The role of ultrasound and the patient acceptable symptom state in shoulder pain management

Gui Tong Tran

Submitted in accordance with the requirements for the degree of
Doctor of Philosophy

The University of Leeds
Leeds Institute of Rheumatic and Musculoskeletal Medicine
School of Medicine

January 2019

Intellectual Property and Publication Statements

The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Acknowledgements

There are many people I would like to thank for their help and support with this thesis. Firstly, I would like to acknowledge the importance and support of my supervisors. Professor Philip Conaghan, Dr Sarah Kingsbury and Dr Elizabeth Hensor were invaluable in helping me secure the research grant to complete my doctorate. During this PhD, they have provided advice, enthusiasm and dedication to my research. Philip, Sarah and Liz have not only been first-rate supervisors but have been great role models for how to be a successful academic. I am eternally grateful for their support.

Secondly I would like to thank the National Institute of Health Research for the Doctoral Research Fellowship grant that funded the research for this PhD.

For the systematic literature review in Chapter 3, I would like to thank Jenny Makeham in Leeds Teaching Hospitals NHS Trust library for helping me with my literature search, Professor Conaghan, Dr Sarah Kingsbury, Mr Paul Cowling, Dr Adam Lucas, Dr Julie Bury and Dr Toby Smith for helping design the study and writing of the manuscript.

For the retrospective study in Chapter 4, I would like to thank Professor Conaghan, Dr Sarah Kingsbury, Dr Aaron Ray and Dr Elizabeth Hensor for assisting in the design of the study and writing the manuscript.

For the work in Chapters 5 and 6 I would like to thank Professor Conaghan, Dr Sarah Kingsbury, Dr Elizabeth Hensor and Mr Bright Dube for assisting in the design of the study and writing the manuscripts. Bright has been a great help in the statistical analysis.

Finally I would like to thank my wife Kate, for her love, belief, patience and understanding in undertaking this thesis, particularly during the birth of our beautiful children, Felix and Ellie, during my doctorate. I would also like to acknowledge my parents, brothers and sister, Lau, Dinh Phu, Tak, Ying and Fu, for their constant support and enduring confidence in me to succeed at anything I put my mind to.

Co-author contributions:

This research has been carried out by a team with my own contributions and the contributions of the other members explicitly indicated below:

Chapter 3: What imaging detected pathologies are associated with shoulder symptoms and their persistence? A systematic literature review

GT and PC were involved in the conception and design of the work, data collection, data analysis and interpretation. TS, AB and SK helped with the analysis and interpretation of data. PGC was involved in conception and design of the work, data analysis and interpretation. GT wrote the Chapter.

Chapter 4: A retrospective cohort study to determine if groups of imaging detected pathologies exist and if these groups differ in their outcomes

GT designed the study, undertook the data acquisition, data interpretation and writing of the Chapter. EH participated in the design of the study, performed the statistical analysis and was involved in the data interpretation. AR made substantial contribution to the data acquisition and interpretation. SK made contributions to the design of the study. GT wrote the Chapter.

Chapter 5: A prospective cohort study to confirm groups of imaging detected pathologies exist and understand how these groups differ in their outcomes

GT and PGC designed of the study was involved in the data interpretation and writing of the manuscript. GT undertook the data acquisition. EH participated in the design of the study, performed the statistical analysis and was involved in the data interpretation. SK made contributions to the design of the study. GT wrote the Chapter.

Chapter 6: Defining a cut-off for the Patient Acceptable Symptom State: data from a community cohort using the Shoulder Pain and Disability Index

GT and PGC designed of the study, undertook the data acquisition and data interpretation. EH participated in the design of the study, supported me in performing the statistical analysis and was involved in the data interpretation. SK made contributions to the design of the study. BD was involved in the statistical analysis and data interpretation. GT wrote the Chapter.

List of publications / presentations arising from the thesis

Original articles

Tran G, Cowling P, Smith T, Bury J, Lucas A, Barr A, Kingsbury SR, Conaghan PG. What Imaging-Detected Pathologies Are Associated With Shoulder Symptoms and Their Persistence? A Systematic Literature Review. *Arthritis Care Res (Hoboken)*. 2018

Tran G, Hensor EM, Ray A, Kingsbury SR, O'Connor P, Conaghan PG. Ultrasound-detected pathologies cluster into groups with different clinical outcomes: data from 3000 community referrals for shoulder pain. *Arthritis Res Ther.* 2017

International Conference Presentation

Oral Presentation:

Patients with ultrasound-detected shoulder pathologies cluster into groups with different clinical associations: first results from the LOCUS study

European League Against Rheumatism (EULAR) Annual Conference, Amsterdam, 2018

National Conference Presentation

Oral Presentation:

Patients with ultrasound-detected shoulder pathologies cluster into groups with different clinical associations

Annual Combined Northern and Yorkshire Rheumatology meeting, York, 2018

Abstract

Shoulder pain is a common musculoskeletal condition and affects a large proportion of the UK population. Over half of those affected continue to have pain eighteen months from onset. In order to help with the diagnosis and management of shoulder pain, the use of ultrasound scans has been increasing. Despite this rise in ultrasound scans, the predictive value of ultrasound-based pathology findings with outcomes remains unclear. Not all patients in pain necessarily require investigations or treatment. Evaluating the relationship between pain and an acceptable symptom state is also important to understand which patients require interventions. The over-arching hypothesis underlying this thesis was that aspects of the shoulder pain pathway can be improved through better utilisation of ultrasound and applying the concept of a patient acceptable symptom state.

A systematic literature review on the role of imaging and shoulder symptoms identified a paucity of studies evaluating multiple concurrent imaging pathologies with shoulder symptoms. A retrospective study using latent class analysis demonstrated that groups of ultrasound-detected pathologies existed. A prospective study confirmed the existence of these groups. However, there was no difference in 6 months outcome or response to treatments between these groups or individual pathologies. Patients with worse symptoms at baseline were more likely to find worse symptoms acceptable at 6 months. Patients who reported acceptable symptoms at baseline also received fewer treatments.

In summary, the current use of ultrasound scans in managing patients with shoulder pain needs re-evaluation, and understanding clinical criteria such as the patient acceptable symptom state will help improve shoulder pathways. These findings should inform future trial designs and shoulder care pathways.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ACJ	Acromioclavicular Joint
AIC	Akaike's Information Criterion
ASES	American Shoulder And Elbow Surgeons
AUC	Area Under The Curve
BIC	Bayesian Information Criterion
BIPQ	Brief Illness Perception Questionnaire
BLRT	Bootstrap Likelihood Ratio Test
BMI	Body Mass Index
cAIC	'Consistent' AIC
CHAID	Chi-square Automatic Interaction Detector
CI	Confidence Interval
COS	Core Outcome Set
CT	Computerised Tomography
DASH	Disabilities Of The Arm, Shoulder And Hand Score
ES	Effect Size
ESWT	Extracorporeal Shockwave Therapy
GHJ	Glenohumeral Joint
GP	General Practitioner
GRADE	Grade Of Recommendations Assessment, Development And Evaluation
HADS	Hospital Anxiety And Depression Scale
ICC	Intra-Class Correlation
ICD	International Classification Of Diseases

IQR	Inter-Quartile Range
LCA	Latent Class Analysis
LOCUS	Leeds Observational Cohort Ultrasound Study
MCID	Minimal Clinically Important Difference
MDC	Minimal Detectable Change
MRA	Magentic Resonance Arthrogram
MRI	Magentic Resonance Imaging
NICE	National Institute Of Clinical Excellence
NPV	Negative Predictive Value
NRS	Numerical Rating Score
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OMERACT	Outcome Measures In Rheumatology
OSS	Oxford Shoulder Score
PASS	Patient Acceptable Symptom State
PAST	Pain Study
PEMF	Pulsed Electromagnetic Field Therapy
PET	Positron Emission Tomography
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items For Systematic Reviews And Meta-Analyses
PROM	Patient Reported Outcome Measure
PSEQ	Pain Self-Efficacy Questionnaire
QALYs	Quality Adjusted Life Years
RC	Rotator Cuff

ROC	Receiver Operator Characteristic
ROM	Range Of Motion
SAB	Subacromial Bursa
SAS	Shoulder Activity Scale
SEM	Standard Error Of Measurement
SF-36	Short Form 36
SIS	Subacromial Impingement Syndrome
SLAP	Superior Labral Anterior-Posterior
SPADI	Shoulder Pain And Disability Index
SRM	Standardised Response Means
SST	Simple Shoulder Test
UCLA	University Of California At Los Angeles
US	Ultrasound
VAS	Visual Analogue Scale
XR	X-Ray

1 Chapter 1 - Introduction

1.1 Background

Shoulder pain is one of the most common musculoskeletal complaints worldwide, and often results in long-term pain and disability. In the UK it affects 6.9% of the population (1). Importantly, for our aging population, the prevalence of shoulder pain increases with age (2).

Shoulder pain also poses a large socio-economic burden: estimated annual costs to the individual can be over £3,500 (3) and costs to society over £310 million (4). It also results in a significant loss to work productivity (5) and substantial healthcare utilisation (6, 7).

However, pain alone does not give an understanding of those who seek medical care: patients may have shoulder pain but consider their symptoms acceptable. Evaluating an individual's level of Patient Acceptable Symptom State (PASS), defined as the value on a scale beyond which the patient feels good enough to continue in that state, may have implications for future shoulder care pathways as it would inform clinicians about who should be investigated and treated.

Improvements in shoulder outcomes may be limited by a lack of consensus on the appropriate classification criteria for shoulder disorders. Currently, there are many different classifications of shoulder symptoms based on clinical symptoms and/or structural pathologies. The identification of subgroups within a population may be important to allow appropriately targeted therapy, which may increase treatment success (8).

Radiological investigations are frequently used to aid in the diagnosis of shoulder disorders, and their use has been increasing. For example, in Australia there has been a fourfold rise in shoulder ultrasound scans from 2001-2009 in primary care (9). This increase in imaging investigation results in additional healthcare costs.

Imaging tests are often used to diagnose individual pathologies which are targeted for treatment, but multiple pathologies of the shoulder often co-exist. The utility of diagnostic tests to inform patient care remains unknown and a combination of multiple pathologies may be important in determining outcomes.

A review of imaging has highlighted that further studies are required to determine the extent to which diagnostic tests on shoulder pain inform and affect patient management and outcomes (10). A recent report by the Academy of Medical Sciences has also highlighted the importance of rational diagnostic tests to improve patient care and reduce costs (11).

Treatment of shoulder pain includes physiotherapy, corticosteroid injections, analgesia and surgery. However, the use of these treatment modalities in shoulder pathways remain inconsistent and response to treatments may vary between patients. Physiotherapy is used to treat most shoulder disorders and can be delivered by primary or secondary care. Corticosteroid injections provide short-term response to inflammatory conditions of the shoulder and can also be delivered in primary or secondary care, with or without ultrasound guidance. Analgesia can be prescribed by a clinician or obtained over the counter by the patient. Surgery is undertaken when other treatment modalities have failed and after imaging has been undertaken, although the optimum timing remains unknown. Despite these treatment options 51% of patients continue to complain of pain 18 months later, which reflects the uncertainty of the optimum treatment pathway (12).

This thesis describes the identification of ultrasound-derived subgroups using unbiased classification techniques and explores the medium-term outcomes of these groups in the usual care pathway. Four different subgroups based on ultrasound pathologies have been identified, although these groups have similar outcomes and similar responses to treatment within the current pathway. PASS was evaluated for the Shoulder Pain and Disability Index (SPADI), a patient reported outcome measure for shoulder symptoms. PASS was shown to be dependent on baseline score: patients who were more symptomatic at baseline reported that higher levels of disability at 6 months

were still considered acceptable. However, there was very little effect of baseline SPADI pain on the level of pain considered acceptable at 6 months. Patients reporting PASS were also found to receive fewer treatments. Further work is required to understand the value of ultrasound and PASS for future therapeutic trials of shoulder pain and their role in the shoulder care pathway.

1.2 Structure of the thesis

The over-arching hypothesis underlying this thesis was that aspects of the shoulder pain pathway can be improved through better utilisation of ultrasound and applying the concept of a PASS.

1.2.1 Chapter 2: Literature review

This is a narrative literature review covering shoulder symptoms, focusing on the classification, epidemiology, aetiology, pathogenesis, assessment and treatment.

1.2.2 Chapter 3: What imaging detected pathologies are associated with shoulder symptoms and their persistence? A systematic literature review

This Chapter presents a systematic literature review on the relationship between imaging detected features and the prevalence and persistence of shoulder pain and dysfunction. This review highlights a paucity of studies evaluating multiple imaging pathologies concurrently with respect to shoulder symptoms.

1.2.3 Chapter 4: A retrospective cohort study to determine if groups of imaging detected pathologies exist and if these groups differ in their outcomes

A large retrospective study was conducted to determine if patients with shoulder pain can be grouped according to multiple ultrasound pathology patterns. It identified 4 groups of ultrasound pathologies which may differ in outcomes, requiring further evaluation in a prospective study.

1.2.4 Chapter 5: A prospective cohort study to confirm groups of imaging detected pathologies exist and understand how these groups differ in their outcomes

Following the work in Chapter 4, a prospective study was performed to confirm the existence of 4 groups of pathologies. The long-term outcomes of these groups were then evaluated, and this showed that the change in symptoms and response to treatments did not differ between groups at 6 months, when accounting for differences at baseline.

1.2.5 Chapter 6: Investigating cut-offs for the Patient Acceptable Symptom State: data from a community cohort using the Shoulder Pain and Disability Index

This Chapter aimed to identify, in a prospective study, the level of symptoms that patients would find acceptable and the key determinants of this. It found that the threshold for acceptability is dependent on severity of baseline disability score and patients who reported PASS received fewer treatments.

1.2.6 Chapter 7: Discussion, future directions and conclusions

This Chapter brings together the results of this thesis and the conclusions that can be drawn. An update on the literature review is provided and future directions for shoulder care based on the thesis work are discussed.

2 Chapter 2 - Literature review

This Chapter reviews the definitions, epidemiology, aetiology and pathogenesis of shoulder symptoms. There are many different tools for assessing shoulder symptoms, including the Shoulder Pain and Disability Index (SPADI). The performance metrics and validation of these scores will be discussed. Imaging modalities for assessing the shoulder include radiographs, ultrasound, and magnetic resonance imaging (MRI), and their use have increased over time. Finally, this Chapter describes the management of shoulder pain and the various guidelines.

