The Understanding Persistent Pain Where it ResiDes Study of Low Back Pain Cohort Profile

Luke C. Jenkins *PhD*
Centre for Pain IMPACT, Neuroscience Research Australia (NeuRA), Randwick, New South Wales; School of Health Sciences, Western Sydney University, Penrith, Australia

Wei-Ju Chang *PhD, PhD, MPhty (Orthopedics, Sports and Manual), BPhty*
Centre for Pain IMPACT, Neuroscience Research Australia (NeuRA), Randwick, New South Wales; School of Health Sciences, College of Health, Medicine and Wellbeing, University of Newcastle, Callaghan, New South Wales, Australia

Valentina Buscemi *PhD*
Centre for Pain IMPACT, Neuroscience Research Australia (NeuRA), Randwick, New South Wales; School of Health Sciences, Western Sydney University, Penrith, Australia

Matthew Liston *PhD*
Centre for Pain IMPACT, Neuroscience Research Australia (NeuRA), Randwick, New South Wales; School of Health Sciences, Western Sydney University, Penrith, Australia

Michael Nicholas *PhD, MPsychol(Clin), MSc(Hons), MAPS, FFPMANZCA(Hon)*
Pain Management Research Institute, University of Sydney at Royal North Shore Hospital, Sydney, Australia

Thomas Graven-Nielsen *MedDr, PhD, MScEE*
Center for Neuroplasticity and Pain (CNAP), Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

Paul W. Hodges *DSc MedDr PhD BPhty(Hons) FAA FACP APAM(Hon)*
The University of Queensland, School of Health and Rehabilitation Sciences, Brisbane, Australia

Valerie C. Wasinger *PhD*
Bioanalytical Mass Spectrometry Facility, Mark Wainwright Analytical Centre, University of New South Wales, Kensington; School of Medical Science, University of New South Wales, Kensington, Australia

Laura S. Stone *PhD*
Department of Anesthesiology, Faculty of Medicine, University of Minnesota, Minneapolis, USA

Susan G. Dorsey *PhD, RN, FAAN*
Department of Pain & Translational Symptom Science, University of Maryland Baltimore, Baltimore, USA

James H. McAuley *PhD*
Centre for Pain IMPACT, Neuroscience Research Australia (NeuRA), Randwick, New South Wales; University of New South Wales, Neuroscience Research Australia, Sydney, Australia

Siobhan M. Schabrun *PhD, BPhty(Hons)*
Centre for Pain IMPACT, Neuroscience Research Australia (NeuRA), Randwick, New South Wales, Australia; School of Physical Therapy, University of Western Ontario, and The Gray Centre for Mobility and Activity, Parkwood Institute, St. Joseph's Healthcare, London, Ontario, Canada

ABSTRACT

Despite chronic low back pain (LBP) being considered a biopsychosocial condition for diagnosis and management, few studies have investigated neurobiological risk factors thought to underpin the transition from acute to chronic LBP. The aim of this research is to describe the methodology, compare baseline characteristics between acute LBP participants and pain-free controls, and compare LBP participants with or without completed follow-up. One hundred and twenty individuals experiencing acute LBP and 57 pain-free controls were recruited to participate in the Understanding persistent Pain Where it ResiDes (UPWaRD) study. Neurobiological, psychological, and sociodemographic data were collected at baseline, and at 3 and 6 months. Ninety-five participants (79%) provided outcome data at 3-month follow-up and 96 participants (80%) at 6 months. Compared to controls, LBP participants in the UPWaRD cohort were older, had a higher BMI, a higher prevalence of comorbidities, and higher medication usage. Higher depression, anxiety and stress, lower pain self-efficacy, and higher pain catastrophising during acute LBP were correlated with higher 6-month pain and disability. This cohort provides novel and significant opportunities to increase understanding of neurobiological risk factors of LBP. Future findings endeavour to provide new targets for treatment and prevention of chronic LBP. Additional priorities include exploring epigenetic and proteomic biomarkers of poor LBP outcome.

Jenkins, L., Chang, W.-J., Buscemi, V., Liston, M., Nicholas, M., Graven-Nielsen, T., Hodges, P. W., Wasinger, V. C., Stone, L. S., Dorsey, S. G., McAuley, J. H., & Schabrun, S. M. (2023), The Understanding persistent Pain Where it ResiDes study of low back pain cohort profile. *New Zealand Journal of Physiotherapy, 51*(3), 199–216. https://doi.org/10.15619/nzjp.v51i3.375z

Key Words: Acute to Chronic, Demographic, Low Back Pain, Neurobiological, Psychological, Social

INTRODUCTION

The worldwide monthly prevalence of low back pain (LBP) is approximately 23%, with 83% of the world's population experiencing LBP at least once during their lifetime (Hoy et al., 2012; Manchikanti et al., 2014). The clinical course of LBP is complex, with many people reporting ongoing pain and disability 1 year following an acute episode (Costa et al., 2012; Henschke et al., 2008; Kongsted et al., 2015). LBP is a leading cause of disability worldwide (Vos et al., 2017) and associated with substantial economic burden, with $135 billion spent on low back and neck pain in the US in 2017 (Dieleman et al., 2020). Despite the scale of the problem, identifying those with acute LBP who are at risk of chronic or recurrent symptoms remains challenging.

Most cases of LBP have no identifiable pathoanatomical cause or clear nociceptive source that could explain chronic symptoms (Maher et al., 2017). This has led to a focus on the identification of psychological, social, and demographic risk factors to explain the transition to chronic LBP (Ardakani et al., 2019). Unfortunately, risk factors such as pain intensity, disability, psychological distress, smoking, and physical inactivity explain only some of the variance in LBP outcome (Hartvigsen et al., 2018; Kent & Keating, 2008; Lin et al., 2011; Shiri et al., 2010).

Investigation of biological risk factors in the development of chronic pain has been limited. Although some data are beginning to show that systemic inflammation and pain sensitivity interact with psychological features (Klyne et al., 2018; Klyne et al., 2019), the role of several other biological risk factors has not been investigated. The Understanding persistent Pain Where it ResiDes longitudinal cohort study (UPWaRD) aimed to recruit and follow a cohort of adults living in Australia who experienced an acute episode of LBP. The primary aim, as reported a priori in the study protocol (Jenkins et al., 2019), was to use this cohort to identify neurobiological, psychological, and sociodemographic risk factors that predict future LBP outcome. The neurobiological risk factors selected for investigation in the protocol were those with a putative link to the development of aberrant cortical and spinal neuroplasticity, hypothesised to explain why some individuals develop chronic pain after an acute episode.

In this paper we present a cohort profile. Cohort profiles describe the rationale, methodology, baseline data, and future plans of a longitudinal cohort study. A cohort profile bridges the gap between study protocol and results, providing readers with an honest experience of conducting the cohort study, potentially facilitating collaboration (Ebrahim, 2004).

Therefore, the overarching aim of this paper is to present a cohort profile for the UPWaRD study. Specifically, this paper addresses the aims of a cohort profile through (a) describing the design, participant recruitment, and measurement procedures of the UPWaRD study; (b) comparing baseline characteristics of the cohort (health, sociodemographic, psychological, and lifestyle factors) between individuals with or without acute LBP; (c) describing the recovery trajectories (pain and disability) of individuals with acute LBP over a period of 6 months; and (d) reporting future plans for data obtained within this cohort.

METHODS

Study design

The UPWaRD study was a multicentre, prospective, longitudinal, cohort trial of people with acute (within 6 weeks of pain onset) LBP, and pain-free controls, with 3- and 6-month follow-up. The study received funding from the National Health and Medical Research Council of Australia (Grant ID, 1059116). All study procedures were approved by the Human Research Ethics Committees of Western Sydney University (H10465) and Neuroscience Research Australia (SSA:16/002) and in accordance with the Helsinki Declaration of 1975, as revised in 1983. All participants provided written, informed consent for participation in the study and its related procedures.

Recruitment and follow-up

Participants were recruited through flyers around university campuses and the local community, social media posts, local hospitals in South Eastern Sydney and South Western Sydney Local Health Districts, New South Wales, Australia, primary care practitioners (e.g., GPs and physiotherapists), and newspaper advertisements. Screening was conducted via email and phone. Potential participants who contacted the research team or were referred from a practitioner were contacted over the phone within 24 hr to discuss the study purpose and methodology. Participants were then sent a detailed participant information sheet and screening form via email. Participants who returned the screening form were considered "screened" and any reason for exclusion was documented.

Acute LBP participants were eligible if they experienced pain in the region of the lower back, superiorly bounded by the thoracolumbar junction and inferiorly by the gluteal fold (Müller et al., 2019). Pain must have been present for more than 24 hours and persisted for less than 6 weeks following a period of at least 1 month pain-free (De Vet et al., 2002; Müller et al., 2019; Stanton et al., 2008; Williams et al., 2014). Participants remained eligible if they reported a previous history of LBP. As we sought to identify predictors of recovery from an acute episode of LBP, regardless of the history of LBP, inclusion of strictly first episode LBP was not required to achieve our study aims. Given the prevalence of LBP in the community and the identification that most LBP is recurrent, the generalisability of a strictly first episode LBP cohort would also be questionable. All participants with pain referred beyond the inferior gluteal fold underwent a physical examination by a trained physiotherapist (study staff) to identify any sensory or motor deficit of the lower extremity. Participants with suspected lumbosacral radiculopathy characterised by the presence of weakness, loss of sensation, or loss of reflexes associated with a particular nerve root, or a combination of these, were excluded (Lin et al., 2014). Individuals who presented with suspected serious spine pathology (e.g., fracture, tumour, cauda equina syndrome), other major diseases/disorders (e.g., schizophrenia, chronic renal disorder, multiple sclerosis), a history of spine surgery, or any other chronic pain conditions were excluded. As transcranial magnetic stimulation (TMS) was an important variable measured in the UPWaRD study, all participants were additionally screened for contraindications to the use of TMS (as described by Keel et al. (2001).

Exclusion criteria for pain-free controls were LBP within the

past 12 months, previous history of spine surgery, any other chronic pain conditions, other major diseases/disorders, or contraindications to the use of TMS. Pain-free participants were carefully screened to ensure they were pain-free prior to study enrolment and at the time of baseline testing.

Data collection

Participants completed a laboratory testing session and a battery of questionnaires (online or in person) at baseline, 3, and 6 months. All variables were measured in a standardised order for all participants and four assessors performed all laboratory sessions between Western Sydney University, Campbelltown Campus, or Neuroscience Research Australia. Duration of assessment of all variables was approximately 2.5 hr. Measures were collected within the domains of health (e.g., weight), sociodemographic (e.g., cultural diversity), psychological (e.g., depression, catastrophising, self-efficacy), clinical (Keele StarT Back Screening Tool), neurobiological (e.g., electroencephalography), biological (serum biomarkers), pain processing (e.g., pressure pain sensitivity), and lifestyle (e.g., physical activity – International Physical Activity Questionnaire). Detailed description of all measures obtained in the UPWaRD Cohort and their methodology is described in Appendix A, Table A1. This table includes details of which measures were added after registration/protocol publication. Pain-free controls were followed up at 3 and 6 months to allow comparison of neurobiological and psychological variables between participants with and without LBP, and allow assessment of measurement stability across baseline, 3, and 6 months in pain-free individuals (Cunningham et al., 2021).

