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RESEARCH ARTICLE

Are clinical outcomes associated with baseline sensory profiles in people with musculoskeletal shoulder pain? Protocol for a prospective longitudinal observational study

Danielle Hollis[1,2] | M. Dilani Mendis[1,2,3] | Shu-Kay Ng[2,4] | Michael Thomas[5] | Darryn Marks[5,6] | Jeremy Lewis[7,8] | Julie Hides[1,2,3] | Leanne Bisset[1,2]

[1]School of Health Sciences and Social Work, Griffith University, Nathan, Australia

[2]Menzies Health Institute Queensland, Griffith University, Nathan, Queensland, Australia

[3]Physiotherapy Department, Mater Health, South Brisbane, Queensland, Australia

[4]School of Medicine and Dentistry, Griffith University, Nathan, Queensland, Australia

[5]Orthopaedic Department, Gold Coast University Hospital, Gold Coast, Queensland, Australia

[6]Department of Physiotherapy, Bond University, Faculty of Health Sciences and Medicine, Bond Institute of Health and Sport, Gold Coast, Queensland, Australia

[7]Therapy Department, Central London Community Healthcare National Health Service Trust, Finchley Memorial Hospital, London, UK

[8]Musculoskeletal Research, Clinical Therapies, University of Limerick, Limerick, Ireland

Correspondence

Leanne Bisset, School of Health Sciences and Social Work, Griffith University, Gold Coast Campus, Nathan, QLD 4222, Australia.
Email: l.bisset@griffith.edu.au

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Abstract

Background: Musculoskeletal shoulder pain is a common problem and its symptoms often become persistent. The experience of pain is multidimensional, and therefore, a range of patient characteristics may influence treatment response. An altered sensory processing has been associated with persistent musculoskeletal pain states and may contribute to outcomes in patients with musculoskeletal shoulder pain. The presence and potential impact of altered sensory processing in this patient cohort is not currently known. The aim of this prospective longitudinal cohort study is to investigate if baseline sensory characteristics are associated with clinical outcomes in patients presenting to a tertiary hospital with persistent musculoskeletal shoulder pain. If found, a relationship between sensory characteristics and outcome may lead to the creation of more effective treatment strategies and improvements in risk adjustment and prognosis.

Methods: This is a single-centre prospective cohort study with 6-, 12- and 24-month follow-up. A total of 120 participants aged ≥18 years with persistent musculoskeletal shoulder pain (≥3 months) will be recruited from an Australian public tertiary hospital orthopaedic department. Baseline assessments, including quantitative sensory tests and a standardised physical examination, will be performed. In addition, information will be obtained from patient interviews, self-report questionnaires and medical records. Follow-up outcome measures will comprise information from the Shoulder Pain and Disability Index and a six-point Global Rating of Change scale.

Analysis: Descriptive statistics will be used to report baseline characteristics and outcome measures over time. Change in outcome measures at the primary endpoint of six months from baseline will be calculated using paired *t*-tests. Associations between baseline characteristics and outcomes at a 6-month follow-up will be reported using multivariable linear and logistic regression models.

Discussion: Understanding the relationship between sensory profile and the variable response to treatment in people with persistent musculoskeletal shoulder pain may enhance our understanding of the mechanisms contributing to the presentation. In addition, through better understanding of the contributing factors, the results of this study may contribute to the development of an individualised, patient-centred approach to treatment for people with this highly prevalent and debilitating condition.

KEYWORDS
musculoskeletal, orthopaedic, pain processing, prospective cohort study, quantitative sensory testing, shoulder pain

1 | INTRODUCTION

Musculoskeletal shoulder pain is a common problem with a reported point prevalence of between 6.9% and 26% in the general population (Luime et al., 2004) It is the second to third most prevalent musculoskeletal disorder in the United Kingdom (Parsons et al., 2007; Urwin et al., 1998), the Netherlands (Picavet & Schouten, 2003) and New Zealand (Taylor, 2005), and the third most frequent musculoskeletal presentation to general practice consultation in Australia (Britt et al., 2016). Approximately half of those who experience an episode of shoulder pain recover within 6 months; however, symptoms persist longer than one year in approximately 40% of the cases (Croft et al., 1996; Kuijpers et al., 2006; van der Windt et al., 1996). Persistent pain and dysfunction of the shoulder can negatively impact an individual's activities of daily living, work and social activities and sleep (Gillespie et al., 2017), generating a considerable socio-economic burden (Marks et al., 2019).

The most common diagnoses of musculoskeletal shoulder pain implicate structural pathology of soft tissues such as the rotator cuff muscles and tendons, subacromial bursa and glenoid labrum (Lewis, 2009; Tekavec et al., 2012; van der Windt et al., 1995). However, structural changes as identified on imaging bear little association with the severity or presence of symptoms (Teunis et al., 2014) and diagnosis based on pathology, which provides limited clarity regarding the optimal course of management (Chester et al., 2013; Lewis, 2009, 2016). The lack of association between diagnosis, imaging, clinical severity and treatment outcomes indicates that local tissue pathology is not the only contributor to shoulder pain symptoms.