2.1 Introduction

Shoulder pain is one of the most common musculoskeletal complaints worldwide (2) and increases with age (13). Recovery can be slow, with 51% reporting pain at 18 months (12). Shoulder pain has a significant impact on quality of life (14-16). It poses a significant economic burden, with annual costs to society estimated to be £310 million (4).

2.2 The shoulder

The shoulder consists of four bones: the humerus, scapula, clavicle and sternum. Together they form four joints: the glenohumeral joint, acromioclavicular joint, sternoclavicular joint and scapulothoracic joint. The scapula has important bony landmarks including the acromion and corocoid process.

These bones are held in place by a combination of ligaments, muscles and cartilage. These structures help to provide stability and function to the shoulder. The ligaments of the shoulder include the glenohumeral ligaments, which help form the joint capsule and provide stability to the joint; the coraco-acromial ligament; the coroco-clavicular ligament and acromioclavicular ligament which help attach the scapula to the clavicle and maintain stability.

The shoulder musculature broadly consists of the intrinsic muscles. These include the four muscles which comprise the rotator cuff: supraspinatus, infraspinatus, subscapularis and teres minor. Other intrinsic muscles include serratus anterior, which attaches to the medial border of the scapula and this muscle provides stability and allows abduction and flexion of the arm. These muscles provide stability and movement. Extrinsic muscles include the deltoid, which allows movement in all planes. The muscles of the arm, which originate from the shoulder are the biceps brachii, coracobrachialis and triceps bracchii. Stability of the humerus in the glenoid is enhanced by the capsule, a fibrocartilaginous structure.

Bursae are also present in the shoulder and they serve to reduce friction over two moving surfaces. They are sacs of synovial membrane supported by dense irregular connective tissue. The subacromial bursa covers the anterior 20% of subscapularis, the superior surface of supraspinatus, and infraspinatus posteriorly. Superior to the bursa is the acromion process and the coraco-acromial ligament. Other bursae can also exist, including the scapulothoracic bursa (located between serratus anterior and the chest wall) and the subscapularis bursa (located between subscapularis and serratus anterior).

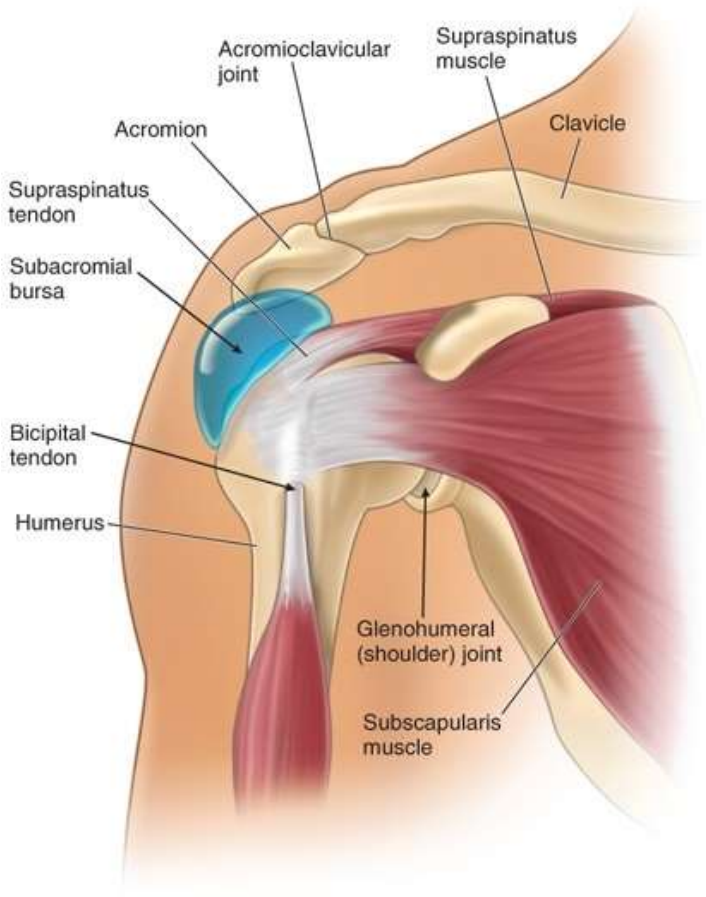


Figure 2.1 Shoulder anatomy

Adapted from (17)

2.3 Classifying shoulder disorders

2.3.1 Current classification of shoulder disorders

The classification of shoulder disorders is a complex and controversial area, which may be a result of our limited understanding on the relationship between symptoms and pathology. This is reflected by a lack of consensus on the appropriate classification criteria for shoulder disorders. There are different classifications of shoulder disorders and this is broadly based on history and examination, with or without detected structural abnormalities. These will be discussed below.

2.3.1.1 Clinical history and examination

Classification of shoulder symptoms is based on presumed anatomical pathology and relies on history and examination findings. Information such as onset of symptoms, precipitating and alleviating factors, age and co-morbidities are important. Examination is routinely practised, with many manoeuvres employed to help classify shoulder disorders. There are many examination techniques involved in the shoulder. The following are those described by Hegedus *et al.* (18) with an emphasis on those with diagnostic accuracy (19).

2.3.1.1.1 Impingement tests

These tests theoretically force the greater tuberosity against the supraspinatus tendon, which is then pushed against the coroca-acromial ligament.

2.3.1.1.1.1 Hawkins Kennedy

Patient is seated or standing, with arm at 90^{o} forward flexion and elbow flexed to 90^{o} also. The scapula is stabilised. The humerus is then passively internally rotated until pain occurs.

2.3.1.1.1.2 Neer

Patient is seated or standing with scapula fixed. Passive forward flexion of the straightened arm is then undertaken to elicit pain.

2.3.1.1.1.3 Painful arc

Pain on abduction of the arm

2.3.1.1.2 Rotator Cuff tests

2.3.1.1.2.1External rotation lag sign

This test is used to determine a tear of the infraspinatus or supraspinatus tendons, as suggested by a lag sign of more than 5°. The test involves the patient seated, with the examiner behind them. The shoulder should be in 20º abduction, the elbow in 90º flexion and maximal external rotation minus 5º. The examiner holds the arm in that position and then releases, asking the patient to maintain that arm position. The test is considered a positive lag sign when there is a drop.

2.3.1.1.2.2 Drop arm test

Designed to assess for supraspinatus and infraspinatus tears. Patient is sat with arm abducted and the arm is actively lowered. Pain during the last 90° of descent or leaning to affected side may indicate pathology.

2.3.1.1.2.3 Supine impingement test

The patient lies supine and examiner forward flexes the arm, which is also internally rotated. An increase in pain is theoretically indicative of rotator cuff tear, as the motion narrows and compresses the subacromial space

2.3.1.1.2.4 Belly press test

Patient has palm on abdomen and patient exerts pressure on the abdomen with the hand until maximal internal rotation. In patients with subscapularis tears, the patient cannot maintain maximal internal rotation and feels weaker.

2.3.1.1.3 Labral tears

2.3.1.1.3.1Biceps load test

Patient is supine, with the arm abducted 120º, maximally externally rotated, the elbow flexed at 90º and the forearm supinated. Active elbow flexion is resisted by the examiner. A positive test is when pain is felt, and this may represent the superior labrum detaching from the glenoid margin.

2.3.1.1.3.2 Anterior slide test

Patient standing with hands on the hips. A forward and slightly superior force is applied to the elbow and upper arm, which is resisted by the patient. A positive test is when pain is felt as a result of anterior-superior humeral head migration, resulting in traction on the biceps tendon and the consequent stretching of the labral complex.

2.3.1.1.4 Instability tests

2.3.1.1.4.1 Apprehension

The patient has their arm 90º abducted and maximal external rotation, with elbow flexed at 90º also. The examiner's hand is placed on the posterior aspect of the humeral head and anterior motion force is applied, whilst maximal external rotation is maintained. This application of force is intended to cause subluxation of the shoulder and therefore apprehension or pain is a positive test.

2.3.1.1.4.2 Relocation

Similar to apprehension test, although this time posterior force is applied to the humeral head. Improved ability to maintain maximal external rotation and pain relief is a positive test.

2.3.1.1.4.3 Anterior release

Similar to relocation test, except the applied posterior force is then withdrawn. The humeral head can then sublux anteriorly, causing pain and apprehension. This indicates a positive test.

2.3.1.1.5 Acromioclavicular test

2.3.1.1.5.1 O'Brien's

The aim of this test is to push the greater tuberosity against the acromion, thus compressing the ACJ. The patient's arm in 90° forward flexion, 10–15° adduction and full internal rotation. The examiner applies downward force with the patient resisting this force. The test is repeated with the arm fully externally rotated. Pain around the ACJ, especially with resisted internal rotation is a positive test.

2.3.1.1.5.2 ACJ tenderness

A positive result occurs when there is pain on palpation of the ACJ.

2.3.1.1.6 Glenhohumeral test

2.3.1.1.6.1 External rotation

Pain or limitation of external rotation of the glenohumeral joint is suggestive of either adhesive capsulitis or gleno-humeral osteoarthritis.

2.3.1.2 Clinical classification

The simplest classification can include "shoulder pain" without any subgroups. Other classification criteria are based on the presenting feature of pain, which are then sub-grouped according to the clinical findings. In the last decade, a Delphi process was undertaken in The Netherlands to classify the terminology of shoulder complaints not caused by acute trauma or by any systemic

disease (20). A consensus was achieved to classify 6 shoulder disorders as specific diagnoses, rather than “a non-specific shoulder disorder”. This included RC tears; bursitis; labral lesions of the shoulder; instability; suprascapular nerve lesions; and adhesive capsulitis. The definitions of these specific disorders were not explained.

McClure *et al.* proposed four common categories: subacromial pain syndrome; adhesive capsulitis; glenohumeral instability; other causes (including glenohumeral OA, ACJ OA, fractures and nerve impingement) (21). Key positive and negative findings are highlighted in Table 2.1. Subacromial pain syndrome was used to encompass subacromial impingement, bicipital tendinopathy, RC tendinopathy, RC tears and subacromial bursitis as it was felt that these lesions could not be easily differentiated by history and examination alone. Subacromial impingement syndrome (SIS) was previously used to describe the RC contacting with the subacromial arch but a recent SLR has shown that it is not a distinct diagnosis, but an umbrella term used to define other pathologies such as RC tendinopathy. These pathologies are not accurately determined by clinical history and examination (22, 23). Furthermore, the classification of SIS has been shown to vary amongst clinicians and it has been suggested that more precise diagnostic language should be used with the help of imaging (24).

Table 2.1 Classification of shoulder pain: Staged Approach for Rehabilitation

	Subacromial Pain Syndrome	**Adhesive Capsulitis**	**Glenohumeral Instability**	**Other Common Diagnoses**
Key positive findings	Impingement signs (Neer, Hawkins, Jobe tests) Painful arc Pain with isometric resistance Weakness Atrophy (tear)	Spontaneous progressive pain Loss of motion in multiple planes: external rotation most limited Pain at end-range of motion	Age usually <40y History of dislocation or subluxation Apprehension test Relocation test Generalized laxity	GHJ OA Fractures ACJ Neural entrapment
Key negative findings	Significant loss of motion Instability signs	Normal motion Age <40 y	No history of dislocation or subluxation No apprehension with testing	

Adapted from (21)

Mitchell *et al.* advocated similar classification criteria to McClure *et al.* for patients managed by primary care *(25)* (see Figure 2.2). They proposed four main categories based on the presenting features of pain: RC disease (tendinopathy and tears); GHJ disease (including adhesive capsulitis); instability; ACJ disease. The authors felt that further subgrouping of these classifications was unnecessary as it would not alter management.

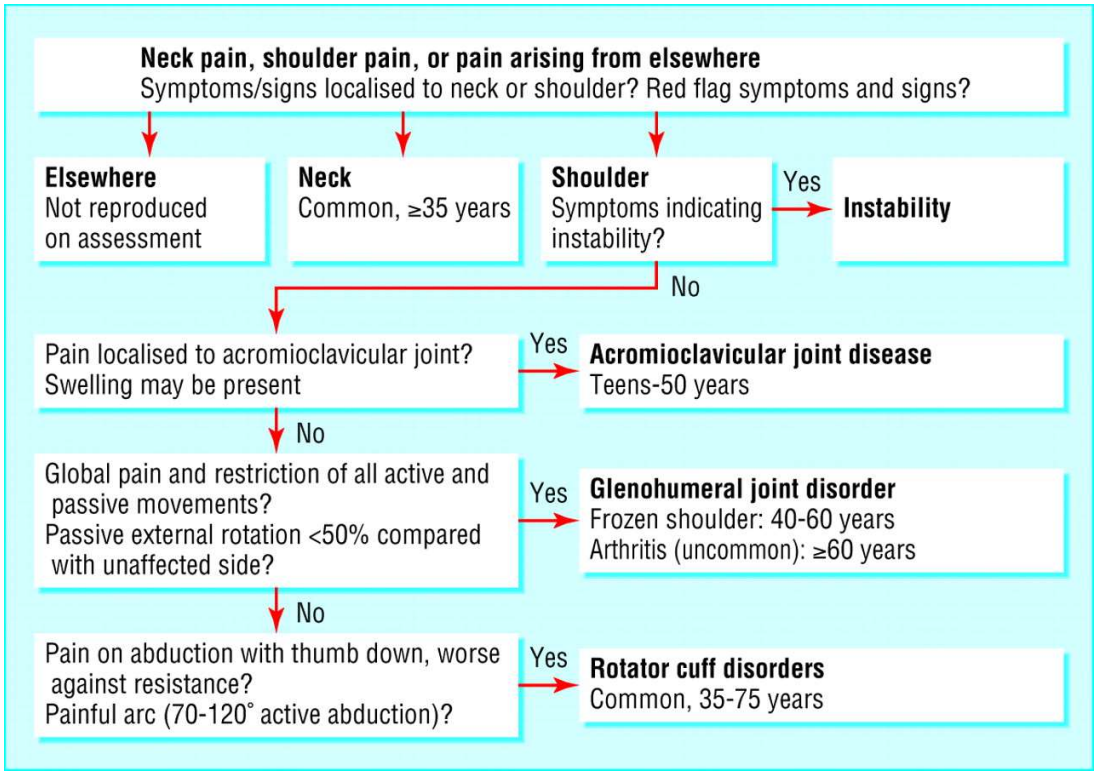


Figure 2.2 Shoulder pain diagnosis and management in primary care

From (25)

The Dutch College of General Practitioners developed clinical guidelines for the classification of shoulder complaints and described five similar categories: subacromial syndrome (RC tendinopathy, RC tear, chronic bursitis); acute bursitis; capsular syndrome (adhesive capsulitis or arthritis); acromioclavicular syndrome; others (see Table 2.2)

Table 2.2 The Dutch College of General Practitioners clinical guidelines for the classification of shoulder complaints

Syndrome	Criteria
Capsular syndrome	Restriction of lateral rotation, abduction and medial rotation. Pain in C5 dermatome.
Acute bursitis	Restriction of abduction. Severe pain in C5 dermatome. Acute onset, no evident preceding trauma.
Acromioclavicular syndrome	Restriction of horizontal adduction. Pain in the area of the ACJ and/or C4 dermatome.
Subacromial syndrome	Pain in the C5 dermatome. No restriction of passive range of motion. At least one positive resistance test: bursitis - variable/little pain, normal power tendinitis - pain, normal power cuff tears - little pain, loss of power
Rest of group (unclear clinical pictures, fractures, etc.)	