In brief, neurobiological measures were selected based upon a theoretical association between cortical and spinal plasticity and the development of chronic LBP and supporting evidence from cross-sectional studies (Baumbauer et al., 2020; Flor et al., 1997; Hayden et al., 2009; Linton, 2000; Schabrun et al., 2017; Tsao et al., 2011). For psychological measures, three questionnaires were used to assess specific aspects of psychological status with evidence of relevance to the development of chronic LBP: the 21-Item Depression, Anxiety and Stress Scales Questionnaire (DASS-21) (Antony et al., 1998; Parkitny et al., 2012), the 13-item Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995), and 10-item Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas, 2007). A commonly used clinical prediction tool, The Keele StarT Back Screening Tool was also administered among LBP participants at baseline assessment (Hill et al., 2008). Sociodemographic, environmental, and lifestyle factors were selected based on the Australasian Electronic Persistent Pain Outcomes Collaboration minimum dataset recommendations (Tardif et al., 2017). Guidelines for that minimum dataset were first developed in 2011 by an expert team, consisting of members of the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists, Australian Pain Society, and New Zealand Pain Society. Participants were free to seek and utilise any treatment, and data were collected on healthcare utilisation and medication consumption. No form of treatment or advice was provided within this study.

Average pain intensity over the week preceding baseline and follow-up assessment was self-reported by participants using the 11-point numerical rating scale (NRS) anchored with "no pain" at 0 and "worst pain possible" at 10. Disability was assessed using the 24-point Roland Morris Disability Questionnaire (RMDQ) on the day of baseline and follow-up testing. An item receives a score of 1 if it is applicable to the respondent or 0 if it is not, with a total range of 0 (no disability) to 24 (severe disability) (Roland & Morris, 1983).

Sample size

Sample size for the primary study aim (i.e., to determine whether cortical reorganisation, an individual's capacity for neuroplasticity, central sensitisation, psychosocial factors, and their possible interaction, predict LBP outcome) was initially calculated (pre study commencement) based on an assumption the prediction model would include 17 candidate predictors, five a priori interactions, and nine sociodemographic variables. Allowing for 10% loss to follow-up, a power of 80% with a 5% level of significance and a medium effect size, a sample size of 264 participants was required. Once data collection commenced, a slower than expected rate of participant recruitment made the target sample size unachievable. On this basis, the sample size calculation for the primary aim was revised using the rule of thumb that 10 subjects per variable are required to adequately power a linear regression model (Harrell Jr, 2015) and a minimum of five events per candidate variable is required for logistic regression analysis (Vittinghoff & McCulloch, 2007) resulting in a required sample size of 120 individuals with acute LBP. Prior to the completion of data collection and analysis, the UPWaRD study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12619000002189) and the protocol for the primary study aim was published (Jenkins et al., 2019). Both documents include description of the revised sample size calculation and this sample size (n = 120) was achieved as planned.

Statistical analyses

Statistical Package for the Social Sciences software (version 27; IBM Corp) was used for all analyses in this study. Statistical significance was accepted at $p \leq 0.05$ and all analyses were conducted on complete cases, with missing data described in Appendix A, Table A2. First, the distribution of individual variables was inspected using histograms. Continuous data are presented as mean and standard deviation (normally distributed) or median and interquartile range (non-normally distributed), and categorical data presented as number and percentage.

To explore potential differences in LBP recovery trajectories at 3 and 6 months, participants were divided into three sub-groups based on standardised criteria: (a) unresolved LBP if participants reported an increase or no change in pain intensity (NRS) and disability (RMDQ) from baseline, or a pain NRS score of ≥ 7/10, corresponding with severe pain (Boonstra et al., 2016); (b) partially resolved LBP if participants reported a decrease in pain and/or disability from baseline (≥ 1-point reduction on NRS and/or RMDQ from baseline scores); or (c) resolved LBP if participants reported no pain and disability (NRS and RMDQ = 0) at follow-up (Boonstra et al., 2016; Klyne et al., 2018).

Comparisons were made between participants who did or did not complete follow-up, and between participants with or without LBP using independent samples t-test, non-parametric Mann-Whitney U test and Fisher's exact test for normally

distributed, non-normally distributed, and categorical data, respectively. Spearman's rank correlation coefficients and the corresponding bootstrapped and bias-corrected 95% confidence intervals were used to determine whether depression and anxiety (DASS-21), pain catastrophising (PCS) or pain self-efficacy (PSEQ) were correlated with 6-month pain intensity (NRS) or disability in the UPWaRD LBP participants. A one-way multivariate analysis of variance (MANOVA) was used to compare differences in moderate and vigorous physical activity minutes at baseline, 3 months, and 6 months between pain-free controls, participants with resolved LBP or participants with partially or unresolved LBP.

RESULTS

Participant recruitment

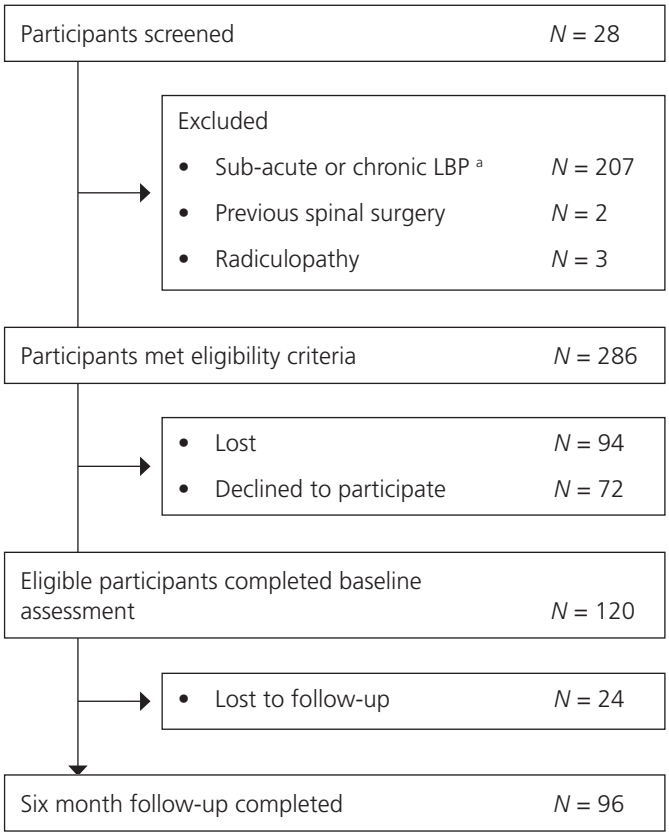
Between 14 April 2015 and 25 July 2019, 498 participants who presented with LBP were screened and 120 participants were included in the cohort (Figure 1; mean age 39 (*SD* 15) years; range = 21–83 years, female:male sex = 59:61). Two hundred and seven participants (41.5%) were ineligible because they had chronic LBP, two participants were excluded because they had previous spinal surgery, and three were excluded because physical examination by the study investigator suggested a diagnosis of lumbosacral radiculopathy. Of the 286 eligible participants, 94 (32.9%) failed to respond to contact attempts organising baseline assessment and 72 (25.2%) declined participation after reviewing the study information sheet. Baseline data were obtained on average 2.4 (*SD* 1.4) weeks (range 1 day–6 weeks) after the onset of acute LBP.

Between October 2016 and February 2019, 57 pain-free controls who reported no current or prior LBP during the 12 months preceding study entry, and with age and sex distribution similar to the UPWaRD LBP cohort were recruited (mean age 35 (*SD* 14) years; range = 19–68 years, female:male sex = 28:29) (Table 2).

Participant attrition

Of the 120 eligible acute LBP participants who were enrolled in the study and provided baseline data, 95 (79%) provided outcome data at the 3-month follow-up and 96 (80%) at 6 months. Missing follow-up cases were due to participants failing to respond to multiple contact attempts to schedule their laboratory assessment within a 1 month time window of their 3- or 6-month follow-up date. At 3- and 6-month follow up, 15 (16%) of the 95 LBP participants and 12 (13%) of the 96 LBP participants declined assessment of all laboratory measures, respectively. These participants agreed to complete questionnaire data, and, thus, remained in the cohort. The number of participants who provided valid data for each of the 3- and 6-month questionnaire-based items are shown in Appendix A, Table A2. Of the 57 control participants, follow-up was completed in 43 (75%) at 3 months and 39 (68%) at 6 months. Reasons for participant attrition among controls were (a) only consented to single laboratory testing session (n = 7); (b) withdrew from the study due to intolerance of laboratory testing and/or duration of the testing protocol (n = 4); (c) no reason given (n = 6); or (d) developed LBP (n = 1).

Figure 1
UPWaRD Low Back Pain Cohort Flow Diagram



[a] defined as LBP lasting for longer than 6 weeks and/or an LBP episode preceded by a period of less than 1 month without pain.

Participants with higher DASS depression (p = < 0.01), DASS anxiety (p = 0.03), and DASS stress (p = < 0.01) scores and lower PSEQ (p = 0.02) scores were less likely to complete the 3-month follow-up. At 6 months, participants who did not complete follow-up reported higher rates of pain affecting their work (p = 0.04), pain interference with their usual work (p = 0.03), pain interference with their walking (p = 0.04), and pain interference with their relations (p = 0.04). Higher levels of self-reported moderate physical activity time per day (p = 0.03) and lower PSEQ scores (p = 0.04) were also observed in participants who did not attend their 6-month follow-up appointment (Table 1).