There has been an evolving understanding of the factors that may influence the experience and trajectory of painful musculoskeletal conditions, including biophysical, psychological, social and genetic factors as well as lifestyle and comorbidities (Caneiro et al., 2021; Kosek et al., 2016; Moseley & Butler, 2015; Moseley & Flor, 2012). A range of factors have shown some prognostic value in patients presenting with shoulder pain in primary care; however, there is currently limited evidence to support the use of any proposed prognostic models (Karel et al., 2017; Kuijpers et al., 2006; Struyf et al., 2016; Vergouw et al., 2011). Notably, there is a lack of prospective research investigating the factors that may contribute to outcomes in patients with persistent symptoms and longer care trajectories (i.e., patients referred to tertiary care centres) (Rønnow et al., 2021).

Persistent musculoskeletal pain states are commonly associated with alterations in the central processing of noxious stimuli (Arendt-Nielsen et al., 2010). Changes that occur at the level of the spinal cord and brain can lead to amplification of nociceptive processing, resulting in widespread sensory hypersensitivity or hyperalgesia (Woolf, 1983). There is conflicting evidence of altered sensory processing in people with shoulder pain. Studies have reported hypersensitivity, allodynia and dysfunction of descending inhibitory neural pathways (Noten et al., 2017; Sanchis et al., 2015; Woolf, 2011). In contrast, a recent study found evidence of local but not widespread sensory changes in people with musculoskeletal shoulder pain (Haik et al., 2019). Furthermore, the impact of altered sensory processing on the effectiveness of treatments provided to this population is presently unclear (Haik et al., 2022).

Given the high individual and societal costs associated with persistent shoulder pain and the variable response to non-surgical and surgical treatments, further research is required to investigate the effects of sensory processing on patient outcomes with the goal of informing future clinical decision-making, improving utilisation of healthcare resources and optimising patient recovery.

2 | AIMS AND OBJECTIVES

The primary aim of this study is to investigate whether baseline sensory profiles are associated with six-month outcomes of pain and disability in patients with persistent musculoskeletal shoulder pain in a tertiary care setting.

The primary objectives are to:

1. Describe the sociodemographic, psychological, clinical and sensory characteristics.
2. Assess the changes in clinical outcomes at the primary endpoint of six months (medium-term).
3. Determine whether baseline sensory characteristics are associated with clinical outcomes at the primary endpoint of six months.

The secondary objectives are to:

1. Assess the changes in clinical outcomes at 12- and 24-month follow-up (long-term).
2. Determine whether baseline sensory characteristics are associated with clinical outcomes at 12- and 24-month follow-up.

3 | METHODS

3.1 | Study design and setting

This study is a single-centre, prospective, observational cohort study with follow-ups at 6, 12 and 24 months (Figure 1). Participants will be recruited via the outpatient Orthopaedic Department at the Gold Coast University Hospital, Australia. Data collection commenced in August 2019 and is anticipated to be completed by November 2024. Participant recruitment was suspended in December 2019 and recommenced in May 2021 in response to the COVID-19 pandemic. This study is observational, in that all participants will receive usual treatment as informed by the treating health clinicians. Implementation and reporting of the study will adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (von Elm et al., 2007).

3.2 | Study population

Participants will be included in the study if they are aged 18 years or over, have a referral to the hospital Orthopaedic Department for shoulder pain of at least three months duration and have sufficient proficiency in the English language to read trial information and questionnaires and provide full informed written consent. Exclusion criteria include (1) any known inflammatory conditions such as rheumatoid arthritis, (2) known malignancy, (3) uncontrolled high blood pressure, (4) a history of cardiac disease, (5) haemophilia or other bleeding disorders, (6) current pregnancy or breast feeding, (7) known neurological disorders (including radiculopathy), (8) any serious recent shoulder injury (e.g. fracture or dislocation in the past 6 months), (9) any open wounds or other contraindications (e.g. Raynaud's disease), that will prevent the person from immersing their hand in cold water and (10) use of medication known to affect sensory sensitivity (e.g. opioids and neuropathic medications). The exclusion criteria have been developed to establish the homogeneity of the participants and to optimise participants' safety (Peckerman et al., 1991, 1994; Sendowski et al., 2000; Sevre & Rostrup, 1999).

3.3 | Recruitment and consent

Recruitment will occur via consecutive sampling from the Orthopaedic Department referral lists. The lists will be screened to identify potentially eligible patients who will be contacted by telephone by a researcher associated with the study who has completed good clinical research practice and consent training prior to their scheduled appointment. Potential participants may also be approached during a clinic appointment to inform them of the study. Patients who express an interest in the study will be provided with the study information document and given time to review it and ask questions. The patient's decision regarding their participation in this study will in no way interfere with or influence their treatment or affect their relationship with the investigators, other health professionals or the hospital in general. Eligible patients will provide informed written consent prior