Adapted from (6)

The international classification of diseases-10 also classifies shoulder lesions (26). The most common shoulder diagnoses detectable by history and examination is highlighted in Table 2.3.

Table 2.3 The most common ICD-10 shoulder diagnoses detectable by history and examination

ICD-10	Criteria
Subacromial pain syndrome	Typical pain **and** positive impingement test **and** pain with isometric abduction or external rotation
Adhesive capsulitis	Reduced passive range of GH motion >30° in two planes
Multidirectional instability	Positive sulcus sign and passive range of GH external rotation >90°

Adapted from (27)

In order to determine if a different type of shoulder classification could yield potential improvements in treatment, De Winter et al. (28) performed hierarchical cluster analysis on 101 patients with shoulder pain presenting in a primary care setting in the Netherlands, using a number of variables in the medical history and examination. They found three meaningful and stable clusters at baseline: one group with limitation in scapula-humeral mobility and short duration of complaints; one group with 30-50% limitation of ROM; one group with no limitation but long duration of symptoms. At week 2 follow-up similar clusters were found, although patients had shifted between clusters and the degree of limited ROM in the shoulder found in these clusters were smaller than in week 0. The authors suggested that more detailed criteria for the classification of shoulder pain was unnecessary and that physical examination for pathological anatomic classification may be overstated.

Classification has also been evaluated in the context of rehabilitation pathways. McClure *et al.* looked at tissue irritability (high, medium, low) and the authors have suggested using this classification to guide intensity of treatment in the shoulder model (21).

In summary, there are many different classifications of shoulder pain based on clinical findings. Shoulder pain itself, without any further subgroups, may be one type of classification. The majority of other classification criteria include “subacromial pain syndrome”, which includes RC tendinopathy, bursitis, RC tears and biceps tendinopathy. These subgroups are difficult to determine by

history and examination and are often included under one unified term; adhesive capsulitis; and instability.

2.3.1.3 Structural classification

Structural classification is based on imaging or arthroscopic findings. Often imaging or arthroscopy is used to confirm or change the clinical diagnosis, especially as history and examination may be inaccurate in comparison (18, 29, 30). Accurate imaging has enabled the differentiation of pathologies which were previously termed “impingement syndrome” (22), such as subacromial bursitis, RC tendinopathy and RC tear, biceps tendinitis and calcific tendinitis (23). OA is also confirmed on imaging.

The most common shoulder diagnoses requiring structural confirmation as classified by ICD-10, is highlighted in Table 2.4 (26, 27).

Table 2.4 The most common ICD-10 shoulder diagnoses requiring structural confirmation

ICD-10	Criteria
ACJ OA	Pain with joint palpation. Osteoarthritis on X-ray, US or MRI
GHJ OA	Osteoarthritis on X-ray or MRI
SLAP lesion	Positive sulcus sign and passive range of GH external rotation >90°

Adapted from (27)

Uhthoff *et al* proposed a classification system for soft tissue disorders of the shoulder using both clinical findings and imaging features (31). The authors classify pain according to RC tendinopathies, including enthesopathies, calcification, impingement and tears; adhesive capsulitis; and biceps tendonitis.

2.3.2 The problem with classifying shoulder disorders

2.3.2.1 Nomenclature

Defining shoulder symptoms have been confusing, with heterogeneity in nomenclature and varying descriptions of different anatomical sites. Multiple definitions of the same disease are often used in different studies, which leads to further confusion (32). For example, shoulder impingement, SIS and painful arc syndrome have all been used to describe the same pain. Impingement can be taken to mean either a painful arc alone or bursitis and tendinitis (13). RC tendinitis, tears, subacromial bursitis, impingement and calcific tendinitis have all been classified under the umbrella term “RC disorders” and “subacromial pain syndrome (33, 34).

Further confusion often arises where definitions using the same terminology vary. For example, subacromial bursitis in one study can be defined as the presence of fluid collection and enhancement (i.e. uptake of contrast agent) of the subacromial bursa (35), whereas another study may define it as enhancement with thickness >3mm (36).

Determining true shoulder pain may also be difficult as pain is often either referred from the cervical spine or is coincident with neck pain. Some studies have tried to encompass these findings by using terminology to include both neck and shoulders. However, this has led to further discrepancies as these inclusive terms vary between studies. Terms such as cervicobrachial syndrome, neck and upper limb disorders, neck-shoulder problems and shoulder girdle pain have all been used synonymously (37).

2.3.2.2 Problems with clinical classifications

History and examination of shoulder disorders have been shown to be unreliable. In a UK study, 3 rheumatologists evaluated 26 patients with shoulder pain separately, and the diagnostic agreement was found to be only 46% (38). When an additional 18 patients were examined by these rheumatologists together, only 78% agreement was obtained. In a subsequent

study of 86 consecutive patients with shoulder pain and mean shoulder symptoms of 25 months, the inter-observer reliability between a rheumatologist and an orthopaedic surgeon was evaluated (39). They found large differences in agreement over the history of shoulder pain, with κ ranging from -0.02 to 0.90. There was also poor agreement in clinical examination between the two clinicians, with κ <0.4 in the majority of cases. Another study involved two physiotherapists assessing 201 community, orthopaedic and rheumatology patients (28). They found κ for the classification of shoulder disorders was 0.45. In another study, 136 patients with shoulder pain referred to a teaching hospital were assessed for RC lesions by a rheumatology specialist, rheumatology trainee and a research nurse (40). They found that κ ranging from 0.16 (diagnosis of impingement between consultant and nurse) to 0.77 (diagnosis of adhesive capsulitis/osteoarthritis between consultant and trainee). In a study involving 349 patients with soft tissue disorders attending primary care, the overall κ was found to be 0.31 between GPs and physiotherapists (41-43). The physiotherapists were not blinded to the GP diagnosis. In contrast to the other findings, one study has found almost perfect agreement between physiotherapists, with a κ 0.875 (44). However, only 21 patients were recruited to this study and therapists were not blinded to the history.

The reasons for these low levels of agreement may due to differences amongst the clinicians in interpreting the test. Inter-observer variability in assessing shoulder ROM could also contribute to variation in examination technique, and therefore interpretation (45). A multivariate logistic regression analysis by de Winter et al. (28) found that bilateral shoulder involvement, disease duration > 6 months, and high pain severity (mean pain score according to both examiners > 7.2) were independently associated with diagnostic disagreement. Conversely, Liedeck et al. found longer duration of shoulder pain improved reliability (41). A lack of mutual exclusivity of diagnostic categories used in shoulder disorders may also contribute. For example, pain as a result of adhesive capsulitis would prohibit further assessment of the shoulder.

As well as the poor reliability of shoulder examinations, the diagnostic ability of shoulder examination is limited. Three systematic review of studies involving diagnostic tests including those for impingement, instability, labral lesions and RC integrity have shown that there is uncertainty in clinical examination for the utility of clinical examination in discriminating pathologies of the shoulder. The majority of studies were of poor quality (18, 29, 30).

In a study of medical records from data collected at a large steel company, the accuracy of ICD-9 for identifying soft tissue disorders including the neck and upper limb was shown to be poor and did not accurately reflect the underlying problems documented in the medical records (46). Furthermore, there was poor agreement between the diagnostic labels recorded in the medical records and the ICD-9 codes, suggesting that terms are used interchangeably. For example, the codes used to classify diagnoses of sprain and strain, inflammation and pain were used interchangeably.

2.3.2.3 Problems with structural classifications

The difficulties with establishing pathology on imaging has led to variability in definitions. For example, a full thickness RC tear was defined in one study as an inability to visualise any part of the RC (47) but was also be classified as a full thickness tear if the RC was <2mm thick (48). Similarly tendon pathology was classified in one study as thickened if >6mm (49), whereas in another study it was classified as an increase in > 8mm in heterogenous tendon (50). Schmidt *el al*. published some standard reference values for normal shoulder ultrasound to reduce misdiagnosis (51). Mean and standard deviation values of tendon, bursal and cartilage thickness as well as AC and acromio-humeral distance were provided from 102 caucasian volunteers between the ages 20-60. The authors noted that healthy asymptomatic individuals can have fluid in the bursa and peritendinous region.

In summary, the lack of uniformity in labelling shoulder disorders may be a significant factor in our inability to demonstrate effectiveness, efficacy and appropriateness of different therapies. These problems may also limit our understanding of the epidemiology and natural history of shoulder symptoms.

These limitations have serious implication across both clinical and research aspects of shoulder disorders. It has been suggested that the use of labels be abolished and the general term “shoulder pain” should be employed. Possible subgroups with better prognosis and treatment results could then be formed, based on easily reproducible and valid characteristics identified within these populations (32).

2.4 Epidemiology and risk factors of shoulder disorders

Shoulder disorders can be classified based on: clinical symptoms; symptoms and structural pathologies; and asymptomatic structural pathologies. Clinical symptoms include: shoulder pain; subacromial pain syndrome; adhesive capsulitis; and instability. Structural pathologies include subacromial bursitis; RC tendinopathy; RC tears; biceps tenosynovitis; ACJ or GHJ OA and calcific tendinopathy. The literature regarding shoulder symptoms is derived from patients presenting with pain and this will be the focus of this section.

2.4.1 Prevalence

2.4.1.1 Clinical symptoms

Shoulder pain is a very common musculoskeletal complaint in the community. In the UK and Japan, it is the third most common musculoskeletal disorder and a significant contributor to disability (52, 53). In the Netherlands, shoulder pain is the second most reported musculoskeletal symptom (54). Amongst Finnish university student, neck-shoulder complaints were the most prevalent musculoskeletal complaint over a 12 year period (55)

The prevalence of shoulder pain differs globally, and varies according to nomenclature. In a postal survey of 500 people, diagnosis ranged from 31% (definition as “pain in shoulder”) to 48% (questions about symptoms in a pre-shaded area), with 51% of people reporting shoulder pain according to at least one definition (7). Prevalence ranges from 1.2 % in the Philippines (56), 7% in USA (57), 2.36% (2) to 16% (52) in the UK, 18-22% in Sweden (58), 30%

in Finland (59) and 14% in Nigeria (60). Most of these studies involved self-reported questionnaires.

The prevalence of shoulder pain also varies by age. In a postal survey of a town in Northern England with an overall prevalence of shoulder pain of 6.9%, shoulder pain was reported in 0.7% of 16-24 year olds, and increased to 15.9% in over 85 year olds (1). This trend was observed in a further study (2), and a community survey of elderly patients >70 in the UK found pain to be present in 27% of the population. In an American study involving standardised questions administered by trained interviewers, the prevalence of shoulder pain of 1 month or more was 18.9% (61). Troublesome shoulder pain was most prevalent in the 45- to 64-year-age groups (62) and similarly, in a longitudinal survey of the Dutch population randomly selected from a population register, the peak prevalence of shoulder pain was in the age group 45-64 (54). In a systematic review, middle age was thought to be a poor prognostic marker for shoulder pain in the occupational setting (63). The reported lower prevalence amongst older age-groups may be due to under-reporting, as the elderly may not seek medical attention for shoulder pain and it has been shown that fewer than 40% of patients >70 sought medical help for shoulder pain (64).

Over a 10 year period, the annual prevalence of shoulder complaints ranged from 4.1% to 4.8% (65). The 1 year prevalence of shoulder pain (defined with a diagram) over 14 years was evaluated in a longitudinal observational study involving questionnaires in a Norwegian population (66). At 14 year follow-up, 77.4% of the respondents continued to have shoulder pain. The 1 year prevalence may capture episodic pain and explain the higher rate of reported continued pain compared to other studies.

The prevalence of shoulder pain appears to have increased over time (55, 67). Harkness *et al.* conducted two cross-sectional surveys 40 years apart in northwest UK and found the prevalence of shoulder pain more than doubled in men to 15.9% and tripled in women to 18.7%. However, the populations studied were in different areas of northwest UK with different sociodemographic characteristics. Furthermore, there were differences in

methodologies between the two surveys: definition of shoulder pain varied between the two studies and one study was conducted using interviews and the other via postal surveys. Another study examined the 1 week prevalence of neck-shoulder symptoms amongst Finnish university students between 2000 and 2012 using surveys (55). They found that prevalence increased from 24.8% to 28.7%. The amount of paid sick leave as a result of neck and shoulder pain has increased over time, although this may be an overestimation due to increased awareness of shoulder pain amongst employees or employers (68).

Determining the prevalence of subacromial pain syndrome is made difficult by the changing nomenclature as previously discussed. In a systematic review, RC lesions were found to contribute to 70% of cases of shoulder pain (69). In secondary care, 36% of patients with shoulder pain had subacromial pain syndrome (27)

The prevalence of adhesive capsulitis affects 2% and 5% of the general population in the UK and Sweden respectively (70) (69). 11% of patients with shoulder pain presenting to secondary care had adhesive capsulitis (27) and 22% with shoulder pain had adhesive capsulitis in a primary care study in the Netherlands (6).

2.4.1.2 Symptomatic structural pathologies

The relationship between structure and pain remains poorly understood and therefore determining the prevalence of structural pathologies that contribute to symptoms is difficult. The prevalence of symptomatic structural pathologies have been derived from studies including patients presenting with “shoulder pain” or “subacromial pain syndrome” (71, 72). Prevalence varies between studies due to the different population included (age group, gender and ethnicity), imaging modality employed and varying definitions of pathologies.