Pain and disability recovery trajectories

Overall, mean NRS scores of pain intensity for participants with LBP decreased (p < 0.001) from 4.3 (*SD* 1.9) at baseline to 2.3 (*SD* 2.3) at 3 months, remaining stable at 6 months (M = 2.3, *SD* = 2.2). Disability scores (RMDQ) decreased (p < 0.001) from a median score of 5.0 (IQR = 2.0–8.3) at baseline to a median score of 2.0 (IQR = 0.0–5.0) at 3 months, and a median score of 1.0 (IQR = 0.0–4.0) at 6 months. Reporting unresolved LBP at 3 months was not significantly associated with experiencing unresolved LBP at 6 months (p = 0.21). Conversely, partially resolved (p = 0.01) and resolved (p < 0.001) LBP status at 3 months was significantly associated with 6-month partially resolved and resolved LBP status, respectively. Twenty-four

Table 1

Comparison of Baseline Characteristics Between Participants with LBP Who Did (FU), and Did Not (NFU), Complete 3- and 6-month Follow-up

Characteristic	Summary statistics					
	3 months		*p*	6 months		*p*
	FU (*n* = 95)	NFU (*n* = 25)		FU (*n* = 96)	NFU (*n* = 24)	
Health						
Age (years), *Mdn* [IQR]	34 [28–55]	34 [28–41]	0.51	32 [28–55]	38 [30–49]	0.45
Height (cm), *M* (*SD*)	173.0 (10.8)	175.1 (11.1)	0.39	172.5 (10.9)	175.6 (10.7)	0.24
Weight (kg), *M* (*SD*)	77.7 (19.4)	81.9 (15.0)	0.38	77.9 (19.1)	80.1 (17.7)	0.62
Sex: Female, *n* (%)	51 (51)	8 (40)	0.47	51 (53)	8 (33)	0.08
Body mass index (kg/m^2), *Mdn* [IQR]	23.7 [21.6–29.4]	24.9 [22.5–31.6]	0.30	23.7 [21.6–30.2]	24.7 [22.5–29.1]	0.61
Comorbidities: Yes, *n* (%)	31 (32)	6 (30)	1.00	30 (32)	7 (32)	0.87
Previous LBP: Yes, *n* (%)	73 (75)	18 (90)	0.07	72 (77)	19 (86)	0.32
Health care usage: Yes, *n* (%)	56 (57)	11 (58)	1.00	51 (54)	16 (73)	0.10
Medication usage: Yes, *n* (%)	55 (56)	8 (42)	0.32	53 (44)	10 (46)	0.36
Sociodemographic, *n* (%)						
Cultural diversity: Yes	44 (45)	9 (50)	0.80	40 (43)	13 (62)	0.11
Education: Secondary school/below	14 (14)	5 (25)	0.19	16 (17)	3 (14)	0.73
Employment: Full/part time	72 (73)	13 (65)	0.59	69 (73)	16 (67)	0.56
Compensation: Yes	3 (3)	1 (5)	0.51	3 (3)	1 (5)	0.74
Sickness benefits: Yes	0 (0)	1 (5)	0.16	1 (1)	0 (0)	0.62
Pain affected work: Yes	28 (29)	9 (47)	0.12	26 (27)	11 (50)	0.04
Psychological, *Mdn* [IQR]						
DASS depression	2.0 [0.0–6.0]	14.0 [4.0–18.0]	< 0.01	2.0 [0.0–8.0]	8.0 [0.0–15.0]	0.77
DASS anxiety	2.0 [0.0–6.0]	5.0 [1.5–12.5]	0.03	2.0 [0.0–6.0]	2.0 [0.0–10.0]	0.15
DASS stress	6.0 [2.0–15.0]	14.0 [18.0–24.0]	< 0.01	6.0 [2.0–16.0]	12 [7.5–20.0]	0.10
Self-efficacy (PSEQ), *Mdn* [IQR]	50.5 [40.0–57.0]	41.0 [27.0–52.0]	0.02	51.0 [40.0–57.0]	45.0 [32.0–52.0]	0.04
Catastrophising (PCS), *Mdn* [IQR]	8.0 [2.8–14.3]	12.0 [6.0–19.0]	0.13	8.0 [3.0–16.0]	12.0 [7.0–16.0]	0.14
Pain (Numerical Rating Scale), *M* (*SD*) [a]						
Worst pain	6.3 (1.9)	6.7 (1.9)	0.41	6.4 (1.9)	6.6 (1.8)	0.62
Least pain, *Mdn* [IQR]	2.0 [0.0–4.0]	2.0 [1.0–3.0]	0.71	2.0 [1.0–4.0]	2.0 [1.0–3.0]	0.79
Average pain	4.2 (2.0)	4.7 (1.5)	0.24	4.2 (2.0)	4.6 (1.3)	0.25
Current pain	3.0 (2.2)	3.5 (2.0)	0.37	3.0 (2.2)	3.5 (1.9)	0.42
Pain (Brief Pain Inventory), *M* (*SD*) [a]						
Pain interference: Activity	4.5 (2.9)	5.4 (3.1)	0.25	4.4 (2.8)	5.7 (3.0)	0.06
Pain interference: Mood	4.0 (3.0)	5.1 (2.3)	0.14	4.0 (2.9)	5.0 (2.6)	0.15
Pain interference: Walking	3.3 (3.0)	4.6 (2.5)	0.08	3.3 (2.9)	4.6 (2.5)	0.04
Pain interference: Usual work	4.1 (3.0)	5.2 (2.8)	0.13	4.0 (2.9)	5.5 (2.9)	0.03
Pain interference: Relations, *Mdn* [IQR]	1.0 [0.0–5.0]	2.0 [1.0–5.0]	0.17	1.0 [0.0–4.0]	2.0 [1.0–6.0]	0.04
Pain interference: Sleep	3.8 (3.1)	4.6 (2.5)	0.30	3.9 (3.0)	4.0 (2.8)	0.86
Pain interference: Enjoyment	3.9 (3.1)	4.3 (2.9)	0.63	3.8 (3.1)	4.5 (2.9)	0.31
Disability						
Disability (RMDQ), *Mdn* [IQR]	5.0 [2.0–8.0]	5.0 [3.0–10.0]	0.74	5.0 [2.0–8.0]	6.0 [3.0–10.0]	0.28
Clinical						
StartBack score, *n* (%)						
Low risk	67 (73)	15 (63)	0.56	66 (70)	16 (73)	0.71
Medium risk	20 (22)	7 (29)		23 (24)	4 (18)	
High risk	5 (5)	2 (8)		5 (5)	2 (9)	
Lifestyle (IPAQ), *Mdn* [IQR] [a]						
Vigorous activity days/week	1.0 [0.0–3.0]	0.0 [0.0–3.0]	0.37	1.0 [0.0–3.0]	1.0 [0.0–3.3]	0.76
Vigorous activity time/day (min)	30.0 [0.0–67.5]	0.0 [0.0–60.0]	0.31	30.0 [0.0–60.0]	20.0 [0.0–67.5]	0.69
Moderate activity days/week	2.0 [0.0–4.0]	2.0 [0.0–3.3]	0.34	2.0 [0.0–4.0]	2.5 [2.0–4.0]	0.22
Moderate activity time/day (min)	37.5 [0.0–90.0]	25.0 [0.0–120.0]	0.90	30.0 [0.0–60.0]	60.0 [11.5–195.0]	0.03
Days/week walking ≥ 10 min	7.0 [5.0–7.0]	7.0 [3.0–7.0]	0.50	7.0 [5.0–7.0]	7.0 [2.0–7.0]	0.28
Walking time/day (min)	60.0 [28.9–120.0]	37.5 [20.0–60.0]	0.31	60.0 [30.0–120.0]	37.5 [18.8–60.0]	0.12
Sitting time/day (min), *M* (*SD*)	297.4 (172)	270.6 (192.4)	0.58	294.6 (171.5)	288.0 (193.1)	0.88

Note. DASS = 21-item depression anxiety stress subscale; FU = completed follow-up; IQR = interquartile range; LBP = low back pain; NFU = did not complete follow-up; PCS = pain catastrophising scale; PSEQ = Pain Self-efficacy Questionnaire. Baseline variable (characteristic) summary statistics compared between LBP participants who did, and did not follow-up, at 3- and 6-month time-points using *t* tests (continuous data, normally distributed), Mann-Whitney U tests (continuous data, not normally distributed), or Fisher's exact test (categorical data).

[a] Except where indicated.

(25.0%) LBP participants were completely recovered and 60 (62.5%) were partially recovered after 6 months. Twelve (12.5%) participants LBP were unresolved at 6 months (Table 2).

Health-related characteristics

Compared to controls, LBP participants were slightly older, had a higher body mass index (BMI), a higher prevalence of comorbidities, and higher medication usage (Table 3). The most reported comorbidities among participants with LBP were depression/anxiety (*n* = 12, 29.3%), hypertension (*n* = 9, 22.0%), and asthma (*n* = 5, 12.2%). Among controls, six comorbidities were self-reported: vision impairment (*n* = 1), hypothyroidism (*n* = 1), osteoporosis (*n* = 1), prolactinoma (*n* = 1), mild depression/anxiety not requiring intervention (*n* = 1), and heart disease (*n* = 1). The most frequently used medication within the control group was a contraceptive (*n* = 4). Types of health care utilised by LBP participants were allied health (*n* = 59, 50.4%), GPs (*n* = 30, 25.6%), diagnostic tests (*n* = 13, 11.1%), and specialist physicians (*n* = 5, 4.3%). During the follow-up period, three (2.6%) participants presented to their local emergency department because of their LBP but none were admitted to hospital. Among participants experiencing an acute episode of LBP, 55 (46.6%) did not use any medication and two (1.7%) did not specify their medication use. Eighteen (15.3%) used nonsteroidal anti-inflammatories and 19 (16.1%) used acetaminophen. Seven (5.9%) LBP participants were prescribed opioids and three (2.5%) were prescribed benzodiazepines. Nine (7.6%) LBP participants were taking anti-depressant medication for the management of co-existing depressive symptoms. Three (2.5%) LBP participants were prescribed an anti-convulsant. No LBP participants in the UPWaRD cohort received an epidural steroid injection. Thirty-three participants with LBP were taking medication not related to pain (e.g., anti-hypertensive or oral contraceptives).

Sociodemographic characteristics

Fifty-three (46.1%) LBP participants and 30 (56.6%) pain-free controls identified as culturally diverse. Only one participant with LBP was receiving a sickness benefit (0.9%) at the time of baseline testing and four (3.4%) were receiving compensation

Table 2

UPWaRD LBP Cohort Pain and Disability Outcomes At 3- and 6-month Follow-up

Classification	3 months		6 months		*p*
	n	%	*n*	%	
Unresolved recurrent or chronic LBP	16	16.8	12	12.5	0.21
Partially resolved recurrent or chronic LBP	57	60.0	60	62.5	0.01
Resolved	22	23.2	24	25.0	< 0.001

Note. LBP = low back pain. Summary statistics compared between 3- and 6-month time points using Fisher's exact test. LBP outcome within the UPWaRD Cohort was dichotomised at 3 and 6 months using standardised criteria defined as: (a) unresolved – increase or no change in pain intensity (numerical rating scale, NSR) and disability (Roland Morris disability questionnaire, RMDQ) from baseline, or a pain NRS score of ≥ 7/10; (b) partially resolved – decrease in pain and/or disability from baseline (≥ 1-point reduction on NRS and/or RMDQ from baseline scores); (c) resolved – no pain and disability (NRS and RMDQ = 0) at follow-up.

Table 3

Baseline Demographic and Health-related Characteristics of the UPWaRD Cohort

Health-related characteristic	Summary statistics		*p*
	LBP (*n* = 120)	Control (*n* = 57)	
Age (years), *Mdn* [IQR]	34 [28–53]	31 [25–40]	0.02
Height (cm), *M* (*SD*) [a]	173.1 (10.9)	170.6 (8.2)	0.10
Weight (kg), *M* (*SD*) [a]	78.3 (8.8)	69.0 (13.7)	< 0.001
Sex: Female, *n* (%)	59 (49)	28 (49)	0.56
Comorbidities: Yes, *n* (%)	37 (32)	6 (11)	< 0.01
Previous LBP: Yes, *n* (%)	91 (78)	2 (4.0)	< 0.001
Health care usage: Yes, *n* (%)	67 (57)	NA	NA
Medication usage: Yes, *n* (%)	63 (53)	12 (21)	< 0.001
Body mass index (kg/m^2), *Mdn* (IQR)	24.2 [21.7–29.8]	22.5 [21.2–25.8]	0.01

Note. IQR = interquartile range; LBP = low back pain, NA = not applicable. Summary statistics compared between LBP and control participants using *t* test (continuous data, normally distributed), Mann-Whitney *U* test (continuous data, not normally distributed), or Fisher's exact test (categorical data).

