelve participants had one missing value. Participants that were missing values for the answers to questions one or four were coded as missing as omission of these answers means that it is impossible to generate the total Pittsburgh Sleep Quality Index score. For participants who had one missing value from the remaining

questions that give a score from zero to three, the mean of this type of question was calculated and imputed.

Conditioned pain modulation.

In 17 participants it was not possible to achieve a baseline test stimulus, rated by the participant as having a pain intensity of 6/10 on an NRS. Therefore no test stimulus could be determined, and the CPM protocol could not be completed. These data were therefore coded as missing.

Table 3.

Baseline Descriptive Statistics for Participants who Completed Baseline Assessment (n=294)

Variable	n	Summary Statistic
Demographics		
Age median (IQR) (min, max)	294	50 (38, 60) (18, 70)
Female n (%)	294	168 (57.1)
Pain Characteristics		
Baseline pain intensity (NRS) mean (SD) (min, max)	294	5.8 (1.9) (2, 10)
Baseline disability (RMDQ) median (IQR) (min, max)	294	9 (6, 13) (5,24)
Duration of CLBP (months) median (IQR) (min, max)	290	120 (36, 240) (3, 720)
100% of pain in low back region n (%)	294	147 (50.0)
Aggravated by activity (StEP) n (%)	293	252 (86.0)
Aggravated by position (StEP) n (%)	293	240 (81.9)
Baseline bothersomeness (very / extremely bothersome) n (%)	294	154 (52.4)

Variable	n	Summary Statistic
Tissue Sensitivity Dimension		
PPT (wrist), kPa median (IQR) (min,max)	294	269.2 (181.7, 345) (55.3, 1200)
PPT (lumbar), kPa median (IQR) (min,max)	294	263.7 (162.3, 446) (36.7, 1600)
CPT (wrist), °C median (IQR) (min,max)	294	5.3 (4, 12.9) (4,30.6)
CPT (lumbar), °C median (IQR) (min,max)	294	4 (4, 24) (4, 31.2)
HPT (wrist), °C median (IQR) (min,max)	294	45.3 (42.8, 47.9) (32.2, 50)
HPT (lumbar), °C median (IQR) (min, max)	294	42.7 (39.8, 45.6) (33.6, 50)
MDT (wrist), mN median (IQR) (min, max)	294	3.9 (3.9, 5.9) (0.1, 19.6)
MDT (lumbar), mN median (IQR) (min, max)	294	5.9 (3.9, 13.7) (0.1, 58.8)
Two-point discrimination, cm median (IQR) (min, max)	294	6.0 (4.5, 7.0) (0.5, 10)
Baseline CPM pressure, kPa median (IQR) (min,max)	277	433 (260, 655) (60, 1700)
CPM change score (NRS) mean (SD) (min, max)	277	1.0 (1.3) (-3, 4)
Decreased vibration perception n (%)	294	72 (24.5)
Temporal summation n (%)	294	54 (18.4)
Pinprick hyperalgesia n (%)	294	44 (15.0)

Variable	n	Summary Statistic
Movement Dimension		
Change in pain intensity following repeated forward bending (NRS) median (IQR) (min, max)	292	1 (0, 2) (-6, 8)
Change in pain intensity following repeated backward bending (NRS) median (IQR) (min, max)	292	0 (0, 1) (-5, 8)
Forward bend time, sec median (IQR) (min, max)	292	18 (14.5, 22) (9, 186)
Backward bend time, sec median (IQR) (min, max)	292	16 (14, 20) (8, 57)
Communicative behaviours, forward bending median (IQR) (min, max)	292	0 (0, 0) (0, 7)
Protective behaviours, forward bending median (IQR) (min, max)	292	5 (0, 7) (0, 16)
Communicative behaviours, backward bending median (IQR) (min, max)	292	0 (0, 0) (0, 2)
Protective behaviours, backward bending median (IQR) (min, max)	292	0 (0, 5) (0, 15)

Variable		n	Summary Statistic
Psychological Dimension			
DASS depression median (IQR) (min, max)		294	6 (2, 14) (0, 42)
DASS anxiety median (IQR) (min, max)		294	4 (2, 8) (0, 42)
DASS stress median (IQR) (min, max)		294	12 (6, 20) (0, 42)
DASS combined total median (IQR) (min, max)		294	22 (12, 38) (0, 126)
FABQ-W median (IQR) (min, max)		284	16 (7.5, 27) (0, 42)
FABQ-PA mean (SD) (min, max)		294	15 (11, 19) (0, 24)
PCS rumination median (IQR) (min, max)		293	6 (3, 10) (0, 16)
PCS magnification median (IQR) (min, max)		293	3 (1, 5) (0, 12)
PCS helplessness median (IQR) (min, max)		293	8 (4, 13) (0, 24)
PCS total median (IQR) (min, max)		293	17 (9,27) (0,52)
PSEQ median (IQR) (min, max)		294	42 (32, 50) (1, 60)
AEQ classification n (%)	Adaptive	292	77 (26.2)
	Distress endurance	292	84 (28.6)
	Eustress endurance	292	97 (33.0)
	Fear-avoidance	292	34 (11.6)
TSS mean (SD) (min, max)		293	2.2 (1.7) (0, 6)
BES mean (SD) (min, max)		294	3.0 (1.1) (0, 6)
CPAQ-8 pain willingness median (IQR) (min, max)		294	9 (6, 12) (0,22)
CPAQ-8 activity engagement median (IQR) (min, max)		294	18 (14, 21) (0, 24)
CPAQ-8 total median (IQR) (min, max)		294	26 (21, 31) (0, 45)
Frustration (NRS) median (IQR) (min, max)		294	8 (7, 10) (1, 10)
MAAS median (IQR) (min, max)		291	4.2 (3.7, 4.7) (1.3, 6)
Perceived risk of persistent pain median (IQR) (min, max)		292	9 (8, 10) (3, 10)
FreBAQ median (IQR) (min, max)		294	9 (4, 14) (0, 32)