Studies have found SAB pathology (thickening, effusion or calcification) in 31% - 100% of patients (36), RC tendinopathy in 14.7% - 73.9%, RC tears (full or partial) in 20% - 34.8% and biceps pathology in 17%-30%. 12%-71.3%

of patients with shoulder pain had ACJ OA and 17% - 50% had GHJ pathology (71). Reported prevalence of symptomatic calcific tendinopathy has been found to range from 6.8% to 42.5% (73, 74).

2.4.1.3 Asymptomatic structural pathologies

Subacromial bursal effusion have shown a prevalence of 11.3% (75) to 40% (76) in asymptomatic individuals, and this increases with age (76). Tendinopathic features were found in between 22% (77) to 30% (78) of asymptomatic individuals and 5.32% (79) to 39% (76) had supraspinatus tendinopathy.

The prevalence of complete RC tears in the asymptomatic population ranges from 2.1% (75) to 22% (80) (80, 81). In a study involving 411 asymptomatic volunteers, the prevalence of complete RC tears was found to be age and sex-dependent, with an average prevalence of 22.1% in a Japanese village (81). Asymptomatic RC tears were more common in males and ranged from 13% in those aged 50 to 59 years, to 20% aged 60 to 69 years, 31% aged 70 to 79 years and 50% age > 80 years. It has been shown that there are twice as many asymptomatic tears than symptomatic tears (82). An average 22% (77) to 40% of the population (71) had partial RC tears.

Biceps tenosynovitis increased with age and had an average prevalence of 4% (76) to 19.4% (75) across all age groups. ACJ OA was observed in between 35% (78) to 82% (83) of patients and 89% in those over 40 years (77). 70% of patients had GHJ OA on radiographs, and 80% had osteoarthritic features on MRI (71). Studies of asymptomatic patients have shown a calcific tendinopathy prevalence of between 2.7% – 20% (73). Approximately 50% of patients with calcification become symptomatic (74).

2.4.2 Incidence

There are difficulties with evaluating the incidence of shoulder pain. Often, symptoms have a poorly defined onset and the onset may be several years in the past. Shoulder pain may also have a relapsing remitting course and the

true onset of initial pain may be difficult to recall. Therefore identifying the true incidence of shoulder pain may be limited by recall bias and the misunderstanding that an 'incident' case may in fact be a new prevalent episode of pain. Determining the incidence of both symptomatic and asymptomatic structural pathologies is also difficult, and no studies have been found regarding this.

2.4.2.1 Clinical symptoms

In the UK survey of GPs, the incidence of shoulder pain has been estimated to be 1% for those over 45 years old (84). Another study retrospectively reviewed patient records to evaluate the incidence of shoulder pain, which was defined as GP consultations without any prior consultations in the last 3 years (2). They found the overall incidence of shoulder problems to be 1.47%, and found an increasing incidence with age. One study in Stockholm evaluated the incidence of shoulder pain in an unselected population with no previous shoulder pain and clinically confirmed restricted movement on examination (85). They found an annual incidence of 0.9% for those aged 31 – 35 years, 2.5% for 42 – 46 years, 1.1% for 56 – 60 years, and 1.6% for those aged 70 – 74 years. The authors reported a statistically significant peak of incidence of painful shoulders in those aged 42-46 years when compared to other age groups. In the Netherlands the incidence of shoulder pain in the community was prospectively evaluated by assessing General Practice appointments (6). Defining incidence as not having consulted their general practitioner in the preceding year, the annual cumulative incidence for overall shoulder pain was 14.7/1000 people, when adjusted for missed reports. In a retrospective review of notes in the Netherlands the average annual incidence of generalised shoulder pain was 2.93% for women and 2.22% for men over a 10 year period, (65).

The incidence of subacromial syndrome in Netherlands is 5.0/1000/year (6). Using electronic records, Linsell et al. observed that "rotator cuff shoulder syndrome" accounted for 13.7% of the 1.47% incidence of shoulder disorders (2). Ostor et al. clinically examined a community-based cohort in the UK

presenting with an episode of shoulder pain. They found the incidence of RC pathology was present in 85% of shoulder pain and ACJ disease was present in 24% (86). Multiple pathologies were often found in the same patient. The incidence for acromioclavicular disorders was 0.5/1000/year in the Netherlands (6).

The incidence of adhesive capsulitis was 2.4/1000/year in a community based cohort in the Netherlands (6). In a study of electronic records in 425 general practices in the UK, the incidence of adhesive capsulitis was found to be 3.38 per 1,000 person-years in women and 2.36 per 1,000 person-years in men (87) and another study found adhesive capsulitis accounted for 15% of incident shoulder pain (86).

Instability of the shoulder can be a result of laxity of the shoulder, trauma or both. It can also be classified as anterior, inferior, posterior or multidirectional. The incidence of anterior instability is estimated to be 0.08 per 1000 person-years in USA (88).

2.4.3 Natural history of shoulder pain

2.4.3.1 Clinical symptoms

Shoulder pain often becomes chronic, despite treatment. In the UK, 51% of patients initially presenting to GPs continued to report shoulder pain after 18 months (12). In Japan, shoulder pain is the second most common anatomical site leading to persistent pain (53) and 44.8% of people complaining of shoulder pain continued to have pain after 1 year (89). In a telephone survey of 15 European countries and Israel, shoulder pain was the 6th most common chronic musculoskeletal complaint, as defined by pain duration ≥ 6 months (90). In a population-based Dutch survey (54), 15.1% had chronic (≥ 3 months) shoulder pain at the 12 month follow-up period.

Predictors of long-term shoulder pain have been evaluated. In a systematic review, worse baseline functional ability, higher pain intensity and longer duration of pain predicted a poorer outcome in a primary care population in studies with a varying follow-up from 2 months to 7 years (63). In a subsequent

prospective study of primary care patients in the Netherlands, acute pain (patients with <6 weeks prior to presentation with the GP) and low functional disability were also found to be favourable prognostic markers for improvements in pain, although higher pain intensity at baseline was also associated with a favourable outcome at 6 months in contrast to Kuijpers *et al.* (91). The reason for this discrepancy may be a result of the methodology. Relingh *et al.* assessed severity using VAS 0-10. Van der Windt *et al.* used VAS also, but assessed pain at 12 months rather than 6 months. Patients were also asked about severity of shoulder pain at day and night (92). Macfarlane *et al.* quantified intensity by pain in a smaller area on a diagram or pain at follow-up (93). High pain severity at baseline, longer duration of pain, gradual onset, males, being >55, poor general health, perception of high job demand or low social support and large number of sick leave was also found to be associated with increased duration of shoulder pain (94).

In an observational cohort study in the Netherlands, predictors of progression were evaluated in primary care patients presenting with neck or shoulder symptoms (95). Although neck symptoms were not analysed separately from shoulder symptoms, factors which significantly predicted a reduced recovery and persistent pain at 3 months were severe pain at baseline, a longer duration of symptoms before presentation, a history of neck or shoulder symptoms, frequent discomfort, more resting, and reduced perceived health and quality of life.

There are difficulties evaluating the natural history of subacromial pain syndrome, as different studies use varying definitions for the evaluation of the different subgroups (e.g. tendinopathy or impingement) under the term “subacromial pain syndrome”. In studies with clinically diagnosed RC tendinopathy, patients may only improve with intervention, compared to the no treatment group (96, 97). In another study, 19% of patients with tendinopathy improved with no active treatment (98).

Patients with adhesive capsulitis are classically described as going through 3 phases: a painful “freezing” phase, where the patient’s shoulder becomes stiff. Pain typically precedes stiffness, but occasionally restricted ROM may be the

first symptom; stiff “frozen” phase where pain reduces but stiffness remains; recovery “thawing” phase with resolution of symptoms. The contralateral shoulder may also become affected (70). In patients with adhesive capsulitis, studies have shown between 49 – 61% of patients continued to have pain or stiffness after 24 months (99). However, studies vary in their interpretation of resolution of symptoms, with the possibility that there is residual restriction or pain but not within the functional limitations of the patient. The true number of patients with resolution of symptoms, therefore, may be lower. A recent review found that no treatment resulted in some, but not complete, improvement and that improvement tended to occur at the earlier stages of disease. Symptoms may last for years (100).

The natural history of instability is uncertain (101). Instability is often seen in patients with joint laxity, which can be congenital (e.g. Marfan’s syndrome) or acquired (e.g. gymnasts). Instability usually develop due to high demand or provocative positions (102). Patients can respond well to physiotherapy, especially those greater awareness of their condition and those who modify their activities (101). Male gender, younger age (<20 years) and patients with higher activity levels are at an increased risk of ongoing symptoms and may require surgical intervention (88).

2.4.3.2 Symptomatic structural pathologies

There have been very few studies evaluating the natural history of imaging detected RC tendinopathy, bursitis, biceps tenosynovitis or OA.

The natural history of symptomatic RC tears has been evaluated (103). There are conflicting studies on tear size progression. In one study, tear size progressed in 48% of symptomatic patients treated non-operatively, with full RC tears likely to progress more than partial. Increased age was associated with an increase in tear size (104). In another study, there was no change in tear size after 3.5 years (105). The association of pain with tear size remains controversial, and there are several conflicting reports (103). 75% of patients may symptomatically improve with conservative treatment.

Studies have reported that 50% of patients with calcific tendinopathy improve with non-operative treatment (analgesia, steroid injections, physiotherapy) after 6 months, with 72% improving after a mean period of 16.1 months (106, 107). In a longer term study of 194 patients with a mean follow-up of 14 years, 45% continued to have poor outcomes defined as a Western Ontario Rotator Cuff score of <80 (108). Ogon *et al*. demonstrated that certain factors may affect the prognosis and response of calcific tendinopathy to non-operative therapies. Negative prognostic factors include female, bilateral involvement, smoking, longer duration of symptoms, anterior subacromial localisation and increased size of deposit (106, 108, 109); positive prognostic factors include transparent features on radiographs and lack of sonographic sound extinction. Another study found location of the calcific deposits, initial radiologic type and size, and the extent of initial symptom did not affect the clinical results (107).

2.4.4 Risk factors for the onset of shoulder pain

2.4.4.1 Age, gender and race

2.4.4.1.1 Clinical symptoms

Gender has been shown to be a contributory factor in the onset of shoulder pain. Studies have shown that females have a significantly higher prevalence of shoulder pain compared to males, irrespective of duration of pain (53, 58, 61, 110). In a systematic review of work-related neck and shoulder pain, a higher prevalence was found amongst women after adjusting for age (111). There may be several reasons behind this gender bias. This may be a result of under-reporting by males (85). Other explanations may be that the women work in jobs that involve tasks with higher loads, high repetitiveness and less job control (111). Women may also interpret stimuli to be more noxious than males (112) or may be more responsive to mechanical pain stimuli compared to men (113).

In patients with adhesive capsulitis, women had a 40% higher risk of incident pain than men (HR 1.40, 95% CI 1.38–1.43) (87). Instability was more

common in males in active populations, and females amongst sedentary populations (114)

Age also appears to be a risk factor in the development of shoulder pain. In a community-based study in the Netherlands, the mean incidence was 2.22% in those aged between 18–44 and 3.71% aged over 65; the highest incidence was 4.02% in those aged 45–64 (65). In the UK, the incidence of adhesive capsulitis also increases with age (87). Instability is more common in individuals aged under 40 (114).

There are few studies evaluating the racial difference in shoulder pain. In an American study of people aged >70 years, the authors found that black women over the age of 70 had significantly more shoulder pain than white males and females (61). Studies have shown that differences exist between ethnic groups of health seeking behaviour, pain tolerance and treatment compliance which may account for these differences (115, 116). For shoulder instability, caucasian race was a risk factor (117).

2.4.4.1.2 Structural pathologies

Studies regarding structural pathologies and risk factors were limited and none were found for bursitis, tendinopathy or biceps tenosynovitis.

The prevalence of symptomatic RC tears increases with age and, in patients with full RC tears, pain development has been associated with increasing tear size, muscle atrophy and fat degeneration (118, 119). Hand dominance may also be a risk factor (120).

Prevalence of GHJ OA has been shown to increase with age and affects women more than men, and ACJ OA appears most commonly in patients >40 years old (118, 121)

Women have an increased risk of onset of symptomatic calcific tendinopathy (73, 122). Patients aged between 30 and 60 years had higher odds of developing symptomatic calcific tendinopathy (73, 122).

2.4.4.2 Genetics

2.4.4.2.1 Clinical symptoms

Genetic factors may be implicated in the aetiology of shoulder pain. In a survey of patients comparing musculoskeletal complaints in monozygotic with dizygotic twins, case wise concordance (the probability of a co-twin being affected if their twin has the disorder) showed a heritability of 42% for adhesive capsulitis, after adjusting for age, indicating the presence of a genetic component to this (123).

2.4.4.2.2 Structural pathologies

In a retrospective review of patients with RC tears, Harvie *et. al* found that there was an increased relative risk of 4.65 for RC tears amongst siblings compared to spouses (124). Unfortunately, the studies included were heterogeneous in terms of definitions and inclusion and exclusion criteria.

The dynamic link between genotype and phenotype, gene-gene interaction, gene-environment interaction and epigenetic modification also needs to be fully understood, which limits our interpretation of the genetic associations.

2.4.4.3 Smoking and obesity

2.4.4.3.1 Clinical symptoms

In a questionnaire survey of community-based patients and armed service personnel in the UK, there was an increased prevalence ratio of shoulder pain the past year amongst current and ex-smokers (125). These findings were adjusted for age, sex, stress and workload (lifting weights >10kg/day, work above shoulder height).

In a large (n= 9,415) French cohort study involving self-administered questionnaires, obesity (BMI≥30 kg/m^2) was found to an independent risk factor for developing severe shoulder pain, after adjusting for workload (126). Similarly, in a large working population (n = 44,793) using the data from The Netherlands Working Conditions Survey, obesity was found to be significantly

associated with shoulder/neck pain after adjusting for age, gender, smoking, education, working conditions and activities (127). In a Finnish health survey of >6,000 people, obesity and smoking were associated with an increased prevalence of shoulder pain (128).

2.4.4.3.2 Structural pathologies

Obesity was associated with an increased risk of requiring repair of RC tear (129). Symptomatic calcific tendinitis was associated with high BMI >25 (122).