[a] Welch's *t*-test was performed.

related to their LBP. Thirty-seven (31.6%) LBP participants reported pain that was affecting their occupation. Table 4 outlines the education and occupational status of the UPWaRD cohort.

Psychological characteristics

DASS depression scores were higher at baseline in acute LBP participants compared with pain-free controls ($p = 0.01$). Although the median total DASS-21 scores appeared higher at baseline in the acute LBP participants compared with pain-free controls, the distributions overlapped and did not differ significantly ($p = 0.13$; Table 5). PCS and PSEQ scores were not obtained at baseline from pain-free participants; however, the median scores for these measurements among LBP participants are presented in Table 5.

Table 6 reports correlations between psychological variables of interest and 6 month pain (NRS) and disability (RMDQ) in the LBP cohort (NRS). All psychological variables at baseline displayed a statistically significant correlation with 6-month pain intensity and disability.

Lifestyle characteristics

Compared to pain-free controls, participants in the UPWaRD LBP cohort engaged in lower levels of vigorous and moderate physical activity in the week preceding their first laboratory session ($p < 0.05$; Table 7). Among the complete cases, there was no difference in moderate physical activity minutes between groups (controls, resolved LBP, partially or unresolved LBP) at 3-month follow-up ($F_{6, 176} = 0.96$, $p = 0.45$; Wilks' $\lambda = 0.94$, $\eta p^2 = 0.03$), and a similar result was observed at 6-month follow-up ($F_{6, 174} = 1.25$, $p = 0.28$; Wilks' $\lambda = 0.92$, $\eta p^2 = 0.04$). Vigorous physical activity minutes among complete cases also did not differ between groups at 3 months ($F_{6, 192} = 0.85$, $p = 0.53$; Wilks' $\lambda = 0.95$, $\eta p^2 = 0.03$), or at 6 months ($F_{6, 192} = 0.86$, $p = 0.52$; Wilks' $\lambda = 0.95$, $\eta p^2 = 0.03$).

DISCUSSION

LBP is a heterogenous condition (Hoy et al., 2010) and contributors to pain chronicity and disability are multifactorial (Hartvigsen et al., 2018). This cohort profile highlights that LBP participants were slightly older, had a higher average BMI, and participated in lower levels of vigorous and moderate physical activity in the week preceding baseline testing than their pain-free counterparts. Although this might be expected for individuals with pain, a recent systematic review, including individuals free from chronic LBP at study inception, suggests lower levels of moderate (1–3 times per week), or vigorous/high (≥ 3–4 times per week) leisure physical activity may increase the risk of developing chronic LBP (Shiri & Falah-Hassani, 2017). A significant causal relationship has recently been identified between BMI and back pain development (Elgaeva et al., 2019).

An important finding of the cohort profile presented here was that over 50% of the UPWaRD LBP cohort utilised at least one form of health care because of their LBP episode, most commonly, allied health (e.g., physiotherapist, chiropractor)

Table 4

Education and Occupational Status of Participants Enrolled in the UPWaRD Study

Sociodemographic characteristic	LBP		Control	
	n	%	*n*	%
Education				
Some secondary school or less	7	5.9	0	0.0
Completed secondary school	12	10.2	11	19.6
Certificate III/IV	5	4.2	11	19.6
Diploma	31	26.3	0	0.0
Bachelor's degree	37	31.4	16	28.6
Post-graduate degree	26	22.0	18	32.1
Not specified	2	1.7	1	1.8
Occupational status				
Full-time employment	50	43.1	17	38.6
Part-time employment	31	26.7	12	27.3
Studying	12	10.3	10	22.7
Volunteer	2	1.7	0	0.0
Unemployed/prolonged absence due to pain	5	4.3	0	0.0
Unemployed not due to pain	1	0.9	0	0.0
Retraining/limited hours	2	1.7	2	4.5
Home duties	3	2.6	0	0.0
Retired	8	6.9	3	6.8
Not specified	5	4.2	13	22.8

Note. LBP = low back pain. Certificate III/IV corresponds to the Australian Qualifications Framework Level 3 and 4 and provides the knowledge and skills required to undertake skilled work or further learning across a range of contexts.

Table 5

Baseline Psychological Characteristics of the UPWaRD Cohort

Psychological characteristic	Summary statistics				*p*
	LBP (*n* = 120)		Control (*n* = 57)		
	Mdn	IQR	*Mdn*	IQR	
DASS total	16.0	4.0–28.0	10.0	4.0–22.0	0.13
DASS depression item	2.0	0.0–10.0	2.0	0.0–4.0	0.01
DASS anxiety item	2.0	0.0–6.0	2.0	0.0–4.0	0.12
DASS stress item	8.0	2.0–16.0	8.0	4.0–12.0	0.37
PCS	8.0	3.0–15.5	NA		NA
PSEQ	48.0	37.5–56.0	NA		NA

Note. DASS = 21-item depression anxiety stress subscale; IQR = interquartile range; LBP = low back pain; NA = not applicable; NRS = numerical rating scale; PCS = pain catastrophising scale; PSEQ = pain self-efficacy questionnaire. Summary statistics compared between LBP and control participants using Mann-Whitney *U* test (continuous data, not normally distributed).

Table 6

Spearman's Correlation Coefficients Between Measures of Baseline Psychological Status and 6-month Pain and Disability

Characteristic	Spearman's correlation coefficient (BCa 95% CI)				
	DASS	PSEQ	PCS	NRS	RMDQ
DASS	–	–0.67 (–0.78, –0.51)	0.68 (0.55, 0.78)	0.42 (0.27, 0.57)	0.44 (0.25, 0.61)
PSEQ		–	–0.59 (–0.73, –0.40)	–0.36 (–0.53, –0.18)	–0.37 (–0.54, –0.19)
PCS			–	0.37 (0.19, 0.54)	0.40 (0.20, 0.57)
NRS				–	0.68 (0.55, 0.79)
RMDQ					–

Note. BCa = Bias-corrected and accelerated; CI = confidence interval; DASS = 21-item depression anxiety stress subscale; PCS = pain catastrophising scale; PSEQ = pain self-efficacy questionnaire; RMDQ = Roland Morris disability questionnaire. Spearman's correlation coefficients and the corresponding 95% confidence intervals were estimated with 1000 bootstrap samples and are bias-corrected and accelerated.

Table 7

Baseline Physical Activity Levels of the UPWaRD Cohort Based on the International Physical Activity Questionnaire

Lifestyle-related characteristic	Summary statistics				*p*
	LBP (*n* = 120)		Control (*n* = 57)		
	Mdn [a]	IQR	*Mdn* [a]	IQR	
Vigorous activity days/week		0.0–3.0	2.0	1.0–4.0	0.01
Vigorous activity time/day (min)	30.0	0.0–60.0	60.0	20.0–90.0	0.01
Moderate activity days/week	2.0	0.0–4.0	3.0	2.0–5.0	0.01
Moderate activity time/day (min)	30.0	0.0–90.0	60.0	30.0–120.0	0.02
Days/week walking ≥ 10 min	7.0	4.0–7.0	7.0	5.0–7.0	0.15
Walking time/day (min)	45.0	25.0–120.0	60.0	30.0–120.0	0.16
Sitting time/day (min), *M* (*SD*)	293.4 (174.8)		291.0 (205.1)		0.94

Note. IQR = interquartile range; LBP = low back pain. Comparisons made between LBP and control participants using *t* test (continuous data, normally distributed) or Mann-Whitney *U* test (continuous data, not normally distributed).

[a] Unless indicated otherwise.

or general practitioners. Notably, 11% of the UPWaRD LBP cohort underwent diagnostic imaging for their acute LBP episode, 6% received opioids for management of their LBP symptoms, and 4% received a specialty consultation (e.g., spinal surgeon). Routine use of diagnostic imaging, opioid medication, and specialist consultation in the absence of serious pathology is not recommended for acute LBP (Oliveira et al., 2018). As all participants in the UPWaRD cohort were carefully screened for the presence of serious pathology and signs of lumbosacral radiculopathy, this finding is likely to represent care that is discordant with current clinical practice guidelines. The observation of discordant care is consistent with studies of individuals with acute LBP presenting to Australian emergency departments (Machado et al., 2018). A recent prospective cohort study identified a linear relationship between guideline discordant care and increased risk of transition to chronicity (Stevans et al., 2021).

Previous research has linked psychological risk factors with the transition from acute to chronic LBP (Linton, 2000; Pincus et al., 2002). Psychological risk factors (i.e., depression, anxiety and stress, pain catastrophising, and pain self-efficacy beliefs) assessed in the UPWaRD acute LBP cohort at baseline were comparable to those of the pain-free participants, a finding that has been observed in previous comparable cohorts (Pengel et al., 2007). However, among the UPWaRD acute LBP participants, higher levels of depression, anxiety and stress, higher pain catastrophising, and lower pain self-efficacy at baseline were correlated with higher 6-month pain intensity and disability (Table 6). Systematic reviews of 13 LBP cohorts report similar findings, with depression and catastrophising consistently identified as significant risk factors for poor LBP outcome (Pinheiro et al., 2016; Wertli et al., 2014).

On average, LBP participants included in the UPWaRD cohort demonstrated a significant reduction in pain and disability between baseline and 3 months, yet no significant change in pain intensity and disability from the 3- to 6-month assessment. This is typical of LBP studies. A meta-analysis of 33 discrete cohorts identified a comparable recovery trajectory (Costa et al., 2012). Further, the UPWaRD LBP cohort reported similar recovery rates to other acute LBP cohorts (Klyne et al., 2020). At 6 months, 12 (12.5%) LBP participants in the UPWaRD cohort reported worse pain and disability from baseline or severe pain (NRS $\geq$ 7), 60 (62.5%) participants reported less pain and disability compared to baseline, and 24 (25%) participants reported no pain or disability. In the cohort described by Klyne and colleagues (2020), 15 (15.5%) participants reported worse or severe LBP, 66 (68.0%) reported less pain and disability, and 16 (16.5%) reported no pain or disability at 6-month follow-up. Similar rates of ongoing LBP at 6-month follow-up have been reported in other LBP cohorts (Baumbauer et al., 2020; Baliki et al., 2012; Müller et al., 2019).

The cohort profile presented here provides a transparent foundation for future longitudinal analyses; however, the UPWaRD study is not without limitations. Although missing data are inevitable in longitudinal trials, the presence of incomplete cases does represent a threat to the depth of the results. The UPWaRD cohort profile reports similar rates of missing data to most recent prospective cohort studies examining biological risk factors during an acute LBP episode (Klyne et al., 2020; Müller et al., 2019; Vachon-Presseau et al., 2016). Most missing data in this cohort occurred after the first laboratory session, and many baseline characteristics, with some exceptions, were similar between those who did and did not return for follow-up. Study attrition was likely due to inclusion of a high burden of laboratory measures that some participants found difficult to tolerate, and the time commitment involved in the study. In this cohort, individuals who were lost to follow-up at 3 or 6 months reported, at baseline, higher levels of depression, anxiety, stress, and pain catastrophising, higher pain interference, higher levels of moderate physical activity, and occupational difficulties due to pain. Future longitudinal cohort studies might benefit from considering this finding and implementing targeted, innovative methods to reduce attrition in participants with similar baseline characteristics.