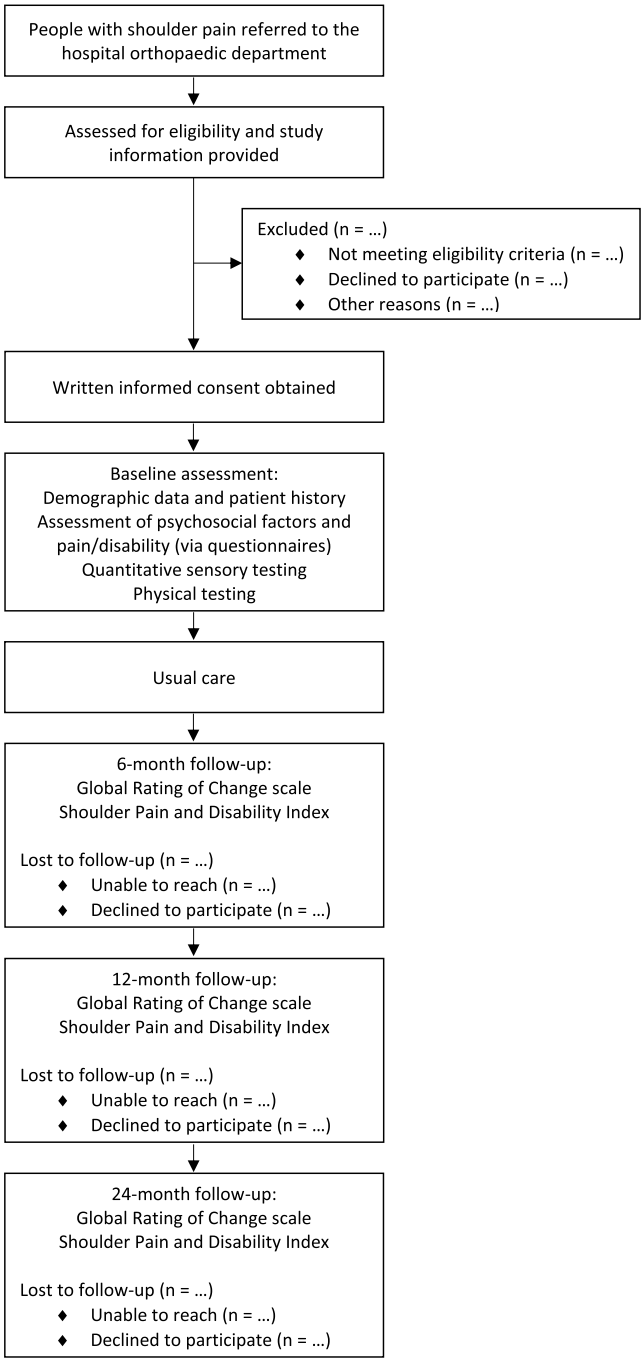

FIGURE 1 Participant flow chart.

to enrolment in the study. As this is an observational study, all participants will follow a usual care pathway that will not be altered due to their involvement in the study.

3.4 | Data collection

Assessments will occur at baseline and at 6, 12 and 24 months following the baseline assessment (Table 1). Baseline measurements will be conducted at an initial face-to-face appointment, with follow-up outcome measures completed via telephone, mail or an online survey.

3.4.1 | Clinical outcome measures (dependent variables)

The primary outcome measures are the Global Rating of Change (GROC) (Kamper et al., 2009) and the Shoulder Pain and Disability Index (SPADI) (Roach et al., 1991).

The GROC will be assessed using a six-point Likert scale that ranges from 'completely recovered' to 'much worse' to capture the participant's impression of the overall change in their shoulder condition at 6, 12 and 24 months following their baseline assessment. The GROC has been previously used in research on painful shoulder conditions (Michener et al., 2013) and is a recommended core outcome measure of global improvement for participants with chronic pain (Dworkin et al., 2005) A dichotomous measure of treatment success will be derived from the GROC, with those participants who report themselves as either 'much improved' or 'completely recovered' categorised as a 'Success' with all other responses categorised as 'Non-success' at the associated follow-up time point. The measure of success will be used in the analyses.

The SPADI is a region-specific questionnaire and consists of 13 items divided into subscales of pain (five items) and disability (eight items) (Roach et al., 1991). Each item is scored from 0 to 10. The two subscales are scored separately and then an overall score is calculated. The overall score is converted to a percentage, where 0% signifies no pain or disability and 100% signifies maximum pain and disability. The SPADI has been widely used in research of shoulder conditions and has demonstrated validity, excellent reliability and no floor and no or very low ceiling effects (Roy et al., 2009). It has been shown to be as responsive as the QuickDASH (Chester et al., 2017; Staples et al., 2010) with the ability to discriminate between clinical improvers and non-improvers in patients undergoing treatment for shoulder pain (Chester et al., 2017). The SPADI will be measured at baseline and at all follow-up time points, and scores will be sub-grouped according to the SPADI score at a six-month follow-up: <20 = Mild, SPADI score 21–49 = Moderate and SPADI score ≥50 = Severe (Wynne-Jones et al., 2021).