2.4.4.4 Occupation

2.4.4.4.1 Clinical symptoms

Occupational workload appears to be associated with shoulder pain, although its precise role in the onset and persistence of pain remains unknown. In 2015, 26% of occupational disorders in France were attributed to shoulder pain (130).

In a prospective longitudinal Finnish study using questionnaires, forestry workers were followed-up after 1 year. Work with a heavy load, awkward work postures (such as working with the trunk flexed forward), mental stress and obesity were found to be risk factors for the incidence of new shoulder pain (131). Supporting these findings, a case control study of automobile manual workers found severe shoulder flexion or abduction for more than 10% of the shift increased the likelihood of shoulder pain (132). Overload at work, defined as difficulty at work or hurrying at work, was associated with the persistence of shoulder pain (131). In a systematic review of mainly cross-sectional studies, heavy work load, awkward postures, repetitive movements, vibration, and duration of employment was associated with shoulder pain (133) . The three case-control studies which were evaluated found that repetitive motion, working at or above shoulder height (134-136) and stress (135) were associated with shoulder pain.

A further systematic review investigating factors associated with musculoskeletal disorders of the neck-shoulder region supported the findings that repetitiveness, previous workload and static effort had both a cross-

sectional and longitudinal association (137). Unfortunately, inclusion and exclusion criteria were not reported in this review, and neck symptoms were not analysed separately from shoulder symptoms.

Occupational psychosocial stressors, such as social relationships at work, poor control at work, poor social support, job dissatisfaction or job insecurity, have also been shown to be associated with shoulder pain (133, 138).

Van Rijn *et al.* performed a systematic review to quantify the relationship between specific shoulder disorders and risk factors (139). They found that repetitive lifting (>20kg at least 10 times a day), forceful exertion at work and awkward postures (upper-arm flexion ≥45° for ≥15% of time and hand above shoulder level) were associated with significantly increased odds of developing subacromial pain syndrome.

Instability is more common in athletic or active individuals who participate in overhead activities (114).

2.4.4.4.2 Structural pathologies

Occupation involving repetitive overhead lifting and labour intensive occupations has been associated with symptomatic RC tears and surgical repair failure (119).

2.4.4.5 Co-morbidities

2.4.4.5.1 Clinical symptoms

The relationship between shoulder pain and co-morbidities has been recognised. Patients with ischaemic heart disease have increased odds of severe general shoulder pain (61). Metabolic syndrome and type 2 diabetes mellitus were associated with shoulder pain in men (128).

Multiple musculoskeletal symptoms may also be associated with shoulder pain (61). A recent report has shown that only 7.7-8.6% of patients have generalised shoulder pain without any other concomitant musculoskeletal disease (66). The most common co-occurring pain is neck pain (66). In a Finnish survey of University students, 42% of students with neck-shoulder

pain had other musculoskeletal symptoms (55). A recent study using data from a multi-centre population-based observational cohort study of people with knee osteoarthritis found that “shoulder pain” was the most common site to become painful after knee pain, and that persistent pain in one knee increased the relative risk of bilateral shoulder pain by 2.27, following adjustment for demographic factors (140). Titchener *et al.* found other musculoskeletal co-morbidities such as trigger finger, Achilles tendinopathy and carpal tunnel are associated with subacromial pain syndrome (141)

There have been few studies evaluating the role of psychological factors in the persistence of shoulder pain. In a prospective study of primary care patients presenting with shoulder pain, pain catastrophising, distress, somatisation and fear-avoidance beliefs were measured at baseline and persistence was assessed at 3 months (142). No psychological factors were associated with persistence of pain at 3 months. A combination of pain catastrophizing and long duration of pain (≥3 months) at baseline was found to be associated with persistent symptoms. In those with chronic pain (defined as pain >3 months), catastrophizing was shown to be the strongest predictor of higher pain intensity at 6 months in the GP population >18 years (91). Treatment was not incorporated into the multivariable model used in this study. In a cross-sectional study of the elderly population aged between 70-79, high depression scores were found to be associated with shoulder pain (61).

In a recent cross sectional study of patients with type 1 diabetes of ≥45 years duration, patients had a lifetime prevalence of adhesive capsulitis of 76% (118). Co-morbidities may also influence the duration of adhesive capsulitis. In the same cross sectional study, the duration of adhesive capsulitis was 13.6 years in those with diabetes (118) compared to 15 months in a secondary care group where 23% consisted of diabetics (99). The latter study involved a retrospective review of secondary care patient records with spontaneous idiopathic adhesive capsulitis with an average follow up of 14 years, making direct comparisons difficult. Observational studies evaluating the relationship of thyroid disease, dyslipidaemia and hypertension with adhesive capsulitis

have found a higher prevalence in these disorders in patients with adhesive capsulitis and shoulder pain compared to controls (143-145).

2.4.4.5.2 Structural pathologies

In a retrospective observational study, thyroid disease was found to be associated with RC tears, independent of age (146).

2.4.5 Impact of shoulder symptoms

2.4.5.1 Quality of life

Shoulder disorders have a significant impact on the quality of life. Registry data of 2674 patients with different shoulder disorders (including adhesive capsulitis, instability, RC tear and post-operative patients) presenting to a secondary care surgical unit found that quality of life overall was significantly lower compared to controls (147).

In a cross-sectional analysis of 18 Medical Research Council General Practice Research Framework centres, 17% of respondents to questionnaires had at least moderate “troublesome” shoulder pain over the past 4 weeks (62). The measure of troublesomeness has been found to have a high face, content and criterion validity and good test–retest reliability and at least moderately troublesome pain has been shown to have an important health impact in terms of quality of life and function at an individual level (148).

Gartmann *et al.* administered the SF-36 form to patients with subacromial pain syndrome (SIS in the study), adhesive capsulitis, instability and RC tear (149). They found patients with each classification had significant reductions in physical and mental health comparable to people with depression, diabetes and cardiovascular disease. Another study of patients with adhesive capsulitis had significantly reduced quality of life, measured by SF-36 (150).

In patients with degenerative joint disease and adhesive capsulitis, it has been found that multiple co-morbidities (such as diabetes or cardiovascular disease) are correlated with a worse quality of life (151, 152)

Patients with RC tears had worse SF-36 scores with worse function, as determined by the SST questionnaire (153).

2.4.5.2 Health economic impact

The economic impact of shoulder pain can be substantial as a result of work days lost, compensation and healthcare utilisation.

In a cross-sectional survey of computer workers, 20% of people complaining of neck/shoulder disorders reported productivity loss (self-reported sickness absence or reduced work output) (5). Swedish insurance data from 1994 demonstrated that 18% of paid sick leave from musculoskeletal disorders was a result of neck and shoulder disorders (68). In a study using patient electronic records, the mean annual total cost of shoulder pain in primary care was €4139 per patient (3). 80% of the costs were a result of sick leave. In the Netherlands, the mean total costs were €689, 50% of which was contributed to by sick leave (154). 12% of patients generated 74% of the total costs.

In an analysis of American workers' compensation claims data, shoulder injuries were the third most expensive single injury claim, accounting for 3% of claims, and costing an average of $3911 (155).

The utilisation of healthcare resources is also substantial. Generalised shoulder pain accounts for approximately 1% of GP consultations in the UK and consultation rates are between 15 and 25 per 1000 patients (6, 7). 5% of patients in the USA and the Netherlands with shoulder pain are referred to secondary care (64). The diagnoses at time of referral were not reported. In the UK, 6.3% of patients with "rotator cuff shoulder disorders" are referred for a specialist opinion (2). Repeat consultations for shoulder pain are also frequent: in the Netherlands, 40% of patients saw their GP more than once a year following initial consultation (different diagnoses of shoulder pain not reported) (6). In the Netherlands, shoulder pain accounts for 10% of all referrals to physiotherapy (64). In Australia, shoulder pain accounts for 12% of the weekly workload for chiropractors (156).

The annual cost of treating adhesive capsulitis was estimated as €4,521, with 38% of the costs a result of work hours lost (157).

The economic impact of treating shoulder pain is also substantial, with >300,000 RC repairs/year in the USA at a cost of $3 billion (92). In a postal survey of orthopaedic centres in the UK, the rate of total shoulder replacement was found to be 1.12 per 100,000 and hemiarthroplasy as 2.53. This compares to 11.41 and 10.41 respectively in the USA (158). Shoulder surgery is also increasing: in New York State, there has been a 254% increase in subacromial decompressions from 1996 – 2006, and a 475% increase in Minnesota from 1980-2005 (159, 160). In Sweden, there has been an annual 10% rise in shoulder operations since 1998 (3).

In summary, shoulder pain results in substantial economic impact for society and healthcare providers.

2.5 Pathogenesis

Pain is the primary reason for patients seeking medical help with shoulder problems and involves peripheral and central mechanisms. It is important to understand the origin of pain in order to successfully treat it. This section discusses the pathogenesis of shoulder pain and the pathogenesis of structural abnormalities.

2.5.1 Shoulder Pain

2.5.1.1 Peripheral nociceptive pain

Shoulder pain is generated from damaged joint tissues where chemical, mechanical or thermal stimuli activate afferent nociceptive neurons which transmit signals to the sensory cortex via the dorsal horn of the spinal cord.

Nociceptors are found in the skin, muscles, tendons, bursae, labrum and subchondral bone of the shoulder, and histological specimens have shown the presence of molecules involved in the mediation of pain (23, 161). In acute pain, stimuli cause peripheral nociceptors to activate its afferent sensory neurone action potential, which relays with spinal neurones and in turn

transmits to the thalamus and thereafter the sensory cortex. Pathways within the central nervous system provide descending inhibition to modulate and decrease the signal conveying acute pain. In chronic pain, there is a decreased threshold for activation in the peripheral nociceptor, which increases the signal and is termed peripheral sensitisation. Examples of mediators of peripheral sensitisation include neuropeptide Y (NPY), neuronal growth factor (NGF), vasoactive intestinal peptide (VIP), substance P and calcitonin gene-related peptide (CGRP).

2.5.1.2 Central causes of pain

Central sensitisation (CS) may be present in some patients with shoulder pain. CS is defined as “amplification of neural signalling within the central nervous system (CNS) that elicits pain hypersensitivity” (162). It may be a result of or combination of distorted sensory processing in the CNS, changes in descending pain-inhibitory mechanisms and enhanced activity of pain-activating mechanisms (163). CS may be influenced by psychological factors (163). Two reviews have found the presence of CS in a subgroup of patients with shoulder pain and up to 65%-90% of patients with subacromial pain syndrome (termed SIS) may have some form of CS (163, 164).

2.5.2 Structural abnormalities of the shoulder

The pathogenesis of structural abnormalities of the shoulder is not well understood. The cause of shoulder pain may be a result of individual or a combination of structural pathologies. Ultrasound, as a tool which involves dynamic imaging, is able to detect most of the structures which contribute to the peripheral causes of pain: calcific tendinopathy; RC tendinopathy; RC tears; subacromial bursitis; biceps tendinopathy; adhesive capsulitis.

RC tendinopathy is thought to be a combination of extrinsic and intrinsic factors (see Figure 2.3). Extrinsic factors relate to anatomical structure or biomechanical alterations. This results in a chronic repetitive process leading to compression and micro trauma of the RC tendon, which is termed “impingement”. Neer highlighted 3 stages of impingement: stage 1 describes

acute inflammation, oedema, and haemorrhage of the RC conjoint tendon and bursa, is reversible and commonly found in <25 years; stage 2 is the progression to an irreversible form, where the tendon undergoes fibrosis and tendinopathy and affects patients between 25-40 years; stage 3 affects >40 years results in tears and the development of osteophytes (165).

The shape of the acromion, the coroco-acromial ligament and ACJ have all been implicated as extrinsic causes, although there is conflicting evidence on the role of acromion shape and impingement (166). Bigliani has classified the acromion into different types: type I (flat), type II (curved) and type III (hooked).

Biomechanical alterations may include scapulothoracic or glenohumeral dysfunction, leading to compression (167). Rarer causes of impingement includes subcoracoid impingement, where the subscapularis impinges on the prominent coracoid process and lesser tuberosity of the humerus. Internal (or posteriosuperior) impingement occurs when the arm is abducted, extended and externally rotated resulting in contact of the posterior RC (supraspinatus and infraspinatus) with the posterosuperior glenoid. This may be due to instability, posterior capsule contracture or scapular dyskinesis (167).

Intrinsic factors relate to tendon morphology including worsening blood supply, age related degeneration, overload, overuse or trauma (168). In patients with RC tendinopathy, histological specimens have shown degeneration and fibrosis rather than inflammatory components, although recent evidence has shown the presence of inflammatory cytokines (169). Cytokines are normally increased during wound healing, and it may be that tendinopathy arises as a result of an imbalance in cytokines, resulting in both inflammation and degeneration (169).