Difficulties were experienced with recruitment, highlighted by the revised sample size and time taken to recruit the required number of LBP participants. Similar difficulties with recruitment have been reported by other groups conducting experimental LBP cohort studies (Klyne et al., 2020; Müller et al., 2019). Cohort studies conducted alongside randomised trials of new treatments appear to have greater recruitment success (Stevans et al., 2021) and this may be an important consideration for future LBP cohort study designs.

Another important limitation to consider is that pain and disability outcome measures for the UPWaRD LBP cohort were assessed over the week preceding the 3- and 6-month follow-up assessment. Consequently, it is not possible to determine whether the presence of pain and disability at 6 months follow-up reflects chronic LBP (i.e., pain that had persisted since the acute episode) or chronic recurrent LBP (i.e., a new episode of LBP following a pain-free period). This is acknowledged in our classification of the presence of LBP at 3- and 6-month follow-up (i.e., chronic or recurrent LBP). More frequent assessment of pain and disability over the course of the follow-up period (e.g., weekly/second weekly would allow evaluation of differing recovery trajectories (Costa et al., 2021; Klyne et al., 2018; Kongsted et al., 2015).

This cohort has already been used to investigate neurobiological risk factors underpinning transition from acute to chronic LBP, and how these factors are confounded (Jenkins et al., 2022) or interact with sociodemographic and psychosocial variables (Jenkins et al., 2023). Priorities for future research using data collected within the UPWaRD cohort include exploring proteomic and epigenetic biomarkers of poor LBP outcome, and assessing if psychological risk factors mediate 6-month LBP outcome. These research questions will be reported as secondary analyses of the UPWaRD study data. Both national and international collaborations have been formed to address these research questions. UPWaRD cohort data could be combined with other national or international cohorts that have collected similar data increasing confidence in the study findings reported. The UPWaRD team welcomes collaboration and research proposals.

CONCLUSION

This manuscript reports a cohort profile for the UPWaRD study.

Overall, the UPWaRD LBP cohort represents a generalisable sample of participants experiencing an acute episode of LBP within the community, many of whom seek and utilise treatment. Psychological risk factors (i.e., higher depression, anxiety and stress, higher pain catastrophising, and lower pain self-efficacy) assessed during acute LBP were correlated with higher pain and disability at 6 months. Participants experiencing acute LBP were older, had a higher BMI, and participated in lower levels of moderate and vigorous physical activity during an acute LBP episode compared with pain-free control participants. Participants who did not complete follow-up at 3 and 6 months had higher psychological distress, higher pain interference, higher levels of moderate physical activity, and reported occupational difficulties due to pain.

KEY POINTS

1. This cohort profile details the methodology used within the UPWaRD study to investigate a diverse range of neurobiological risk factors longitudinally.
2. Demographic, psychological, and social data described within this cohort profile can allow confounder adjustment or modelling of plausible interactions between biopsychosocial risk factors.
3. Baseline data described in this cohort profile suggest psychological risk factors were correlated with higher pain and disability at 6 months and participants experiencing acute LBP were older, had a higher BMI, and participated in lower levels of physical activity during an acute LBP episode compared with pain-free control participants.

DISCLOSURES

This work was supported by grant from the National Health and Medical Research Council (NHMRC) of Australia (Grant ID, 1059116). SMS and PWH receive salary support from the National Health and Medical Research Council of Australia (1105040 and 1102905, respectively). TGN is a part of Center for Neuroplasticity and Pain (CNAP) that is supported by the Danish National Research Foundation (DNRF121).

PERMISSIONS

All study procedures were approved by the Human Research Ethics Committees of Western Sydney University (H10465) and Neuroscience Research Australia (SSA:16/002) and in accordance with the Helsinki Declaration of 1975, as revised in 1983. All participants provided written, informed consent for participation in the study and its related procedures.

ACKNOWLEDGEMENTS

The authors thank all participants in the study.

ADDRESS FOR CORRESPONDENCE

Dr Siobhan Schabrun, Neuroscience Research Australia, 139 Barker St, Randwick NSW 2031, Australia.

Email: s.schabrun@neura.edu.au

REFERENCES

Antony, M. M., Bieling, P. J., Cox, B. J., Enns, M. W., & Swinson, R. P. (1998). Psychometric properties of the 42-item and 21-item versions of the depression anxiety stress scales in clinical groups and a community sample. *Psychological Assessment*, *10*(2), 176–181. https://doi.org/10.1037/1040-3590.10.2.176

Ardakani, E. M., Leboeuf-Yde, C., & Walker, B. F. (2019). Can we trust the literature on risk factors and triggers for low back pain? A systematic review of a sample of contemporary literature. *Pain Research and Management*, *2019*, 6959631. https://doi.org/10.1155/2019/6959631

Arendt-Nielsen, L., Brennum, J., Sindrup, S., & Bak, P. (1994). Electrophysiological and psychophysical quantification of temporal summation in the human nociceptive system. *European Journal of Applied Physiology and Occupational Physiology*, *68*(3), 266–273. https://doi.org/10.1007/BF00376776

Babiloni, C., Babiloni, F., Carducci, F., Cincotti, F., Rosciarelli, F., Rossini, P. M., Arendt-Nielsen, L., & Chen, A. C. (2001). Mapping of early and late human somatosensory evoked brain potentials to phasic galvanic painful stimulation. *Human Brain Mapping*, *12*(3), 168–179. https://doi.org/10.1002/1097-0193(200103)12:3%3C168::aid-hbm1013%3E3.0.co;2-o

Baliki, M. N., Petre, B., Torbey, S., Hermann, K. M., Huang, L., Schnitzer, T. J., Fields, H. L., & Apkarian, A. V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature Neuroscience*, *15*(8), 1117–1119. https://doi.org/10.1038/nn.3153

Baumbauer, K. M., Ramesh, D., Perry, M., Carney, K. B., Julian, T., Glidden, N., Dorsey, S. G., Starkweather, A. R., & Young, E. E. (2020). Contribution of COMT and BDNF genotype and expression to the risk of transition from acute to chronic low back pain. *The Clinical Journal of Pain, 36*(6), 430–439. https://doi.org/10.1097/AJP.0000000000000819

Bibikova, M., Barnes, B., Tsan, C., Ho, V., Klotzle, B., Le, J. M., Delano, D., Zhang, L., Schroth, G. P., Gunderson, K. L., Fan, J.-B., & Shen, R. (2011). High density DNA methylation array with single CpG site resolution. *Genomics*, *98*(4), 288–295. https://doi.org/10.1016/j.ygeno.2011.07.007

Boonstra, A. M., Stewart, R. E., Köke, A. J., Oosterwijk, R. F., Swaan, J. L., Schreurs, K. M., & Schiphorst Preuper, H. R. (2016). Cut-off points for mild, moderate, and severe pain on the numeric rating scale for pain in patients with chronic musculoskeletal pain: Variability and influence of sex and catastrophizing. *Frontiers in Psychology*, *7*, 1466. https://doi.org/10.3389/fpsyg.2016.01466

Chang, W.-J., Buscemi, V., Liston, M. B., McAuley, J. H., Hodges, P. W., & Schabrun, S. M. (2019). Sensorimotor cortical activity in acute low back pain: A cross-sectional study. *The Journal of Pain, 20*(7), 819–829. https://doi.org/10.1016/j.jpain.2019.01.006

Clarke, S. M., Henry, H. M., Dodds, K. G., Jowett, T. W., Manley, T. R., Anderson, R. M., & McEwan, J. C. (2014). A high throughput single nucleotide polymorphism multiplex assay for parentage assignment in New Zealand sheep. *PloS One*, *9*(4). https://doi.org/10.1371/journal.pone.0093392

Costa, L., Maher, C. G., Hancock, M. J., McAuley, J. H., Herbert, R. D., & Costa, L. O. (2012). The prognosis of acute and persistent low-back pain: A meta-analysis. *CMAJ*, *184*(11), E613–E624. https://doi.org/10.1503/cmaj.111271

Costa, N., Smits, E., Kasza, J., Salomoni, S., Ferreira, M., Sullivan, M., & Hodges, P. W. (2021). ISSLS prize in clinical science 2021: What are the risk factors for low back pain flares and does this depend on how flare is defined? *European Spine Journal*, 30, 1089–1097 https://doi.org/10.1007/s00586-021-06730-6

Cunningham, C. N., Jenkins, L. C., Chang, W.-J., McAuley, J. H., & Schabrun, S. M. (2021). Relative and absolute reliability of somatosensory evoked potentials in response to non-noxious electrical stimulation of the paraspinal muscles in healthy participants at an interval of 3-months. *International Journal of Neuroscience*, 133(1), 103–109. https://doi.org/10.1080/00207454.2021.1893722

De Vet, C. W. H., Heymans, W. M., Dunn, M. K., Pope, P. D., van der Beek, J. A., Macfarlane, J. G., Bouter, M. L., & Croft, R. P. (2002). Episodes of low back pain: A proposal for uniform definitions to be used in research. *Spine*, *27*(21), 2409–2416. https://doi.org/10.1097/01.BRS.0000030307.34002.BE

Desmeules, J. A., Cedraschi, C., Rapiti, E., Baumgartner, E., Finckh, A., Cohen, P., Dayer, P., & Vischer, T. L. (2003). Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. *Arthritis & Rheumatism*, *48*(5), 1420–1429. https://doi.org/10.1002/art.10893

Dieleman, J. L., Cao, J., Chapin, A., Chen, C., Li, Z., Liu, A., Horst, C., Kaldjian, A., Matyasz, T., Scott, K. W., Bui, A. L., Campbell, M., Duber, H. C., Dunn, A. C., Flaxman, A. D., Fitzmaurice, C., Naghavi, M., Sadat, N., Shieh, P., . . . Murray, C. J. L. (2020). US health care spending by payer and health condition, 1996-2016. *JAMA*, *323*(9), 863–884. https://doi.org/10.1001/jama.2020.0734

Diers, M., Koeppe, M. C., Diesch, M. E., Stolle, M. A., Hölzl, M. R., Schiltenwolf, M. M., van Ackern, K., & Flor, H. (2007). Central processing of acute muscle pain in chronic low back pain patients: An EEG mapping study. *Journal of Clinical Neurophysiology*, *24*(1), 76–83. https://doi.org/10.1097/01.wnp.0000241093.00844.0e

Ebrahim, S. (2004). Cohorts, infants and children. *International Journal of Epidemiology*, *33*(6), 1165–1166. https://doi.org/10.1093/ije/dyh368

Elgaeva, E. E., Tsepilov, Y., Freidin, M. B., Williams, F. M., Aulchenko, Y., & Suri, P. (2019). ISSLS prize in clinical science 2020. Examining causal effects of body mass index on back pain: A Mendelian randomization study. *European Spine Journal*, *29*(4), 686–691. https://doi.org/10.1007/s00586-019-06224-6

Flor, H., Braun, C., Elbert, T., & Birbaumer, N. (1997). Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neuroscience Letters*, *224*(1), 5–8. https://doi.org/10.1016/S0304-3940(97)13441-3

Harrell Jr, F. E. (2015). *Regression modeling strategies: With applications to linear models, logistic and ordinal regression, and survival analysis*. Springer.