3.4.2 | Patient characteristics

Patient characteristics will be assessed at baseline. These will include risk factors (Quantitative sensory testing (QST)) and descriptive characteristics. Selection of the descriptive characteristics is based on obtaining a comprehensive view of our patient population whilst being pragmatic and minimising participant burden. Descriptive variables will include sociodemographic, general health and lifestyle, psychological and behavioural, condition-specific and physical measures. Information will be obtained via patient interview, self-report questionnaires, a standardised physical assessment and by accessing relevant sections of patients' medical records (patients will be asked for consent to access their medical records).

Sensory risk factors

Quantitative sensory testing will be used to assess participants' sensory processing. Quantitative sensory testing involves psychophysical methods that act as a proxy for investigating somatosensory function (Rolke et al., 2006). Testing procedures are described as static or dynamic depending on the sensory function they are designed to evaluate (Arendt-Nielsen & Yarnitsky, 2009). Pressure pain threshold (PPT) is a widely used static QST method that may indicate sensory dysfunction at the peripheral (localised or regional hyperalgesia) or central level (widespread hyperalgesia to remote non-painful areas) (Graven-Nielsen & Arendt-Nielsen, 2010). Temporal summation (TS) and conditioned pain modulation (CPM) are categorised as dynamic QST methods, evaluating ascending facilitatory pain pathways and inhibitory pain modulation processes, respectively (Woolf & Thompson, 1991; Yarnitsky, 2010). Altered pain facilitatory and inhibitory mechanisms as assessed by QST have been identified in many patients with other persistent pain conditions (Arendt-Nielsen et al., 2018). Additionally, TS and CPM have been shown to have the most consistent predictive values for persistent postoperative pain and response to pharmacological interventions (Petersen et al., 2021).

TABLE 1 Data collection time points.

Measure/s	0 months	6 months	12 months	24 months
Patient characteristics	✓	✗	✗	✗
Primary outcome measures				
• SPADI	✓	✓	✓	✓
• GROC	✗	✓	✓	✓
Treatment received during follow-up period	✗	✓	✓	✓

Pressure pain threshold Pressure pain threshold is defined as the minimum amount (kg) of pressure that provokes the first onset of pain. Pressure pain threshold has previously demonstrated good inter- and intra-rater reliability and validity (correlation with self-reported pain severity) (Nascimento et al., 2020; Walton et al., 2011). Participants will be seated comfortably on a standard chair with their elbows positioned in approximately 90 degrees of flexion and forearms pronated and resting on a plinth in front. The PPT will be assessed bilaterally with the probe placed between the second and third metacarpals on the dorsum of the hand, over the middle deltoid muscle and over the upper trapezius muscle using a pressure algometer (Commander Echo Algometer, JTech Medical, USA), with a rubber-tipped probe (1 cm^2) held perpendicular to the skin. The pressure will be applied at a rate of 0.5 kg/s (50 kPa/s) and participants will be asked to report when they first feel the sensation change from pressure to discomfort or pain at which point they will be instructed to say 'stop' and the test will cease (Walton et al., 2011). The average of three measures at each location will then be used in further analyses (Chesterton et al., 2007). Single PPT measures will be taken in a set order of hand, deltoid and upper trapezius on the left side and this sequence will then be repeated two more times on the left side such that the time between each measure over any specific area is approximately 30 s (Tilley & Bisset, 2017). This procedure will then be repeated on the right side.

Temporal summation Temporal summation is a valid method to assess excitability of spinal cord neurons (Rolke et al., 2006). A 256-mN-weighted Pinprick Stimulator (MRC, Germany) will be used to measure mechanical TS (Rolke et al., 2006). The weighted pinprick will be applied as a single stimulus to the skin and an initial measure of perceived pain intensity will be recorded using a 0–10 numerical rating scale (0 = no pain and 10 = worst pain imaginable) after the single stimulus. After 10 s, this will then be repeated with 10 stimuli applied within 1 cm^2 of the same area at a rate of 1 stimulus per second (Korg, MA-1, Solo Metronome), immediately after which participants will again rate their level of pain intensity. Participants will be seated on a standard chair next to a plinth, which will be raised to a level that produces as close to 90 degrees of shoulder abduction as is comfortable for each participant. This will allow application of the weighted pinprick perpendicular to the skin at all measurement points. The forearm resting on the plinth will be in a pronated position with the hand down. Temporal summation will be measured bilaterally between the second and third metacarpals on the dorsum of the hand, over the middle deltoid muscle and over the upper trapezius muscle. Measures will be taken on the left side first in the order of hand, deltoid and upper trapezius before repeating the sequence on the right side. The difference (pain intensity 10 stimuli—pain intensity 1 stimulus) and the windup ratio (pain intensity 10 stimuli/pain intensity 1 stimulus) between the pain scores will be calculated as the outcomes of TS (TS-diff and Temporal summation-wind up ratio, respectively).