Variable	n	Summary Statistic
Health Dimension		
Total diagnosed comorbidities median (IQR) (min, max)	294	5 (2, 8) (0, 21)
Musculoskeletal comorbidities median (IQR) (min, max)	294	0 (0,1) (0, 3)
Functional pain comorbidities median (IQR) (min, max)	294	0 (0, 1) (0, 4)
Other diagnosed comorbidities median (IQR) (min, max)	294	1 (0, 2) (0, 8)
Other comorbid symptoms median (IQR) (min, max)	294	2 (1, 4) (0, 9)
Number of body chart squares filled-in median (IQR) (min, max)	294	13 (7, 20) (1, 84)
Manchester CWP classification n (%)	294	88 (29.9)
Baseline COOP/WONCA overall health rating mean (SD) (min, max)	294	3.0 (1.0) (1, 5)
BMI, kg/m^2 median (IQR) (min, max)	294	26.3 (23.6, 29.9) (17.7, 50.3)

Variable		n	Summary Statistic
Lifestyle and Social Dimensions			
PSQI median (IQR) (min, max)		283	9 (6, 12) (2, 20)
Smoking status n (%)	Non-smoker	294	170 (57.8)
	Ex-smoker		88 (29.9)
	Smoker		36 (12.2)
Moderate and vigourous physical activity (min / week) median (IQR) (min, max)		288	120 (0, 345) (0, 2100)
Years in education mean (SD) (min, max)		280	14.7 (3.6) (5, 27)
Compensation claim n (%)		288	46 (16.0)
Currently at work n (%)		294	224 (76.2)
Manual v. sedentary occupation n (%)	Not working	276	28 (10.1)
	Sedentary		174 (63.0)
	Manual		74 (26.8)
Job satisfaction (NRS) median (IQR) (min, max)		251	7 (5, 8) (0, 10)
Life events median (IQR) (min, max)		294	4 (3, 5) (0, 6)
MPI social support median (IQR) (min, max)		284	4 (2.7, 5) (0, 6)
MPI punishing median (IQR) (min, max)		285	1 (0.2, 2) (0, 6)
MPI solicitous mean (SD) (min, max)		285	2.8 (1.7, 3.7) (0, 6)
MPI distracting median (IQR) (min, max)		285	1.8 (0.8, 2.8) (0, 6)

Note. NRS – numeric rating scale, RMDQ – Roland Morris Disability questionnaire, StEP – Standardised Evaluation of Pain, PPT – Pressure pain threshold, kPa – kilopascals, CPT – cold pain threshold, °C – degrees Centigrade, HPT - Heat pain threshold, MDT – Mechanical detection threshold, mN – millinewtons, cm – centimetres, CPM – Conditioned pain modulation, sec – seconds, DASS – Depression Anxiety Stress scales, FABQ-W – Fear-Avoidance Beliefs questionnaire (Work subscale), FABQ-PA - Fear-Avoidance Beliefs questionnaire (Physical activity subscale), PCS – Pain Catastrophising scale, PSEQ – Pain Self-efficacy questionnaire, AEQ – Avoidance Endurance questionnaire, TSS – Thought Suppression subscale, BES – Behavioural Endurance subscale, CPAQ-8 – Chronic Pain Acceptance questionnaire (Short form), MAAS – Mindful Attention Awareness scale, FreBAQ – Fremantle Back Awareness questionnaire, CWP – Chronic widespread pain, BMI – Body mass index, kg/m^2 – kilograms per metre squared, PSQI – Pittsburgh Sleep Quality index, min / week – minutes per week, MPI - Multidimensional Pain Inventory

Table 4.

Comparison of baseline descriptive statistics for Eligible Participants who did not Complete Baseline Assessment (n=55) and Participants who Completed Baseline Assessment (n=294)

Demographic variable	Summary statistic Did **Not** Complete (n=55)	Summary statistic Did Complete (n=294)	*p*-value
Age median (IQR) (min, max)	48 (31-63) (19, 70)	50 (38, 60) (18, 70)	.34[1]
Female[2] n (%)	29 (61.7)	168 (57.1)	.98[3]
Pain severity (range 0-10) (NRS) mean (SD) (min, max))	6.1 (1.8) (2, 10)	5.8 (1.9) (2, 10)	.36[4]
Disability (range 0-24) (RMDQ) median (IQR) (min, max)	9 (7, 15) (5, 22)	9 (6, 13) (5,24)	.16[1]
100% of pain in low back region n (%)	26 (47.3)	147 (50.0)	.30[3]

Note. [1] Wilcoxon-Mann-Whitney test; [2] missing in 8 people; [3] χ^2 analysis; [4] independent t-test

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9.3.1 Study 1

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