Hartvigsen, J., Hancock, M. J., Kongsted, A., Louw, Q., Ferreira, M. L., Genevay, S., Hoy, D., Karppinen, J., Pransky, G., Sieper, J., Smeets, R. J., & Underwood, M; on behalf of the Lancet Low Back Pain Series Working Group. (2018). What low back pain is and why we need to pay attention. *The Lancet*, *391*(10137), 2356–2367. https://doi.org/10.1016/S0140-6736(18)30480-X

Hayden, J., Chou, R., Hogg-Johnson, S., & Bombardier, C. (2009). Systematic reviews of low back pain prognosis had variable methods and results—Guidance for future prognosis reviews. *Journal of Clinical Epidemiology*, *62*(8), 781–796 e781. https://doi.org/10.1016/j.jclinepi.2008.09.004

Henschke, N., Maher, C. G., Refshauge, K. M., Herbert, R. D., Cumming, R. G., Bleasel, J., York, J., Das, A., & McAuley, J. H. (2008). Prognosis in patients with recent onset low back pain in Australian primary care: Inception cohort study. *BMJ, 337*(7662), a171. https://doi.org/10.1136/bmj.a171

Hill, J. C., Dunn, K. M., Lewis, M., Mullis, R., Main, C. J., Foster, N. E., & Hay, E. M. (2008). A primary care back pain screening tool: Identifying patient subgroups for initial treatment. *Arthritis Care & Research*, *59*(5), 632–641. https://doi.org/10.1002/art.23563

Homan, R. W., Herman, J., & Purdy, P. (1987). Cerebral location of international 10–20 system electrode placement. *Electroencephalography and Clinical Neurophysiology*, *66*(4), 376–382. https://doi.org/10.1016/0013-4694(87)90206-9

Hoy, D., Bain, C., Williams, G., March, L., Brooks, P., Blyth, F., Woolf, A., Vos, T., & Buchbinder, R. (2012). A systematic review of the global prevalence of low back pain. *Arthritis and Rheumatism*, *64*(6), 2028–2037. https://doi.org/10.1002/art.34347

Hoy, D., Brooks, P., Blyth, F., & Buchbinder, R. (2010). The epidemiology of low back pain. *Best Practice & Research Clinical Rheumatology*, *24*(6), 769–781. https://doi.org/10.1016/j.berh.2010.10.002

Jenkins, L. C., Chang, W.-J., Buscemi, V., Liston, M., Skippen, P., Cashin, A. G., McAuley, J. H., & Schabrun, S. M. (2022). Low somatosensory cortex excitability in the acute stage of low back pain causes chronic pain. *The Journal of Pain*, *23*(2), 289–304. https://doi.org/10.1016/j.jpain.2021.08.003

Jenkins, L. C., Chang, W.-J., Buscemi, V., Liston, M., Toson, B., Nicholas, M., Graven-Nielsen, T., Ridding, M., Hodges, P. W., & McAuley, J. H. (2019). Do sensorimotor cortex activity, an individual's capacity for neuroplasticity, and psychological features during an episode of acute low back pain predict outcome at 6 months: A protocol for an Australian, multisite prospective, longitudinal cohort study. *BMJ Open*, *9*(5), e029027. https://doi.org/10.1136/bmjopen-2019-029027

Jenkins, L. C., Chang, W.-J., Buscemi, V., Liston, M., Humburg, P., Nicholas, M., Graven-Nielsen, T., Hodges, P. W., McAuley, J. H., & Schabrun, S. M. (2023). Cortical function and sensorimotor plasticity are prognostic factors associated with future low back pain after an acute episode: The Understanding persistent Pain Where it ResiDes prospective cohort study. *Pain*, *164*(1), 14–26. https://doi.org/10.1097/j.pain.0000000000002684

Keel, J. C., Smith, M. J., & Wassermann, E. M. (2001). A safety screening questionnaire for transcranial magnetic stimulation. *Clinical Neurophysiology, 112*(4), 720. https://doi.org/10.1016/S1388-2457(00)00518-6

Kent, P. M., & Keating, J. L. (2008). Can we predict poor recovery from recent-onset nonspecific low back pain? A systematic review. *Manual Therapy*, *13*(1), 12–28. https://doi.org/10.1016/j.math.2007.05.009

Klyne, D., Barbe, M., Hoorn, W., & Hodges, P. (2018). ISSLS prize in clinical science 2018: Longitudinal analysis of inflammatory, psychological, and sleep-related factors following an acute low back pain episode—The good, the bad, and the ugly. *European Spine Journal*, *27*(4), 763–777. https://doi.org/10.1007/s00586-018-5490-7

Klyne, D. M., Moseley, G. L., Sterling, M., Barbe, M. F., & Hodges, P. W. (2019). Are signs of central sensitization in acute low back pain a precursor to poor outcome? *The Journal of Pain*, *20*(8), 994–1009. https://doi.org/10.1016/j.jpain.2019.03.001

Klyne, D. M., Schmid, A. B., Moseley, G. L., Sterling, M., & Hodges, P. W. (2015). Effect of types and anatomic arrangement of painful stimuli on conditioned pain modulation. *Journal of Pain*, *16*(2), 176–185. https://doi.org/10.1016/j.jpain.2014.11.005

Klyne, D. M., van den Hoorn, W., Barbe, M. F., Cholewicki, J., Hall, L. M., Khan, A., Meroni, R., Moseley, G. L., Nicholas, M., O'Sullivan, L., Park, R., Russell, G., Sterling, M., & Hodges, P. W. (2020). Cohort profile: Why do people keep hurting their back? *BMC Research Notes*, *13*(1), 538. https://doi.org/10.1186/s13104-020-05356-z

Kongsted, A. P., Kent, P. P., Hestbaek, L. P., & Vach, W. P. (2015). Patients with low back pain had distinct clinical course patterns that were typically neither complete recovery nor constant pain. A latent class analysis of longitudinal data. *The Spine Journal*, *15*(5), 885–894. https://doi.org/10.1016/j.spinee.2015.02.012

Lee, P. H., Macfarlane, D. J., Lam, T. H., & Stewart, S. M. (2011). Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. *International Journal of Behavioral Nutrition Physical Activity*, *8*, 115.

Lin, C.-W. C., McAuley, J. H., Macedo, L., Barnett, D. C., Smeets, R. J., & Verbunt, J. A. (2011). Relationship between physical activity and disability in low back pain: A systematic review and meta-analysis. *Pain*, *152*(3), 607–613. https://doi.org/10.1016/j.pain.2010.11.034

Lin, C.-W., Verwoerd, A. J. H., Maher, C. G., Verhagen, A. P., Pinto, R. Z., Luijsterburg, P. A. J., & Hancock, M. J. (2014). How is radiating leg pain defined in randomized controlled trials of conservative treatments in primary care? A systematic review. *European Journal of Pain*, *18*(4), 455–464. https://doi.org/10.1002/j.1532-2149.2013.00384.x

Linton, J. S. (2000). A review of psychological risk factors in back and neck pain. *Spine*, *25*(9), 1148–1156. https://doi.org/10.1097/00007632-200005010-00017

Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the depression anxiety stress scales* (2nd ed.). Psychology Foundation of Australia.

Machado, G. C., Rogan, E., & Maher, C. G. (2018). Managing non-serious low back pain in the emergency department: Time for a change? *Emergency Medicine Australasia*, *30*(2), 279–282. https://doi.org/10.1111/1742-6723.12903

Maher, C., Underwood, M., & Buchbinder, R. (2017). Non-specific low back pain. *The Lancet*, *389*(10070), 736–747. https://doi.org/10.1016/S0140-6736(16)30970-9

Manchikanti, L., Singh, V., Falco, F. J., Benyamin, R. M., & Hirsch, J. A. (2014). Epidemiology of low back pain in adults. *Neuromodulation: Technology at the Neural Interface*, *17*(Suppl 2), 3–10. https://doi.org/10.1111/ner.12018

Müller, M., Curatolo, M., Limacher, A., Neziri, A. Y., Treichel, F., Battaglia, M., Arendt-Nielsen, L., & Jüni, P. (2019). Predicting transition from acute to chronic low back pain with quantitative sensory tests—A prospective cohort study in the primary care setting. *European Journal of Pain*, *23*(5), 894–907. https://doi.org/10.1002/ejp.1356

Nicholas, M. K. (2007). The pain self-efficacy questionnaire: Taking pain into account. *European Journal of Pain*, *11*(2), 153–163. https://doi.org/10.1016/j.ejpain.2005.12.008

O'Connell, N. E., Maskill, D. W., Cossar, J., & Nowicky, A. V. (2007). Mapping the cortical representation of the lumbar paravertebral muscles. *Clinical Neurophysiology*, *118*(11), 2451–2455. https://doi.org/10.1016/j.clinph.2007.08.006

Oliveira, C. B., Maher, C. G., Pinto, R. Z., Traeger, A. C., Lin, C.-W. C., Chenot, J.-F., van Tulder, M., & Koes, B. W. (2018). Clinical practice guidelines for the management of non-specific low back pain in primary care: An updated overview. *European Spine Journal*, *27*(11), 2791–2803. https://doi.org/10.1007/s00586-018-5673-2

Parkitny, L., McAuley, J. H., Walton, D., Costa, L. O. P., Refshauge, K. M., Wand, B. M., Di Pietro, F., & Moseley, G. L. (2012). Rasch analysis supports the use of the depression, anxiety, and stress scales to measure mood in groups but not in individuals with chronic low back pain. *Journal of Clinical Epidemiology*, *65*(2), 189–198. https://www.jclinepi.com/article/S0895-4356(11)00188-0/fulltext

Pengel, L. H., Refshauge, K. M., Maher, C. G., Nicholas, M. K., Herbert, R. D., & McNair, P. (2007). Physiotherapist-directed exercise, advice, or both for subacute low back pain: A randomized trial. *Annals of Internal Medicine*, *146*(11), 787–796. https://doi.org/10.7326/0003-4819-146-11-200706050-00007

Pincus, T., Burton, A. K., Vogel, S., & Field, A. P. (2002). A systematic review of psychological factors as predictors of chronicity/disability in prospective cohorts of low back pain. *Spine*, *27*(5), E109–E120. https://doi.org/10.1097/00007632-200203010-00017

Pinheiro, M. B., Ferreira, M. L., Refshauge, K., Maher, C. G., Ordoñana, J. R., Andrade, T. B., Tsathas, A., & Ferreira, P. H. (2016). Symptoms of depression as a prognostic factor for low back pain: A systematic review. *The Spine Journal*, *16*(1), 105–116. https://doi.org/10.1016/j.spinee.2015.10.037

Roland, M., & Morris, R. (1983). A study of the natural history of back pain: Part I: Development of a reliable and sensitive measure of disability in low-back pain. *Spine*, *8*(2), 141–144. https://doi.org/10.1097/00007632-198303000-00004

Sandoval, J., Heyn, H., Moran, S., Serra-Musach, J., Pujana, M. A., Bibikova, M., & Esteller, M. (2011). Validation of a DNA methylation microarray for 450,000 CpG sites in the human genome. *Epigenetics*, *6*(6), 692–702. https://doi.org/10.4161/epi.6.6.16196