Conditioned pain modulation Conditioned pain modulation will be measured using the cold pressor test as the conditioning stimulus and PPT as the test stimulus. The cold pressor pain has been shown to induce the most efficient CPM response when coupled with PPTs as a test stimulus (Oono et al., 2011). Participants will be seated on a standard chair with their hand on the unaffected (non-painful) side immersed up to the wrist (or foot, for bilateral upper limb cases) in a cold-water bath at a set temperature of 8°C. Participants will be instructed to verbally notify the assessor when they feel the first sensation of cold water induced pain or discomfort in the immersed hand, and the time will be recorded as the cold pressor pain threshold. Cold pain tolerance is reached when the participant withdraws their hand due to pain intolerance, and the total immersion time will be recorded. The maximum immersion time is 2 minutes, as the maximum CPM response is known to occur within this time frame. The cold water temperature is set such that there is negligible-to-no risk of tissue damage occurring within this 2-min exposure. Participants will be asked to rate their pain intensity on a 0–10 numerical rating scale every 30 s from immersion until hand withdrawal and 30 and 60 s after withdrawal (Ng et al., 2014). The test stimulus will be the PPT, with pressure applied over the middle deltoid muscle on the affected (painful) side during and 30- and 60-s following the cold pressor test. Conditioned pain modulation will be calculated by subtracting baseline PPT (middle deltoid muscle) from the PPT measures obtained during and after the cold pressor test. The effect is calculated as the difference in PPT scores between the two test stimuli (post-test minus pre-test) with a positive value indicating an efficient inhibitory (i.e., CPM) response (Ng et al., 2014).

Descriptive variables

Descriptive variables for sociodemographic, general health and lifestyle, psychological and behavioural and condition-specific patient characteristics are described in Table 2. Physical measures will also be assessed and recorded.

Physical measures The standardised physical examination will include:

- Active range of movement of the cervical spine (flexion, extension, lateral flexion and rotation) will be assessed with the participants seated and their feet resting on the floor. Following demonstration of the movement, participants will be asked to independently perform the movement as far as comfortably possible, noting any symptoms. The range of movement will be observed by the assessor and recorded as 'full' or 'impaired' if any movement is deemed to be less than half the normal expected range of movement, based on the assessor's experience and normative values for the age group (Hirsch et al., 2014; Youdas et al., 1991). Visual estimation has previously demonstrated moderated agreement with a validated cervical range of movement device (Whitcroft et al., 2010). Any provocation of cervical spine and/or shoulder pain will be recorded (Chester et al., 2018).

TABLE 2 Patient characteristics—sociodemographic, general health and lifestyle, psychological and behavioural and condition-specific descriptors.

Description	Measure (number of items/response options/score range)
Sociodemographic	
Age	Years
Sex	Male/female/none of these or prefer not to say
Education level	Highest level of education completed (single item, 4 options)
Work status	Current work/employment status (single item, 4 options)
Occupation	Description of occupation
Type of work/regular activity	Single item question (3 options)
Relationship status	Single item question (7 options)
Residential suburb	Index of relative socio-economic advantage and disadvantage by residential suburb
General health and lifestyle	
Body mass index	Calculated using assessed height (centimetres) and weight (kilograms)
Waist/hip circumference	Centimetres
Smoking status	Single item question (4 options)
Alcohol status	Single item question (3 options), number of standard drinks per week
Sleep status	Single item question (3 options), average hours of sleep per 24 h
Exercise	Two single item questions (4 options and 3 options), regularity/duration and intensity of exercise in a typical week
Comorbidities	Self-reported and medical record review
Medications	Self-reported and medical record review
Additional areas of pain	Self-reported, body chart
Quality of life	European quality of life-five-dimensions-five-level scale (EuroQol; EQ-5D-5 L) (5 items, 5 options per item and self-rated own health status via vertical scale 0–100)
	The EQ-5D-5 L has been shown to have excellent psychometric properties across a broad range of populations, including musculoskeletal and orthopaedic problems (Feng et al., 2021).
Psychological and behavioural	
Depression, anxiety and stress	Depression, anxiety and stress scale (DASS-21) (7 items each for depression, anxiety and stress dimensions, each item scored 0–3, total score each dimension 0–21, total score for each dimension multiplied by two for interpretation)
	The DASS-21 has been shown to have good reliability and construct validity (Henry & Crawford, 2005) as well as high internal consistency (Lovibond & Lovibond, 1995).
Catastrophic thinking	Pain catastrophising scale (PCS) (13 items, 5 options each item scored 0–4, total score 0–52)
	The PCS is used extensively in clinical practice and research and has demonstrated high internal consistency (Sullivan, 2009).
Pain self-efficacy	Pain self-efficacy questionnaire (PSEQ) (10 items, 7 options each item scored 0–6 and total score 0–60)
	Pain self-efficacy has been associated with the outcome of conservative (physiotherapy) treatment for patients with musculoskeletal shoulder pain (any duration) at six weeks and six months (Chester et al., 2018). The PSEQ is a valid and reliable measure of self-efficacy beliefs in chronic pain populations (Nicholas, 2007).
Fear of pain with movement	Tampa scale of Kinesiophobia (TSK-11) (11 items, 4 options each item scored 1–4 and total score 11–44)
	Kinesiophobia may be an important factor in the rehabilitation of people with shoulder pain (Lentz et al., 2009; Luque-Suarez et al., 2020); however, it has not been studied