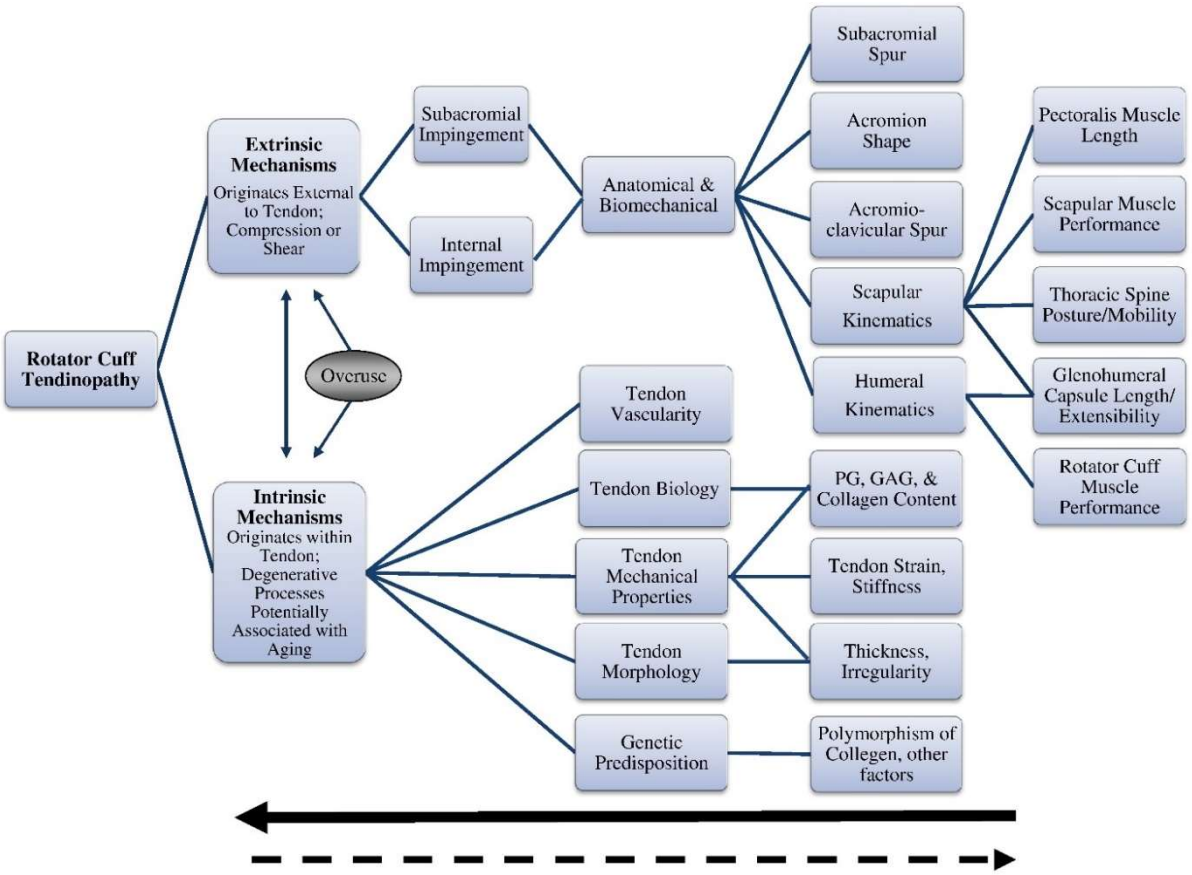


Figure 2.3 Pathogenesis of RC tendinopathy.

Taken from (170). PG = proteoglycans; GAG = glycosaminoglycan

The cause of tears remains uncertain, but is thought to be a progression from chronic tendinopathy. It may be a combination of: changes in collagen composition, reducing the tendon's ability to withstand loading; repetitive micro-trauma leading to small injuries with insufficient time to heal; inflammation; oxidative stress and apoptosis (see Figure 2.4) (171).

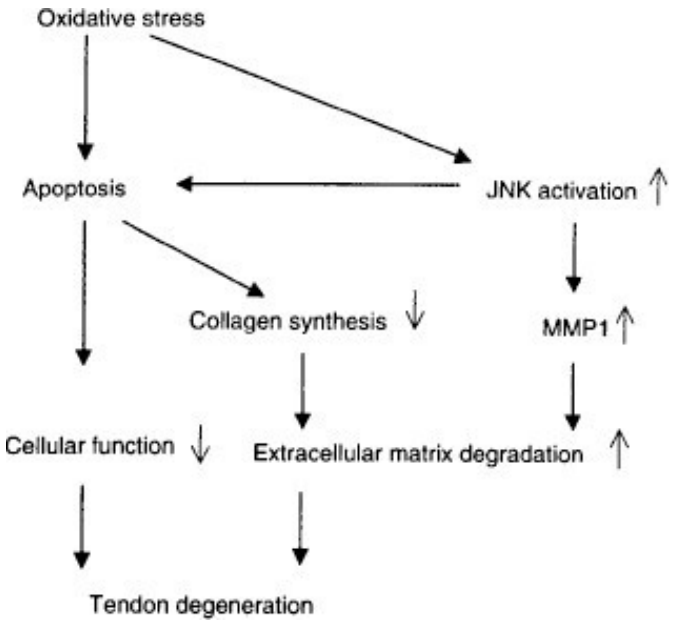


Figure 2.4 Pathogenesis of RC tears

Taken from (171)

JNK = c-Jun N-terminal protein kinase MMP = Matrix metalloproteinase

Bursitis is thought to arise from the same extrinsic factors involved in tendinopathy (165) a pro-inflammatory cytokines have been shown to be present in specimens (161).

Tendinopathy of the long head of biceps (LHB) often occurs with RC tendinopathy. The biceps tendon is in continuation with the GHJ synovial lining and sits in the bicipital groove within a synovial sheath. Tendinopathy may arise due to repetitive traction or friction and can become inflamed secondary to the inflammatory processes affecting the RC (172). Instability and subluxation or dislocation of the LHB usually as a result of failure of the main stabilisers, the superior glenohumeral ligament and the coracohumeral ligament. This is usually found with RC tears (173).

Calcific tendinopathy consists of calcium hydroxyapatite in either crystalline or amorphous form. Approximately 80% of the calcium deposits are located in

the tendon of the supraspinatus, 15% in the infraspinatus, and 5% the subscapularis (174). The development of symptomatic calcification is traditionally separated into the pre-calcification stage (cellular changes begin); calcific stage (calcium is excreted from cells to form deposits; this stage can be divided into the “resting” stage and the “resorptive” stage; the latter is thought to be the painful stage); post-calcific stage (calcium deposit disappears).

The theories of calcification are highlighted in the Table 2.5 below.

Table 2.5 Different theories about aetio-pathogenesis of calcific tendinopathy.

Type	**Cause**
Degenerative calcification	Vascular ischemia
	Repetitive trauma
	Necrosis of tenocytes and intracellular calcium accumulation
Reactive calcification	Active cell mediated process
Endochondral ossification	Endochondral ossification of fibrocartilage at the enthesis of the tendon
Chondral metaplasia	Erroneous differentiation of tendon-derived stem cells (TDSCs)

Adapted from (175)

Adhesive capsulitis is thought to be caused by an initial inflammatory reaction followed by a reactive fibrotic process (see Figure 2.5) (176). The onset of the inflammatory reaction is unknown, and has been postulated to be a result of microscopic tendon injury or an immunological response. Neviasier et al. described four stages: stage 1 synovitis without adhesions or contractures and clinically presents as pain without restriction; stage 2 represents synovitis with early adhesion formation and capsular contracture; in stage 3, there is no synovitis but the axillary fold is obliterated due to significant adhesions. There

is global loss of ROM; stage 4 is the chronic stage - persistent stiffness but minimal pain (177).

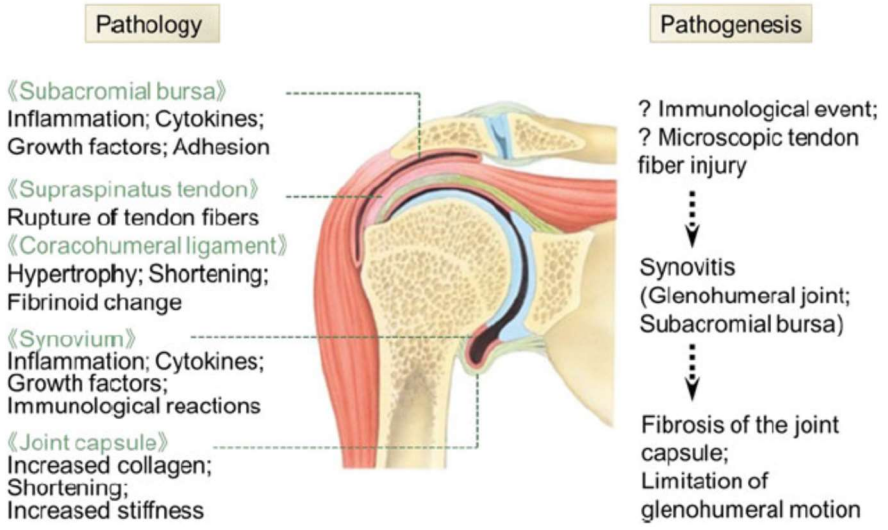


Figure 2.5 Pathogenesis of primary frozen shoulder.

On the left hand side, the pathological findings are listed. On the right, the pathogenesis is listed. Taken from (178)

2.6 Assessing shoulder symptoms

In order to assess shoulder symptoms, appropriate outcomes measures are required to determine the effectiveness of interventions.

2.6.1 Outcome measures in clinical trials

There is a lack of uniformity in the outcome measures in shoulder trials, which limits our ability to compare and synthesise findings (179). To reduce variations in outcome measurements in trials, Outcome Measures in Rheumatology (OMERACT) have developed guidance on creating Core Outcome Sets (COS) (180). COS is a collection of outcome domains (endpoints of interest) recommended for measurement in all shoulder trials. This guides the reporting of important outcomes, reduces the risk of selective

outcome reporting and enables meta-analyses of data. A recent Delphi process identified 4 domains to include in a COS for shoulder disorders: pain; physical functioning; health related quality of life (such as Euro-Qol); assessment of treatment success (which can include Patient Acceptable Symptom State) (181).

Once domains to be measured have been established, then understanding the tools required to assess these domains requires assessment of truth (validity), discrimination (reliability and responsiveness) and feasibility. A broad overview of the psychometric properties of the outcome measures in shoulder studies are discussed below.

2.6.1.1 Construct validity

Construct validity is the degree to which the scores of the instrument measuring shoulder pain relate to measures of similar constructs (either patient reported measures or clinical parameters). Construct validity of shoulder specific questionnaires are often determined by comparing them with questionnaires that determine generic disability measures, including SF-36 or EuroQol (182).

Floor and ceiling effects also contribute to the usefulness of an outcome measure. These are the effects at either extreme of the scale, which would indicate a lack of measurement breadth. These effects may also lead to difficulties in trying to measure change. For example, there would be no place to measure improvement on a scale if everyone scored the maximum score.

Factor analysis may be used to determine if an outcome measure has construct validity. In order to demonstrate this, a factor structure must be unidimensional, which demonstrates a predominant theme, such as shoulder pain (rather than function).

2.6.1.2 Reliability (reproducibility)

Reliability is the overall consistency of a measure over time in a stable population. This is calculated and expressed using the test-retest reliability. If

the instrument is measured by one individual, then the reliability is expressed as an intra-observer reliability or intra-rater agreement. If the instrument is measured by several individuals, then this is expressed as inter-observer reliability or inter-observer agreement. Levels of agreement can be expressed using intra-class correlation coefficient for continuous variables (ICC) or weighted kappa coefficient for categorical variables (Kw). Interpretation of κ can range from 0.00 ‘‘poor’’; 0.00–0.20 ‘‘slight’’; 0.21–0.40 ‘‘fair’’; 0.41–0.60 ‘‘moderate’’; 0.61–0.80 ‘‘substantial’’; 0.81–1.00 ‘‘almost perfect’’ (183).

Reliability may also include a measure of internal consistency. Internal consistency is a measure of the correlation of between different items on the same shoulder questionnaire. This is usually measured using Cronbach’s alpha. An ideal reliable instrument would be for scores on similar items to be correlated (and so be internally consistent), but for each item to contribute unique information as well.

The minimal detectable change (MDC) can also be calculated and is defined as the smallest change in score that likely reflects true change rather than measurement error.

2.6.1.3 Responsiveness

Responsiveness is the ability of a shoulder measure to detect change over time. Responsiveness can be “internal”, which is the ability of a measure to change over time, or “external”, which reflects change compared to the corresponding change in a reference measure (184). Internal responsiveness can also be measured using effect size (ES) or standardised response means (SRM). This can be considered large if >0.8, moderate for 0.5–0.8, and small for 0.2–0.5. External responsiveness can be measured using shoulder specific questionnaires by comparing the shoulder questionnaire with the patient’s change (same, worse or improved).

Correlation in change can also be assessed by measuring the Area Under the Curve (AUC) of a Receiver Operator Characteristic (ROC). A measure of external responsiveness is also the minimal clinically important difference

(MCID), which represents the smallest change that represents an important difference for the patient. Methods for determining MCID can vary (patient perspective, clinician perspective, data driven), and this can often lead to differences in values (185).

2.6.2 Core Outcome Sets for shoulder pain

2.6.2.1 Pain and Function

There are over 30 different patient reported outcome measures for assessing shoulder pain and function (186). Reviews have highlighted the most commonly used tools in terms of publications and citations, and these are found in Table 2.6 (186, 187). SPADI and OSS have be shown to have high levels of validity, discrimination and feasibility, and these will be discussed in more detail as they have been used in subsequent Chapters.

Table 2.6 Table summarising the psychometric of different outcome measures

Measure	Construct validity			Reliability			Responsiveness				Time frame	Time to complete (mins)
	Correlation	Floor/ceiling (%)	Factor analysis	ICC	Cronbach's α	MDC	ES	SRM	ROC	MCID		
ASES		0/1.3		0.84–0.96	0.61-0.96	9.4-11.2	0.9–3.5	0.5-0.81	0.76	6.4-16.9	None	<3
Constant	Strong correlation (≥0.70) with other scales	52 (strength component)/0	When age included 2 constructs found: 1) age, pain, and strength; 2) ADL	0.80 - 0.96	0.60-0.75	N/E	2.23	1.99	0.77	N/E	Last week	5-20
DASH	Strong correlation with pain (≥0.70) and function (≥0.70) subscales	0/0		0.77–0.98	0.93-0.96	6.6–12.75	0.4–1.4	0.5–2.2	0.71	15	Last week	4

OSS	Significant agreement with SF36 and Stanford HAQ	N/E	N/E	N/E	0.84-0.92	6.0	1.2	N/E	N/E	6.0	Last 4 weeks	4
SPADI	Good	0/7	Most items fell into 2 factors: pain and disability	0.85-0.95	0.95	18.1	1.2-2.1	1.17-1.38	0.77-0.91	8	Last week	2
SST	Strong correlation (≥0.70) with other scales	1.6/7.1	Factor analysis suggests that the SST measures two constructs, pain and function	0.97–0.99		N/E	0.8	0.5–1.8		2-3	None	<3
UCLA	Slight-moderate correlation (0.373-0.673) with other scales	N/E		0.51-0.89	N/E	N/E	1.15	0.93			Last 4 weeks	N/E

2.6.2.1.1 Shoulder Pain and Disability Index

SPADI is one of the most commonly used PROM measuring pain and function in clinical shoulder trials (179). The SPADI was developed as a self-administered PROM to measure pain and disability associated with shoulder pathology in the outpatient setting. It was designed to assess the impact of shoulder pathology for both current status and change over time. It consists of 13 items, divided into 5 pain subscale questions and 8 disability subscale questions. Scores range from 0-10 with the higher score indicating a higher level of impairment. The initial tool was scored on a visual analogue scale (VAS) from 0-100. A second version was later developed which used a numerical rating score (NRS) (188). This NRS version was demonstrated to be valid for telephone use.