Schabrun, M. S., Elgueta-Cancino, L. E., & Hodges, W. P. (2017). Smudging of the motor cortex is related to the severity of low back pain. *Spine*, *42*(15), 1172–1178. https://doi.org/10.1097/BRS.0000000000000938

Schabrun, S. M., Jones, E., Elgueta Cancino, E. L., & Hodges, P. W. (2014). Targeting chronic recurrent low back pain from the top-down and the bottom-up: A combined transcranial direct current stimulation and peripheral electrical stimulation intervention. *Brain Stimul*ation, *7*(3), 451–459. https://doi.org/10.1016/j.brs.2014.01.058

Shiri, R., & Falah-Hassani, K. (2017). Does leisure time physical activity protect against low back pain? Systematic review and meta-analysis of 36 prospective cohort studies. *British Journal of Sports Medicine*, *51*(19), 1410–1418. https://doi.org/10.1136/bjsports-2016-097352

Shiri, R., Karppinen, J., Leino-Arjas, P., Solovieva, S., & Viikari-Juntura, E. (2010). The association between smoking and low back pain: A meta-analysis. *The American Journal of Medicine*, *123*(1), 87. e7–e35. https://doi.org/10.1016/j.amjmed.2009.05.028

Skljarevski, V., & Ramadan, N. M. (2002). The nociceptive flexion reflex in humans – review article. *Pain*, *96*(1), 3–8. https://doi.org/10.1016/S0304-3959(02)00018-0

Stanton, T. R., Henschke, N., Maher, C. G., Refshauge, K., Latimer, J., & McAuley, J. H. (2008). After an episode of acute low back pain, recurrence is unpredictable and not as common as previously thought. *Spine*, *33*(26), 2923–2928 https://doi.org/10.1097/BRS.0b013e31818a3167

Stevans, J. M., Delitto, A., Khoja, S. S., Patterson, C. G., Smith, C. N., Schneider, M. J., Freburger, J. K., Greco, C. M., Freel, J. A., & Sowa, G. A. (2021). Risk factors associated with transition from acute to chronic low back pain in US patients seeking primary care. *JAMA Network Open*, *4*(2), e2037371. https://doi.org/10.1001/jamanetworkopen.2020.37371

Sullivan, M. J., Bishop, S. R., & Pivik, J. (1995). The Pain Catastrophizing Scale: Development and validation. *Psychological Assessment*, *7*(4), 524–532. https://doi.org/10.1037/1040-3590.7.4.524

Tardif, H., Arnold, C., Hayes, C., & Eagar, K. (2017). Establishment of the Australasian electronic persistent pain outcomes collaboration. *Pain Medicine*, *18*(6), 1007–1018. https://doi.org/10.1093/pm/pnw201

Tsao, A. H., Danneels, W. L., & Hodges, W. P. (2011). ISSLS prize winner: Smudging the motor brain in young adults with recurrent low back pain. *Spine*, *36*(21), 1721–1727. https://doi.org/10.1097/BRS.0b013e31821c4267

Vachon-Presseau, E., Tétreault, P., Petre, B., Huang, L., Berger, S. E., Torbey, S., Baria, A. T., Mansour, A. R., Hashmi, J. A., Griffith, J. W., Comasco, E., Schnitzer, T. J., Baliki, M. N., & Apkarian, A. V. (2016). Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain*, *139*(7), 1958–1970. https://doi.org/10.1093/brain/aww100

Vittinghoff, E., & McCulloch, C. E. (2007). Relaxing the rule of ten events per variable in logistic and Cox regression. *American Journal of Epidemiology*, *165*(6), 710–718. https://doi.org/10.1093/aje/kwk052

Vos, T., Abate, K. H., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abdulkader, R. S., Abdulle, A. M., Abera, S. F., Abu-Raddad, L. J., Adetokunboh, O., Afshin, A., Agarwal, S. K., Aggarwal, R., Agrawal, A., Agrawal, S., Ahmadieh, H., Ahmed, M. B., Aichour, A. N., Aichour, I., . . . Criqui, M. H; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, *390*(10100), 1211–1259. https://doi.org/10.1016/s0140-6736(17)32154-2

Wertli, M. M., Eugster, R., Held, U., Steurer, J., Kofmehl, R., & Weiser, S. (2014). Catastrophizing—A prognostic factor for outcome in patients with low back pain: A systematic review. *The Spine Journal*, *14*(11), 2639–2657. https://doi.org/10.1016/j.spinee.2014.03.003

Willer, J. C. (1977). Comparative study of perceived pain and nociceptive flexion reflex in man. *Pain (Amsterdam)*, *3*(1), 69–80. https://doi.org/10.1016/0304-3959(77)90036-7

Williams, C. M., Maher, C. G., Latimer, J., McLachlan, A. J., Hancock, M. J., Day, R. O., & Lin, C.-W. C. (2014). Efficacy of paracetamol for acute low-back pain: A double-blind, randomised controlled trial. *The Lancet*, *384*(9954), 1586–1596. https://doi.org/10.1016/S0140-6736(14)60805-9

Appendix A

Table A1

Detailed Description of Measures Collected in the UPWaRD Study

Measure	Description	Assessed in		Units/range
		LBP	Control	
Health				
Age, height [a], weight [a], sex [b]	Self-reported age, height, weight, sex	✓	✓	Years, cm, kg, male/female
BMI [a]	Weight (kg) divided by height^2 (cm)	✓	✓	Numerical
Comorbidities [a, b]	Self-selected comorbid conditions other than LBP from a list (including "other")	✓	✓	Yes/no, type
Health care usage [a]	Self-reported health care usage from a list including GP, medical specialist, health professionals other than doctors, emergency department, hospital admission, and diagnostic tests	✓	✓	Frequency, type
Medication usage [a]	Self-reported medication usage	✓	✓	Dosage, frequency, type
Previous LBP [b]	Self-reported previous incidence(s) of LBP	✓	✓	Yes/no
Sociodemographic				
Cultural diversity [a, b]	Each participant was asked the question: "How do you define your identity, in ethnic or cultural terms?" If the participant identified a cultural or ethnic background other than "English", "Caucasian", or "Australian" they were considered culturally and linguistically diverse for the purpose of this study.	✓	✓	Type
Education level [a, b]	Self-selected highest education level from a list (e.g., primary school, completed secondary school, post-graduate degree).	✓	✓	Type
Employment status [a]	Self-selected employment status from a list (e.g., full-time paid employment, studying, retired).	✓	✓	Type
Impending compensation [a]	Self-reported impending or current compensation case related to the LBP episode.	✓		Yes/no, type
Sickness benefits [a]	Self-reported sickness benefits associated with the participants' LBP episode.	✓		Yes/no
Pain affected work [a]	Self-reported pain affected work hours or whether pain affects the type of work the respondent can complete.	✓		Yes/no
Psychological				
21-item depression, anxiety and stress subscale (DASS-21) (Lovibond & Lovibond, 1995)	Questionnaire: Evaluates symptoms of depression, anxiety and tension-stress. Consists of 21 items with responses quantified on a four-point Likert scale ranging from 0 ("not at all") to 3 ("applied to me very much, or most of the time"). Yields a total score as well as three subscale scores: DASS-depression (low positive affect), DASS-anxiety (psychological hyper-arousal), and DASS-stress (e.g., tension or irritability).	✓	✓	0–63: Higher score = higher distress along the three axes of depression, anxiety, and stress Subscales: depression (0–21; ≥ 11 = severe), anxiety (0–21; ≥ 8 = severe), stress (0–21; ≥ 13 = severe)
Pain self-efficacy questionnaire (PSEQ) (Nicholas, 2007)	Questionnaire: evaluates an individual's confidence in their ability to perform a range of functional activities while in pain. Consists of 10 items. Respondents rate how confident they are in performing each item using a seven-point Likert scale.	✓		0–60: Higher score = higher self-efficacy beliefs

Measure	Description	Assessed in		Units/range
		LBP	Control	
Pain catastrophising scale (PCS) (Sullivan et al., 1995)	Questionnaire: evaluates thoughts and feelings related to catastrophic cognitions when in pain. Consists of 13 items with responses quantified on a five-point Likert scale ranging from 0 ("not at all") to 4 ("all the time"). Yields a total score as well as three subscales: magnification (3 items), rumination (4 items), and helplessness (6 items).	✓		0–52: Higher score = higher pain catastrophising Subscales: magnification (0– 12), rumination (0– 16), helplessness (0– 24)
Clinical				
The Keele StarT Back Screening Tool (SBT) (Hill et al., 2008) [a, b]	Questionnaire: The SBT is a brief, validated tool, designed to screen patients presenting to primary care with acute LBP. Respondents select if they agree or disagree with the first eight items (e.g., "my back pain spread down my leg(s) at some point in the last 2 weeks"), then rate the overall bothersomeness of their LBP using a five-point Likert scale from ("0 = not at all") to 4 ("extremely").	✓		Respondents reporting a score of 0–3 are classified as low-risk and those reporting scores of ≥ 4 overall as medium-risk. Respondents are considered at high-risk of a worse outcome if they score 4 or 5 in the distress subscale score (questions 5–9)
Neurobiological				
Sensory evoked potentials (electroencephalography recording, SEPs)	Laboratory measure: SEPs were assessed based on our previous work demonstrating reliability of this measure in healthy participants (Cunningham et al., 2021). Participants were seated comfortably in a chair with eyes closed. Electroencephalographic SEPs were recorded using gold-plated cup electrodes positioned over the primary sensory cortex contralateral to the side of worst pain for LBP participants, or contralateral to the dominant hand in healthy controls, and referenced to Fz using the International 10/20 System (Homan et al., 1987). A constant current stimulator delivered two blocks of 500 non-noxious electrical stimuli through a single bipolar electrode positioned 3 cm lateral to the L3 spinous process, ipsilateral to the side of the worst LBP, or dominant hand for healthy controls. Individual SEP traces were manually inspected and averaged for analysis. Distinct SEP components are thought to reflect sensory afferent processing within the human cortex and the area under the rectified curve for each component was a candidate predictor reported a priori in the study protocol (N_{80} – primary sensory cortex excitability, N_{150} – secondary sensory cortex excitability, P_{260} – anterior cingulate cortex excitability (Babiloni et al., 2001; Diers et al., 2007; Flor et al., 1997)).	✓	✓	Latency (ms), Area under the rectified curve (μV)