TABLE 2 (Continued)

Description	Measure (number of items/response options/score range)
	extensively (Mintken et al., 2010). The shortened version (TSK-11) has demonstrated similar factor structure, reliability and validity to the original version (Woby et al., 2005) and is appropriate for use in populations with shoulder pain (Mintken et al., 2010).
Treatment expectations	Single item question (7 options), patient expectation of change in their shoulder pain as a result of treatment
Condition-specific	
Symptom duration	Months
Type of onset	Single item question (4 options)
Description of pain	Single item question (4 options)
Pain severity at rest	Numerical rating scale (0–10/10)
Symptom distribution	Self-reported, body chart
Arm dominance	Right/left/ambidextrous
Affected shoulder	Right/left/both
Headaches	Regular headaches (yes/no)
Previous treatment/s	Self-reported and medical record review
History of shoulder pain	Single item question (yes/no), if yes: same shoulder/opposite shoulder/both shoulders
Imaging findings	Medical record review (X-ray, magnetic resonance imaging, computed tomography and ultrasound imaging)

- Shoulder range of movement will be assessed bilaterally for abduction in the scapular plane, external rotation in 0° abduction and hand behind back (Eubank et al., 2016). A universal goniometer will be used to measure active and passive ranges of movement for abduction to the onset of pain as well as the maximum tolerable range as well as active and passive ranges of movement for external rotation. The universal goniometer has been shown to have good intra-rater reliability when consistent landmarks are used (Hayes et al., 2001). A tape measure will be used to record the active range of movement for hand behind back.
- Grip strength will be assessed bilaterally as a measure of general upper body muscle strength and function as low values have been associated with falls, disability, impaired health-related quality of life and increased mortality (Roberts et al., 2011). A standardised protocol using a hand dynamometer (Jamar, Lafayette Instrument Company, USA) will be used (Roberts et al., 2011). Three measures will be taken bilaterally with a mean and maximum grip recorded (kilograms) for each side.
- A 30-s sit-to-stand test will be carried out as a measure of lower limb strength and function (Jones et al., 1999). The test has shown good test–retest reliability and is considered a valid indication of lower body strength in community dwelling older adults (Jones et al., 1999). Participants will be asked to sit on a standard chair (seat height 43 cm), with their arms crossed over their chest, back straight and feet positioned shoulder-width apart on the floor. Participants will be given a demonstration of a full stand (body erect and back straight) and return to original seated position and will be given a practice trial of one repetition to ensure the correct form. Participants will then complete as many repetitions as possible within the 30-s time limit.

3.5 | Procedure

Participants will complete a baseline assessment including measures of all patient characteristics and the SPADI using standardised data collection forms and self-report questionnaires. Baseline data will be collected by one of four researchers. To ensure standardisation of the assessment procedure, all study researchers will be provided with an assessment schedule and training before their involvement in the study. The physical assessments (range of movement, grip strength and sit-stand) will be performed by one researcher who is a physiotherapist with 5 years' of clinical experience.

At 6, 12 and 24 months following their baseline assessment, participants will be contacted by telephone, mail and/or email to complete the GROC and SPADI outcome measures. This data will be recorded electronically (using REDCap) or via paper copy according to the patient's preference. Participants will also be asked what treatment/s (e.g. prescriptions, consultations, investigations and procedures) they have received during the follow-up period, which will be verified by reviewing their medical record. Relevant comorbidity information (e.g. cancer, coronary heart disease and diabetes) will also be extracted from the medical record during the follow-up period.

3.6 | Adverse events

It is not expected that adverse events, defined as unintended and harmful occurrences associated with the study (Therapeutic Goods Administration Australia, 2023), will occur as a result of this observational study. However, serious adverse events (anything requiring assessment and/or treatment by a healthcare practitioner) will be documented and reported to the on-site Medical Monitor (MT), who will assess and advise on further medical management of the event if required. Participants will be encouraged to report any other side effects such as discomfort or problems they may experience during or following the data collection. Additionally, the study's researchers and investigators will report any risks, discomfort or identifications of potential risks directly to the chief investigator (LB). A Study Management Panel has been established to review any adverse events reported on a six-monthly basis.

3.7 | Data management

Study information will be collected using both electronic forms (REDCap) and paper copies. All data will be stored in a de-identified format using a unique study code for each participant. Paper copies will be stored in a locked filing cabinet in a locked administration office at the participating hospital. Data will be transferred to an electronic database (Excel, Microsoft Corporation) using the unique study code identifier. Scanned copies of all signed consent forms and hard copy data and the electronic database will be password protected and stored on a secure university institution server with multifactor authentication login. Hard copy data will be entered into the electronic spreadsheet by a research investigator (DH). To ensure the accuracy of the data entered into the spreadsheet, electronic data collection methods (REDCap) will be set up to automatically calculate scores from questionnaires (which will be checked against manual calculation for the initial 10 participants) and to flag invalid data inputs. Visual double-checking of the hard copy data with the electronic data spreadsheet will also be carried out by the research investigator (DH) for all of the QST measures and for a random sample of 30% of the remaining data. The research team will have personal access to data using a confidential login. During cleaning of data, checks for duplicates, missing data, outliers and errors will be conducted. Cleaned data will be saved in a new file to maintain the integrity of the original raw data.