SPADI has been tested in community based (189) and secondary care settings (190). SPADI has been used as a PROM in pathologies including RC disease (191), OA , rheumatoid arthritis, adhesive capsulitis (192) and post-surgical patients (193).

In order to correct for missing data, the authors advised that at least 11 out of the 13 items are required for calculation of the score (194). In later studies at least 3 of 5 pain and 6 of 8 function items for the subscales were necessary to correct for missing data (186).

2.6.2.1.1.1 Construct validity

SPADI has good construct validity in measuring shoulder pain and function (189, 194). The construct validity of SPADI with disability was evaluated in 94 patients aged 19 to 82 (mean age 44.8) and diagnosed with shoulder disorders in 6 outpatient physical therapy units (190). The authors found a correlation with SPADI and certain domains of the Sickness Impact Profile (SIP), including body care, home management and movement.

SPADI may also have predictive validity. In a recent systematic literature review, a high baseline SPADI predicted chronicity of pain (94).

There was no floor effect but a ceiling effect of 7% has been found (195).

2.6.2.1.1.2Reliability

SPADI was initially developed and tested in 37 males with variable shoulder diagnoses in an ambulatory care setting (194). It has been shown to be reliable, with an intra-class correlation (ICC) 0.66. When test-retest reliability was evaluated for the pain and disability subscale questions, ICCs of 0.64 were found for both. The internal consistency was excellent with a Cronbach's α at 0.95 for the SPADI, 0.86 for the pain subscale, and 0.93 for the disability subscale. The NRS was also shown to be highly concordant with the VAS questionnaire, with an ICC of 0.86 (188). A systematic review has found that SPADI had excellent reliability, with ICCs varying from 0.85 to 0.95 (196)

The MDC of SPADI has been shown to be 18.1 in 78 patients from a local physical and occupational (hand therapy) outpatient clinics in USA (197).

2.6.2.1.1.3Responsiveness

Responsiveness was assessed by examining the correlation with SPADI and its subscales with range of motion at 30 days follow-up. These correlations were shown to be statistically significant ($p<0.05$) (194). NRS was also shown to be responsive to change, by accurately discriminating between subjects who improved and those who stayed the same/worsened (ROC = 0.91) (188). In a longitudinal study of primary care patients with 6 weeks follow-up, the AUC was 0.87 when comparing “improved” with “not improved” (198). An MCID of 8 points has been shown to differentiate between those who improved and those who did not (198), and a change of 13.2 points is associated with a change of 1 on the Global Disability Rating score (197). However, the MDC is 18.1 (197), indicating that a change score of less than this value could be attributed to measurement error. In another study evaluating MCID, changes <10 could not reliably distinguish patients between ‘better’, ‘same’ or ‘worse’. Patients with a SPADI change of >10 was highly specific for improvement (likelihood ratio (LR) 34; 95% CI 1.6-105) and <-10 was highly specific for worsening (LR 12.9 95% CI 1.6-105) (188).

Heald et al. found that the SPADI score had a large degree of responsiveness according to Cohen’s benchmarks, with an SRM of 1.38 for total SPADI and

1.54 and 1.02 for the pain and function subscale respectively (190). Similarly, Paul *et al.* found SRM was 1.17 (198).

2.6.2.1.2 Oxford Shoulder Score

The Oxford Shoulder Score (OSS) is a self-administered 12 item questionnaire designed to be used by patients following any post-operative shoulder procedures except for stabilisation (199). The 12 items assess pain and function. Each item has five response categories and is scored on an increasing severity scale from 1 to 5 (from least difficult to most difficult or severe). This combined to produce a score of ranging from 12 (least symptoms) to 60 (most symptoms). A later version of the OSS amended the scoring system to avoid potential confusion (200). This new system involves scoring each question from 0-4, with 4 representing the best (i.e. the opposite to the original), and so giving a cumulative score of 0-48. This new scoring system has not yet been validated.

The OSS for an asymptomatic population was recently evaluated in an orthopaedic outpatient centre (201). OSS varied by age and gender. The mean OSS for females was 18.8 and for males was 16.3. Regression analysis discovered a formula to predict an age and gender adjusted OSS. This normal score would allow a 'relative OSS' to be calculated, where a standardised comparison to a normal baseline could be made. Such a finding could also be used where a pre-intervention score is not possible, such as in trauma or retrospective studies (202).

The authors of the OSS suggest that it is reasonable to enter the mean value of all the other responses for incomplete items, if one or two questions remain unanswered (200). If there are 3 or more unanswered items, an overall score should not be calculated. If patients indicate two answers for one question, the authors advice to use the most severe response.

2.6.2.1.2.1 Construct validity

Correlation with the Constant shoulder score and the health status questionnaires (SF36 and Stanford HAQ) pre-operatively and at 6 months showed significant agreement ($p<0.01$). Similarly, the correlation between

OSS and Constant score was evaluated in a study of 103 consecutive adult patients treated conservatively for proximal humerus fractures (203). A Pearson correlation co-efficient of 0.84 was found, when all points at baseline, 3 months and 6 months were included in the analysis ($p<0.001$). Regression analysis for the Constant score as a variable dependent on the OSS found an r^2 of 0.70.

Hapuarachchi et al. compared the ASES and OSS in patients undergoing reverse shoulder arthroplasty for cuff tear arthropathy in 29 patients pre-operatively, and at 6 and 12 months follow- up (204). They found a Pearsons's correlation co-efficient of 0.91. Using linear regression analysis, the authors also found that the ASES score could be used to predict the OSS score, and vice versa. The coefficient of determination (r^2) was calculated to be 0.83. This indicates that 83% of the variation of the predicted OSS is explained by the ASES, and vice versa.

2.6.2.1.2.2Reliability

The reliability for the OSS was initially evaluated prospectively on 56 consecutive, post-surgical patients diagnosed with impingement or calcification at baseline and 6 months (199). Cronbach's alpha was 0.89 for the pre-operative assessment and 0.92 at 6 months, indicating high levels of internal consistency.

Reproducibility over 24 hours demonstrated an estimated mean of score differences of -0.12, which was not significantly different from 0.

The MDC was calculated with a test re-test protocol from 0 to 2 weeks, and this was calculated as 6.0 (205).

2.6.2.1.2.3Responsiveness

The ES of the OSS was evaluated by comparing responses prior to surgery and 6 months post-surgery. ES were larger for the OSS (1.2) than the SF36 or HAQ disability index, and equivalent to the HAQ pain VAS (199). This was further confirmed in a later up to a year post surgery (204).

The MCID for the OSS from baseline to 6 months was recently calculated from a cohort of 164 consecutive patients with shoulder problems attending an orthopaedic outpatient clinic (205). This was calculated as 6.0.

2.6.2.1.3 Disabilities of the Arm, Shoulder and Hand score

DASH was designed to be a brief self-administered measure of symptoms and functional status on the upper limb, with particular focus on physical function. It consists of 30 items rated from 1 to 5 (from no difficulty to unable) (206). There is also a separate optional high performance sport/music and/or work section, consisting of 4 items and scored 1-5. General guidelines suggest that it should be used between the ages of 18 to 65 (207).

A score is achieved by the total of the circled responses and subtracting 30. The subtraction of 30 anchors the score to a base of 0, thus changing the response scale to a 0 to 4 equivalent. The figure is then divided by 1.2 to get a DASH function score out of 100. The intention is to enable easier comparison to other measures scaled on a 0-100 scale. The higher the score, the greater the disability. DASH is not recommended to be administered over the telephone and is intended for paper format only (207).

An 11-item shortened version of DASH, called QuickDASH, has been developed, which demonstrated similar responsiveness and reliability in a general cohort (208) and group with shoulder specific pathology (209). Factor analysis has shown that the QuickDASH demonstrated a bidimensional structure suggesting that QuickDASH may measure other concepts as well as function (210).

Missing items are replaced by the mean value of the responses to the other items. DASH score may not be calculated if there are 4 or more items missing (207).

2.6.2.1.4 Constant score

The Constant score was devised in 1987 as an outcome measure designed to assess function (211). It comprises 4 domains and is scored by both the patient and the examiner. Each domain is scored separately: pain reported by

the patient over the last 24 hours (15 points); activities of daily living reported by the patient (20 points); range of movement assessed by the examiner (40 points); strength assessed by the examiner (25 points). The scores combine to a sum of 100, with a higher score indicating better function. In the original version, the pain score was graded on a four point scale (none, mild, moderate, severe which scored 15, 10, 5 and 0 respectively). This was subsequently replaced with a VAS score (212). The ADL score is divided into 4 items (sleep, work and recreation, ability to position hand in space). Pain free ROM is measured with a goniometer. Strength is now measured using a dynamometer or a calibrated spring balance as the previous measure of an unsecured spring balance lacked standardization and precision (213). Criticism of this PROM is that the weighting of the subscales and the use of ordinal catgories for a continuous scale of ROM and strength has not been rationalized or validated.

2.6.2.1.5 Simple Shoulder Test

The SST was developed to evaluate the functional change of patients following a surgical procedure (214). It is a self-completed, 12 item questionnaire with dichotomous “yes/no” answers. A “yes” would score 1, a “no” would score 0, with possible total combined score of 12 (12 = best). There is no particular time frame for the questions. It takes <3minutes to complete the questionnaire (215) and the administrative burden has been reported as minimal (196). There is a significant decrease in SST score with age group (patients aged >60 compared to <60) (p=0.001) (216).

2.6.2.1.6 University of California at Los Angeles score

The UCLA was first published in 1981 and primarily intended for patients undergoing total shoulder arthroplasty for arthritis of the shoulder (217). It has subsequently been used in other shoulder surgery studies (218, 219). Initially devised to be a clinician completed form, it has been shown that patient self-administration is comparable to clinician completion (220). The instrument consists of 5 separate domains, with each domain having 1 possible answer. These domains are: pain, function, active forward flexion, strength of forward

flexion, and overall satisfaction. Pain accounts for 10 points, function for 10 points, forward flexion for 5 points, strength for 5 points, and overall satisfaction for 5 points, giving a maximum combined score of 35 points. The time-point around the questions is the last 4 weeks. A score of ≥27 indicates a good or excellent outcome, whereas those with a score of <27 indicate a fair or poor outcome, although this is not based on any validation study (221).

Similar to the Constant score, the authors did not clarify the reasons for the weightings of each scoring item.

2.6.2.1.7 The American Shoulder and Elbow Surgeons score

The American Shoulder and Elbow Surgeons (ASES) Standardized Shoulder Assessment Form was published by the Research Committee of the American Shoulder and Elbow Surgeons in 1994 (222). It was designed to be used for patients with any shoulder pathology and consists of both patient self-assessment and physician assessment components. The recall period is over 1 week. The form consists of a single item pain VAS scale and a 10-item functional questions, scored on a 4 point likert scale. The scoring is based on these answers: the pain subscale contributes a score of 50 and is calculated by subtracting the VAS from 10 and multiplying by 5; the function score also contributes a score of 50 and is calculated from the sum total of the functional scores and multiplying by 5/3. A maximum score of 100 is obtained, where the higher score indicates a better outcome. (223).

Other questions on this outcome measure include dichotomous “yes/no” answers for questions regarding medications and instability, a 0-10 scale on instability, a pain diagram and a physician component measuring strength, range of motion, signs and instability. These questions do not contribute to the scoring.

A modified version of the ASES was introduced in 1998, which involved the deletion of 2 and addition of 5 function questions. This was designed for assessment of the entire upper extremity rather than the shoulder (224).

2.6.2.2 Health related quality of life

2.6.2.2.1 Quality of life

2.6.2.2.1.1 EQ-5D-5L

The measurement of quality of life is important to assess service quality, health needs, the effectiveness of interventions and economic analysis (225). The EQ-5D-5L is a generic measure of self-reported health status that defines health status in terms of five dimensions: mobility; self-care; usual activity; pain or discomfort; and anxiety or depression (226). There are 5 response options (no, slight, moderate, severe, and extreme problems/unable to). There is also a VAS scale. Each state is referred to in terms of a 5 digit code (ranging from 1 = no problem to 5 = extreme problems). A total of 3125 possible health states are able to be defined in this way. There should be one response for each dimension and more than 1 response should be regarded as missing data. The EQ-5D-5L can also be converted into an index figure (227).

It is the most widely used generic PRO questionnaire internationally (228) and is the instrument recommended by NICE (229). Euro-QoL is one of the most common measures of quality of life in shoulder studies (179). It is incorporated into routine data collection in clinical settings, clinical trials and health population surveys (230).

EQ-5D-5L has been extensively validated in a diverse population (n = 3919) of 8 patient groups (including respiratory disease, depression, liver disease, diabetes, arthritis, personality disorders and stroke) across 6 countries (231). Construct validity was demonstrated by a significant Spearman correlation ($p<0.001$) with the WHO-5 items. Overall, the ceiling effect was 16%, with no floor effect. Mean administration time is 2.2 mins (232). ICC was calculated as 0.82. The SEM for improved groups was considered small (0.33–0.42). For the improved group, the MICD for the EQ-5D-5L index and the EQ-VAS was 0.04 and 0.05 respectively, and 0.05 and 0.09 for the worsened group (232).

2.6.2.2.1.2 The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) (233) is a 14-item scale designed to detect anxiety and depression, independent of somatic symptoms, with a time-anchor of the past week. It consists of two 7-item subscales measuring depression and anxiety. A 4-point response scale (from 0, representing absence of symptoms, to 3, representing maximum symptomatology) is used, with possible scores for each subscale ranging from 0 to 21. Scores for each subset are categorised as normal (0-7), mild (8-10), moderate (11-14) and severe (15-21). Normative data for those with depression and anxiety are 9.29 and 11.42 respectively. It was 3.52 for those without depression and 5.37 for those without anxiety (234, 235). It takes 2-5 minutes to complete (236). HADS is recommended by NICE as to assess depressive states (237).

HADS is a valid, reliable and responsive outcome measure (238). Correlation with other depression and anxiety ranges from 0.60 – 0.80. No floor or ceiling effect has been established (234). Factor analysis has shown a two factor analysis, in accordance with the anxiety and depression subscales. Cronbach α is 0.83 for anxiety and 0.82 for depression. AUCs were found to be 0.84–0.96.

Recently, it has been suggested that missing data can be best corrected using the “half-rule”. This method requires any missing response in the anxiety or depression subscale to be imputed by the mean of the answered items if more than half of the items in a subscale were validly answered. If more than half was not answered, the subscale was discarded (239).