Measure	Description	Assessed in		Units/range
		LBP	Control	
Corticomotor excitability	Laboratory measure: The corticomotor response to transcranial magnetic stimulation (TMS) was assessed using an established mapping paradigm and based on our previous work (Chang et al., 2019; O'Connell et al., 2007; Schabrun et al., 2014; Tsao et al., 2011). Participants sat comfortably in a chair and electrodes were placed on the paraspinal muscles 3 cm lateral to the spinous process of L3 and 1 cm lateral to the spinous process of L5 (Noraxon USA Inc, Arizona, USA). Participants were fitted with a tight-fitting cap, marked with a 6 x 7 cm grid oriented to the vertex. Single-pulse, monophasic stimuli (Magstim 200 stimulator/7 cm figure-of-eight coil; Magstim Co. Ltd. Dyfed, UK) was then delivered over M1 contralateral to the side of the worst LBP, starting at the vertex. For healthy controls, M1 contralateral to the dominant hand was stimulated. Five stimuli were delivered over each site on the grid with an inter-stimulus interval of 6 s at 100% of maximum stimulator output. Participants maintained activation of their paraspinal extensor muscles to 20 ± 5% of their EMG recorded during a maximum voluntary contraction throughout the stimulation with constant feedback of real-time EMG displayed on a monitor. Parameters calculated from the normalised motor cortical maps are described in the study protocol (Jenkins et al., 2019).	✓	✓	Map volume (cm^2) Centre of gravity (cm)
Brain derived neurotrophic factor (BDNF) genotype and serum concentration [b]	Laboratory measure: Buccal swabs were taken on the day of baseline testing (Isohelix DNA Isolation Kit) and immediately frozen and stored at –80°C. Genomic DNA samples were polymerase chain reaction amplified and sequenced by the Australian Genome Research Facility. Genotyping was performed as recommended by the manufacturer with reagents included in the iPLEX Gold SNP genotyping kit (Agena) and the software and equipment provided with the MassARRAY platform (Agena) (Clarke et al., 2014). BDNF serum concentration was analysed using the same methodology as described for analysing serum cytokine levels. Cartridge limits of detection for BDNF serum concentration were 5.25 pg/ml and samples below this level were allocated a value of zero.	✓	✓	Genotype: Met/Met, Met/Val, Val/Val Serum concentration: pg/mL
Biological				
Serum cytokines [a]	Laboratory measure: Serum concentrations of IL-1β, IL-2, IL-4, IL-6, IL-8. IL-10, IL-15, TNF, CRP, TGF-β1. Peripheral venous blood was drawn, clotted (30 min, room temperature), and separated by centrifugation (2500 rpm, 15 min). Serum samples were pipetted into 50 µL aliquots and stored at -80°C until analysis. After thawing, concentrations of each biomarker were determined using "high-sensitive" enzyme-linked immunosorbent assays (ELISA, Protein Simple, CA, USA). Samples were loaded into the cartridge according to a standard procedure provided by the manufacturers and immunoassay scans processed with no user activity. Built in cartridge limits of detection for each biomarker were as follows: (1) IL-1β: 0.064 pg/ml; (2) IL-2: 0.18 pg/ml; (3) IL-4: 0.16 pg/ml; (4) IL- 6: 0.26 pg/ml; (5) IL-8: 0.08 pg/ml; (6) IL-10: 0.14 pg/ml; (7) 1L-15: 0.19 pg/ml; (8) TNF: 0.278 pg/ml; (9) CRP: 1.24 pg/ml; (10) TGF-β1: 5.29 pg/ml. Zero was allocated for values below the reported sensitivity of the test.	✓	✓	pg/mL

Measure	Description	Assessed in		Units/range
		LBP	Control	
Serum proteomic profile [a]	Serum samples for a subgroup of 60 participants with acute LBP were prepared by digesting 3µl of serum (57µg ul-1 +/-7µg) in 50µl of 50mM AMBIC, 2M urea, 10mM DTT at pH 8 using trypsin at 25°C for 16 hours in a 1:100 enzyme to protein ratio. Serum peptides were fractionated using hydrophobic interaction chromatography (HILIC) according to the manufacturer's protocol (PolyLC Inc, MD, USA). Digested and fractionated peptides were reconstituted in 5µL 0.1% formic acid and separated by nano-LC using an Ultimate 3000 HPLC and autosampler (Dionex, Amsterdam, Netherlands). The QExactive (Thermo Electron, Bremen, Germany) mass spectrometer was run in DDA mode. Proteins were identified from the Uniprot database. Protein identifications were accepted if they could be established at less than 5% FDR and contained at least two identified peptides.			Spectral count, normalised by total ion count
Genome-wide DNA methylation [a, b]	Buchal swabs obtained from the cheek of participants on the day of baseline testing were used to prepare genomic DNA for a subgroup of 60 participants with acute LBP (Isohelix DNA Isolation Kit). Samples were immediately frozen at -80°C and stored. Samples were sent to Australian Genome Research Facility (Melbourne node) where they underwent quality assessment using QuantiFluor. The samples were then normalised to approximately 250ng of DNA in 45µL and bisulfite converted with Zymo EZ-96 DNA Methylation kit (Zymo Research, Orange, CA). DNA was whole-genome amplified, enzymatically fragmented, purified, and applied to the Illumina MerthylationEPIC BeadChips (Illumina, San Diego, CA) according to the Illumina methylation protocol (Bibikova et al., 2011; Sandoval et al., 2011). Beadchips were scanned using the Illumina HiScan SQ and the methylation score for each CpG was represented as a β value according to the fluorescent intensity ratio.	✓		Type: Differentially methylated genes
Pain processing				
Pressure pain sensitivity [a]	Laboratory measure: Pressure pain thresholds (PPT) were assessed using a hand help pressure algometer (Somedic, Hörby, Sweden, probe size 1cm^2) at three distinct sites: (1) the site of worst LBP (side of most pain on palpation); (2) 3 cm lateral to the L3 spinous process on the less painful side of the lower back; and (3) the thumbnail bed (PPT) of the hand contralateral to worst LBP. For pain-free controls, PPTs were measured 3 cm lateral to the L3 spinous process bilaterally and over the thumbnail bed of the dominant hand. Pressure was applied at a rate of 40 kPa/s and participants used a hand-held trigger to indicate when the sensation of pressure first changed to one of pain. Three measures were made at each site and averaged for analysis.	✓	✓	PPT (kPa, higher score = higher threshold to pressure pain)

Measure	Description	Assessed in		Units/range
		LBP	Control	
Heat pain sensitivity [a]	Laboratory measure: Heat pain thresholds were measured (Thermal Sensory Analyzer, TSA-2001, Q-Sense-CPM, Medoc Ltd, Ramat Yishai, Israel). A 30 x 30 mm Peltier-based thermode was placed on the skin and HPT measured at three sites: (1) site of worst LBP, (2) the opposite side of the lumbar region, and (3) the ventral aspect of the forearm on the side of worst pain. For pain-free controls, HPTs were measured 3 cm lateral to the L3 spinous process bilaterally and over the ventral aspect of the forearm of the dominant hand. The temperature started at 32°C and increased at a rate of 0.5° C/s. Participants were instructed to push a button when the sensation of heat first changed to one of pain. Three measures were made at each site and the average at each site used for analyses.	✓	✓	HPT (°C, higher score = higher threshold to heat pain)
Descending pain modulation [a]	Laboratory measure: Assessed using an established conditioned pain modulation (CPM) paradigm (Klyne et al., 2015). PPT was used as the test stimulus (TS) and noxious heat (1° C > HPT) as the conditioning stimulus (CS). Participants completed two trials in random order separated by a 15-min break: (Trial 1) TS at the site of worst LBP and CS on the opposite forearm; (Trial 2) TS at the ipsilateral forearm of worst LBP and CS on the low back opposite to the side of worst pain. In pain-free controls the TS for Trial 1 was the lower back at the level of L3 ipsilateral to the dominant hand and CS on the opposite forearm. For Trial 2, the TS was applied to the forearm of the dominant hand and CS on the low back at the level of L3 opposite the side of TS. Three consecutive PPTs were measured before the application of heat (TS_1). Noxious heat was then applied and maintained for the duration of the test, with three consecutive PPTs re-measured 30 s post heat application (TS_2). Participants were instructed to rate their pain on a numerical rating scale (0–100) at 0 s, 30 s and immediately following the final PPT measurement. Pain scores were maintained between 50 and 80/100 during testing. The test stimulus was adjusted by 1° C as required to achieve a pain score within this range. The CPM response was calculated as TS_2 minus TS_1.	✓	✓	CPM (kPa, > 0 = pain inhibition, < 0 = deficient pain inhibition)
Nociceptor flexor withdrawal reflex (NFR) [a]	Laboratory measure: The NFR was recorded from the biceps femoris muscle on the side of worst LBP (or matched side in pain-free controls). Electrical stimuli were delivered to the sural nerve within the retro-malleolar pathway according to a +/- 20 s variable interval schedule. The NFR threshold was determined as the lowest stimulator intensity that elicited a reflex (4 mA increase until reflex detected, then 2 mA decrease until reflex absent). The stimulus intensity was then set at 120% of the NFR threshold and five trials recorded. The NFR was identified as the multiphasic response occurring 90–200 ms after each stimulus (Arendt-Nielsen et al., 1994; Desmeules et al., 2003; Skljarevski & Ramadan, 2002; Willer, 1977).	✓	✓	Amplitude (mV) Latency (ms)

Measure	Description	Assessed in		Units/range
		LBP	Control	
Lifestyle				
International Physical Activity Questionnaire (IPAQ) (Lee et al., 2011) [a]	Questionnaire including seven items evaluating health-related physical activity. Respondents report the volume of physical activity performed over the previous week, including vigorous activity (activities that make breathing much harder than normal), moderate activity (activities that make breathing somewhat harder than normal), walking, and sitting time.		✓	Higher score = higher physical activity (refer to scoring manual for calculating and interpreting MET scores and activity categories)

Note. BDNF = Brain derived neurotrophic factor; CRP = C–reactive protein; EMG = electromyography; IL–1β = interleukin–1 beta; IL–2 = interleukin–2; IL–4 = interleukin–4; IL–6 = interleukin–6; IL–8 = interleukin–8; IL–10 = interleukin–10; 1L–15 = interleukin–15; LBP = low back pain; kPa = kilo Pascal; M1 = primary motor cortex; Met = Methionine; MET = metabolic equivalent of task; SEP = sensory evoked potentials; TGF–β1 = transforming growth factor beta–1; TMS = transcranial magnetic stimulation; TNF = tumour necrosis factor; Val = Valine.

[a] Indicates measure is additional to those reported in the trial registration and study protocol.

[b] Indicates measure was only collected at baseline assessment. All other measures were collected at baseline, 3, and 6 months.

Table A2

Number of Baseline and Follow-up LBP Participants Who Provided Valid Data for All Questionnaire Items

Measure	*N*		
	Baseline (*n* = 120)	3 months (*n* = 100)	6 months (*n* = 96)
Demographic and health			
Age (years)	120	NA	NA
Height (cm)	111	NA	NA
Weight (kg)	114	73	77
Sex	120	NA	NA
BMI (kg/m^2)	111	73	76
Comorbidities	117	NA	NA
Previous LBP	116	NA	NA
Health care usage	117	95	96
Medication usage	118	95	96
Sociodemographic			
Cultural diversity	115	NA	NA
Education	118	NA	NA
Employment status	119	95	93
Impending compensation	118	NA	NA
Sickness benefits	110	83	76
Pain affected work	117	95	96
Pain and disability			
Brief pain inventory short form	118	95	96
Roland-Morris Disability Questionnaire	118	95	96
Lifestyle			
International Physical Activity Questionnaire	116	95	96

Note. LBP = low back pain; NA indicates questionnaire data was not reassessed at 3- and 6-month follow-up.