3.8 | Confidentiality

Data will be kept for 15 years in accordance with Queensland Health Research Management Policy and the Australian Code for the Responsible Conduct of Research 2007, after which time all hard copy data will be shredded and electronic files deleted and/or destroyed. REDCap will be used to collect and store personal information about enroled participants. REDCap complies with international recommendations for confidential data protection. All medical information about the study's participants will be confidential with disclosure to third parties outside of the research team prohibited. Data will be de-identified when exported from REDCap. Published data from this study will exclude names, recognisable photos (except where consent to use photos has been provided by the participant), personal information and any other data that could identify participants.

3.9 | Sample size estimation

A sample size estimation of 98 was initially calculated based on our intended plan of developing a multivariable model that included up to six risk factors. This was calculated for a medium effect size (f^2 = 0.15), alpha 0.05 and power 0.8 (G-Power V3.1.9.6) (Faul et al., 2007). The final six risk factors of interest will be determined by tests of clinical and statistical significance. The target sample size was increased to 120 as a conservative measure to adjust for potential dropouts over the follow-up period.

3.10 | Statistical analysis for the primary aim and objectives

Hard copy data will be entered into a password-protected electronic file (Excel, Microsoft Corporation) and then transferred into SPSS (version 29.0, IBM Chicago) for analyses. A detailed analysis plan will be developed for each of the study objectives, and a brief summary follows here.

Objective 1: Describe the sociodemographic, psychological, clinical and sensory characteristics of patients presenting with persistent musculoskeletal shoulder pain.

Descriptive statistics will be used to report baseline characteristics and the primary outcome measures of GROC and SPADI over time. Continuous variables will be presented as means and standard deviations (SD) and categorical variables will be presented as frequency and percentages. Attrition will be reported for each follow-up time point. For those lost to follow-up, baseline characteristics will be compared to those remaining in the study to assess for risk of attrition bias.

Outcome data will be evaluated for normality using Shapiro–Wilk tests and visual inspection of histograms and quantile–quantile plots (qq-plots). The requirement of data transformation (e.g. logarithmic transformation for non-normally distributed data) will be discussed with a biostatistician prior to further analyses.

Objective 2: Assess the change in clinical outcomes at the primary endpoint of six months (medium-term).

A paired *t*-test will be used to estimate change over time from baseline to a 6-month follow-up using the primary outcome measure of SPADI (continuous measure). Next, participants will be classified as improved or not improved based on the GROC, which will be dichotomised into 'Success' (GROC = 'much improved' or 'completely

recovered') and 'Non-success' and descriptive statistics will be reported.

Objective 3: Determine the association of baseline sensory characteristics with clinical outcomes at the primary endpoint of six months.

We will develop multivariable models for estimating clinical change (SPADI, GROC) over a six-month follow-up. Development of the prognostic prediction models will be guided by the PROGRESS framework (Hemingway et al., 2013; Steyerberg et al., 2013). The risk factors for potential inclusion will be based on existing and emerging evidence regarding the association with clinical outcomes.

To identify which baseline risk factors are significantly associated with clinical outcomes at six months, correlations will be calculated for continuous baseline variables with SPADI, 1-way ANOVAs comparing SPADI for baseline categorical variables, *t*-tests comparing continuous baseline variables between two GROC groups, and Chi-squared tests for categorical baseline variables with GROC.

Clinical subgroups will be defined based on SPADI and GROC values at 6 months. These subgroups will be defined a priori.

- SPADI score <20 = Mild sub-group, SPADI score 21–49 = Moderate sub-group and SPADI score ≥50 = Severe sub-group (Wynne-Jones et al., 2021).
- GROC 'much improved' or 'completely recovered') = Success, all other values = 'Non-success'.

The association of each of the potential baseline risk factors (independent variables) with each primary clinical outcome (dependent variables) will be tested in linear (SPADI) and logistic (Success and Non-success) regression models. Risk factors with an association p value < 0.10 will be included in a multivariate linear regression model with forward stepwise for the continuous outcome of SPADI, and a multivariate logistic regression model for Success/Non-success at the 6-month follow-up. Sensitivity analyses will be conducted using backward stepwise for both models. All assumptions (linearity between independent continuous variables, log odds and multicollinearity) will be checked before model building. The predictive ability of included variables in each multivariate model will be evaluated by unstandardised regression coefficients with 95% confidence intervals. Standardised regression coefficients will also be calculated to determine which of the independent variables had a greater effect on the dependent variable. Overall performance of the final models will be evaluated with Nagelkerke R^2, which estimates the percentage of explained variation of the model.

4 | DISCUSSION

The variable response to treatments observed in people with persistent shoulder pain may be related to an altered functioning of neural pathways involved in the processing of sensory stimuli. There is a growing body of evidence to suggest that interventions that target local tissue pathology are not effective when a person's pain modulation processes are affected (Coombes et al., 2015; Sterling et al., 2003, 2012). When pain persists, the brain and spinal cord adaptations can occur that augment nociceptive processing, leading to widespread sensory hyperalgesia (Woolf, 2011) (Fitzcharles et al., 2021). Evidence of generalised mechanical hyperalgesia, allodynia and impaired descending inhibitory pathways has been reported in some people with shoulder pain (Noten et al., 2017); however, the evidence is limited and therefore the role of sensory disturbances in the perpetuation of shoulder pain remains poorly understood (Sanchis et al., 2015).

Psychophysical measures designed to assess endogenous pain modulation mechanisms have been previously described. These include CPM protocols, representing descending inhibitory mechanisms that exert analgesic effects and TS protocols, representing ascending facilitatory pathways that amplify pain perception in response to a series of similar noxious stimuli (Yarnitsky, 2010). These dynamic parameters are thought to provide a better assessment of an individual's pain modulation system than traditional static measures such as threshold testing and could serve as biomarkers for assessing an individual's 'pain modulation profile' (Yarnitsky, 2010). Conditioned pain modulation and TS paradigms have been used to assess pain profiles in patients with upper limb musculoskeletal conditions and also as a method to predict patients who are at risk of developing persistent pain prior to surgery (Granot et al., 2008; Yarnitsky et al., 2012). Growing evidence suggests that the consideration of sensory disturbances is of clinical importance in the management of persistent musculoskeletal pain (Nijs et al., 2016). For example, changes in pain modulation may influence an individual's response to treatment, particularly active interventions, as dysfunction of the usual activation of endogenous analgesia associated with exercise can be impaired (Daenen et al., 2015; Nijs et al., 2012). Importantly, the effectiveness of standard treatments, such as physiotherapy, injection therapies and surgery, may negatively impact individuals with impaired pain modulation processes. Despite the available literature, the full range of sensory disturbances or their ability to modify treatment effects in patients with musculoskeletal shoulder pain is yet to be described.

Additionally, authors of a recent systematic review have suggested that psychological factors, in particular high levels of depressive symptoms, anxiety, pain catastrophising and fear of movement, are implicated in the perpetuation of pain and disability in people with persistent shoulder pain; however, the quality of the evidence to support this is described as very low (Martinez-Calderon et al., 2018). Randomised controlled trials addressing the rehabilitation of people with persistent musculoskeletal pain have identified factors, including self-efficacy, depression and pain catastrophising as well as physical activity as important influences on patient outcomes (Miles et al., 2011). Psychological factors are known to interact with physiology to modulate the experience of pain (Garland, 2012; Moseley & Flor, 2012) and additionally, could impact the level of patient engagement in active interventions such as therapeutic exercise. Therefore, this study will also

comprehensively describe the psychological characteristics of this patient population.

This cohort study will provide insight into the sociodemographic, general health and lifestyle, psychological, clinical, sensory and condition-specific characteristics of patients referred to a tertiary care hospital for shoulder pain. Importantly, to the authors' knowledge, this study will be the first prospective longitudinal study to comprehensively investigate measures of pain modulation in this population. This will provide a basis for future research that could help in guiding efficient clinical decision-making and the development of alternative treatment pathways.

In pain medicine, it is unknown why some individuals respond to treatment while others do not. There is emerging evidence that measures of pain modulation may be associated with a response or a lack of response to standard treatment. Identifying biomarkers that are linked to outcomes will help individualise treatment, improve treatment effectiveness and reduce the economic burden to the patient and the health care system. The identification of dysfunctional pain modulation (whether inhibitory or facilitatory) may be the key to choosing the most effective treatment for long-lasting pain alleviation. This has never been investigated in common yet costly musculoskeletal conditions such as shoulder pain but has the potential to achieve individualised pain medicine.

AUTHOR CONTRIBUTIONS

Study conception and design: Hollis, Marks, Thomas and Bisset. Data analysis plan: Hollis, Mendis, Ng, Hides and Bisset. Drafting the article or revising it critically for important intellectual content: Hollis, Mendis, Ng, Lewis, Hides and Bisset. Final approval of the article: Hollis, Mendis, Ng, Thomas, Marks, Lewis, Hides and Bisset. All authors had full access to the drafting of this manuscript and take responsibility for the accuracy of the content.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

ETHICS STATEMENT

The Gold Coast Hospital and Health Service Human Research Ethics Committee have approved this study (HREC/2019/QGC/52528).

ORCID

Danielle Hollis https://orcid.org/0000-0001-7812-3105
M. Dilani Mendis https://orcid.org/0000-0002-0533-2587
Shu-Kay Ng https://orcid.org/0000-0002-6865-9384
Darryn Marks https://orcid.org/0000-0002-8884-8596
Jeremy Lewis https://orcid.org/0000-0001-7870-9165
Julie Hides https://orcid.org/0000-0002-1830-8121
Leanne Bisset https://orcid.org/0000-0001-8807-7093

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