2.6.2.2.2 Health expectancy

2.6.2.2.2.1 Brief Illness Perception Questionnaire

The Brief Illness Perception Questionnaire (BIPQ) is a valid and reliable nine-item scale designed to rapidly assess the cognitive and emotional representations of illness (240). Dimensions assessed include consequences, timeline, personal control, treatment control, identity, concern, understanding, emotional response and causal representation. Higher scores indicate

stronger perceptions along that dimension. Eight questions are rated on a scale of 0-10, with an open ended response for assessment of causal representation. Responses to the causal item can be grouped into categories such as stress, lifestyle or hereditary.

Floor and ceiling effects were not present for the BIPQ, although there was a ceiling effect of 30% for the timeline item (241).

Construct validity with the longer version of the study has been shown. Test-retest reliability over 3 to 6 weeks has shown significant correlation ($p<0.01$), with the correlation ranging from 0.48 – 0.75 amongst the different dimensions range. Meta-analysis has also shown each subscale demonstrates sensitivity to change after intervention (242). The standard error of measurement (SEM) for the BIPQ scale was 0.63 and the MDC was 1.75 (241)

2.6.2.2.2.2 The pain self-efficacy questionnaire

The pain self-efficacy questionnaire (PSEQ) is an individual's belief or level of confidence that they can successfully perform a particular task (243). In patients with chronic osteoarthritic knee pain, those with high self-efficacy for controlling arthritis pain have been found to have higher pain thresholds. The PSEQ is a ten item questionnaire measuring confidence in given tasks. Each item is scaled from 0 (not at all confident) to 6 (completely confident). A total score is calculated by combining the scores yielding a maximum possible score of 60. Higher scores indicate stronger self-efficacy beliefs. PSEQ demonstrated construct validity when correlated with other similar measures (243). Cronbach's α coefficient, was calculated as 0.92 and the test–re-test reliability found a significant correlation of 0.73 ($p<0.001$) from baseline to 3-months.

2.6.2.2.2.3 Pain-DETECT

The Pain-DETECT Questionnaire (PDQ) is a 9-item questionnaire to determine a neuropathic pain component (244). It measures gradation of pain (7 questions scored from 0-5, never to very strongly), pain course pattern (scored from -1 to +1) and radiation of pain (score of 2 if yes; score of 0 if no). Principal component analysis identified the seven sensory items as the

dominant driver for data structure in the questionnaire. The 9-item score is calculated by addition of the entries, with a maximum possible score = 38, minimum = –1. A score ≤ 12 suggests a neuropathic component is unlikely; a score ≥ 19 suggests a neuropathic component is likely (90% probability). A score between these results suggests uncertainty. 80% of patients had no problems completing the form. AUC has been calculated as 0.91 (244). Cronbach's alpha was 0.76 and 0.80 for the 7- and 9-tem questions respectively on gradation of pain (245). The correlations between average pain severity (using Brief Pain Inventory Short-Form) and PDQ scores were ≥0.4 for pain symptom items but were low (<0.3) for the two non-sensory items (245).

2.6.2.2.3 Activity

2.6.2.2.3.1 Shoulder Activity Scale

The need to specifically evaluate patient activity is important as patients with similar levels of pain/function may have different levels of activity. Patient activity may also be an important prognostic indicator, and patient symptom ratings may be related to activity.

The Shoulder Activity Scale (SAS) is the only specific measure of shoulder activity to date. It captures how frequently patients with shoulder disorders perform each of a range of different shoulder activities e.g. lifting or participating in sports involving contact (246). Patients are asked to report how often they performed each activity at their most healthy and active state during the last 12 months. Five questions relating to activity are asked, ranging from 'never or less than once a month' (score 0), 'once a month' (score 1), 'once a week' (score 2), 'more than once a week' (score 3) or 'daily' (score 4). Two additional multiple choice questions provide a score assessing participation in contact and overhead sports. The total numerical activity scale score is the sum of the individual activity scores, ranging from a minimum score of 0 points (a patient who answers never or less than once a month for all five items) to a maximum score of 20 points (if the patient answers daily for all five items). Scores can be interpreted as ≥16 = high activity level, 7-15 = average activity

level, ≤6 = low activity level. This PROM was assessed in a mixed group of patients with rotator cuff disorders, osteoarthritis and instability.

SAS has been shown to have construct validity, and is significantly correlated ($p<0.01$) with the SST ($r= 0.46$), knee activity rating scale ($r= 0.66$) and self-reported activity ($r= 0.52$). SST was chosen as patients with greater shoulder activity levels (measured by SAS) were expected to have better shoulder function, although some divergence was expected due to the difference between function and activity. The activity rating scale used for comparison was based on the knee, but a positive correlation was expected as both scales measured an aspect of patient activity. Patients were asked to circle a number on a 10-point scale ranging from 0 (not active) to 10 (extremely active). This self-reported shoulder activity level was correlated with SAS. It is also a reliable measure with an ICC of 0.92 (246). The psychometric properties of the sporting questions have not been analysed.

Normative data by age and sex has also been demonstrated, with an overall mean score of 8 in healthy controls (247).

No MCID, floor or ceiling effect has been identified. However, measuring the patient activity over 1 year exposes the SAS to recall bias.

2.6.2.3 Assessment of treatment success

2.6.2.3.1 Patient Acceptable Symptom State (PASS)

PASS aims to provide a clinically meaningful tool to help interpret patient reported outcome measures. It is a patient reported outcome designed to reflect the concept of wellbeing. The definition of PASS varies between studies and OMERACT has sought to standardise this definition, defining it as the value on a scale beyond which the patient feels good enough to continue in that state (248).

2.7 Assessing structural pathology with imaging

Radiological investigations have an important role in clinical practice as they are frequently used to aid in the diagnosis and treatment of shoulder

disorders. A combination of imaging modalities may be employed to determine the diagnosis and help with treatment. The costs of imaging are substantial, accounting for 65% of total treatment costs in patients who ultimately underwent RC tears in the USA between 2004 – 2009 (249). Costs vary significantly between modalities. Overall, the cost of imaging was highest for MRA, followed by MRI, ultrasound and radiographs (250). In England in 2012-2013, the NHS cost of shoulder MR arthrogram was £272 (€321) and for MRI was £153 (€180) (251). In comparison, the costs in the USA were significantly higher: the reported costs for a shoulder were MRA £1535 ($2,339) and £1334 ($2,033) for an MRI (252). In comparison, a plain shoulder X-ray involving two views has been charged at £14.67 (€173) and an ultrasound of the rotator cuff costs £47 (€55) (253).

Imaging-based pathology scores are also used as outcome measures in clinical trials. The studies evaluating the validity and reliability of imaging on shoulder symptoms will also be discussed below.

2.7.1 Clinical practice

2.7.1.1 Radiographs

Radiographs are often the first imaging investigations for both acute and chronic shoulder pain (254, 255). Radiographs can be used to evaluate arthritis, calcification, chronic RC tear, impingement and bony lesions (such as arthritis, fractures and morphological variants of the acromion) (256). They are usually easily accessible and processed relatively quickly. Disadvantages of radiographs include radiation exposure and the inability to detect soft tissue lesions directly.

Radiographs are usually the first line investigations for detecting osteoarthritis, as shown by joint space narrowing, osteophyte formation, subchondral sclerosis and cyst formation. Periarticular calcification can also be detected using radiography, and localised to a particular tendon. The chronicity of calcification can also be approximated, as chronic calcification is usually

sharply demarcated and dense, whereas acute calcification may cause obliteration of the fat planes as a result of surrounding oedema (256).

Although impingement cannot be visualised in radiographs, features associated with this diagnosis have been reported. These include anterior acromial osteophytes (257). Other reported findings associated with impingement include the shape of the acromion, which can be described as flat (type 1), curved (type 2), hooked (type 3) or convex (type 4) (258). Furthermore, acromion slope and extension may be associated with impingement and RC tears, although evidence is conflicting (259, 260). Radiographic assessment of the acromion is sensitive to minor variation in technique, and the inter-observer error in measuring the acromion has been found to be high (261, 262). Signs associated with RC tears may include narrowing of the acromiohumeral space (this is normally > 7mm) and superior subluxation of the humeral head. In chronic RC tears, the humeral head and acromion may remodel, coining the term “RC arthropathy” (256).

Signs associated with instability may also be found on radiographs (263). These may be lesions secondary to chronic instability, such as Bankart or Hill Sachs lesions, or subluxation (by comparing the centre of the humeral head, with the centre of the glenoid and the use of stress views).

There is a paucity of research on the clinometrics of radiographs in detecting pathology. The reliability of radiographic assessment of acromial morphology was found to be fair to moderate with mean $\kappa = 0.35$ and 0.55 for inter-observer and intra-observer reliability respectively (264)

2.7.1.2 Ultrasound

Ultrasound scans have been used to help identify RC tears, tendinopathy, calcification, bursitis and osteoarthritis (265, 266). Ultrasound scan can also visualise superficial ligaments, such as the coroco-acromial ligament. This modality has the advantage of dynamic scanning, which would demonstrate signs of bursal bunching and impingement. Ultrasound offers the option of point of care therapeutic injections if any abnormalities are detected at the

time of the scan. Scans do not expose the patient to radiation. Disadvantages of ultrasound include the operator-dependent nature of this modality. Ultrasound is unable to visualise deeper structures, including the labrum and bone marrow (255).

In 2012, a European radiology group employed a Delphi consensus method to determine the indications for musculoskeletal ultrasound scan of the shoulder (267). They determined that, for detecting RC tears, tendinopathy, long head of biceps tears or ruptures, calcific tendinopathy, bursitis or ACJ arthritis, ultrasound was either the first choice of imaging modality or equivalent to other modalities. Similarly, the American College of Radiologists guidelines advise that ultrasound of the shoulder would be an appropriate next step after radiography, in conditions including RC tears, impingement, bursitis, or biceps tenosynovitis (255). In patients with non-specific history or examination, and non-contributory radiographic findings, ultrasound may also be appropriate, but MRI is usually more appropriate.

Adhesive capsulitis and GHJ instability was not indicated by the European group (267). Despite this, certain ultrasound features have been shown to be associated with adhesive capsulitis. Thickening of the coroco-humeral ligament (268), axillary pouch (269) and power Doppler signal from the RC interval (270) have all been associated with adhesive capsulitis. It has also been suggested that a combination of both dynamic and static parameters can be used to diagnose shoulder adhesive capsulitis (271). A thickening of the coroco-acromial ligament and increased soft tissue in the rotator cuff interval in combination with restricted ROM had a high sensitivity and specificity (100 and 87%, respectively) for diagnosis of adhesive capsulitis.

Recent reviews evaluated the accuracy of US for detecting soft-tissue pathology of the shoulder (272, 273). A summary of their findings is presented in Table 2.7.

Table 2.7 Summary of ultrasound accuracy

Pathology	Sensitivity	Specificity	LR+	LR-
FT RC tear	0.80-0.96	0.86-0.93	10.1-23.8	0.04-0.23
PT RC tear	0.46-0.84	0.75-0.94	1.84-35.5	0.18-0.72
RC tendinopathy	0.79	0.94	13.2	0.2
Bursitis	0.79-0.96	0.90-0.98	9.6-41.5	0.04-0.22
Calcific tendinopathy	1.00	0.85-0.98	6.5–51.8	0.02–0.06
LHB	0.86-1.00	0.98-1.00	43.0	0.14

Adapted from (272, 273)**.** FT = full thickness; PT = partial thickness; RC = rotator cuff; LHB = long head of biceps

A previous study has shown inter-rater reliability to be good between experienced sonographers (κ >0.60), but only fair to slight with inexperienced sonographers for RC tear, tendon calcification, impingement and biceps tendon pathology (κ = 0.05 – 0.83), (274). Even between the experienced sonographers, agreement was fair (κ = 0.33) and slight (κ = 0.05) for subacromial fluid and synovitis respectively. To further help standardise the operation of ultrasound, the European Society of Musculoskeletal Radiologists have published a protocol for scanning the shoulder (275).

2.7.1.3 MRI

MRI scans are useful in determining RC tears and tendinopathy, disorders of the biceps, acromion pathology, bursitis, labral lesions, chondral and osteochondral lesions and marrow abnormalities. MRI may also be indicated to further clarify frozen shoulder (253). MRI offers the additional benefit over ultrasound as it is also able to visualise bony lesions, deeper ligamentous structures and labral lesions (276, 277). MRI may be performed without contrast; with intra-articular contrast injection to increase visualisation of intra-articular abnormalities (known as “direct” MR arthrography (MRA)); or with intravenous contrast to identify hyperaemic lesions by enhancing synovial-lined structures and contents (creating “indirect” arthrographic images). MRI

is able to visualise anatomical structures in multiple planes. MRI does not involve radiation exposure. Disadvantages of MRI include the inability to use in patients with certain metals or foreign bodies. Furthermore, the nature of MRI equipment means that it may be unsuitable for patients with claustrophobia or those with a very high BMI. MRI may also be lengthier and noisier compared to radiographs or ultrasound, so patient comfort needs to be taken into account.

There are few guidelines regarding the use of MR in shoulder pain. The American College of Radiologists and Society of Skeletal Radiology advice that in patients with acute shoulder pain, MRI is an appropriate option in patients with a non-contributory radiograph but persistent pain, and in patients with a suspicion of labral lesions, bursitis, tenosynovitis, RC lesions or impingement (255). Recently, they have updated recommendations to include the use of MRI to evaluate prolonged, refractory, or unexplained shoulder pain; impingement; instability; and limited range of movement (253). There are no national or societal UK guidelines on the application of MRI (278). Recently, Freeman *et al.* evaluated the appropriateness of MRI scans in their local hospital in Southern England (278). Their guidelines advised that MRI should be used for a diagnosis of instability, tumour or infection, or for other diagnoses if other preceding investigations had failed to give a diagnosis. They found that overall, 56 % of MRI scans were ordered inappropriately. Previously, a study of shoulder MRI scans in the United States found 46% of referrals were inappropriate (279).

The sensitivity and specificity for RC lesions for MRI and MRA is outlined in Table 2.8 (9, 273).

Table 2.8 The sensitivity and specificity for RC lesions for MRI and MRA

Pathology	Imaging modality	Sensitivity	Specificity	LR+	LR-
FT RC tear	MRI	0.90-0.94	0.93	12.9-13.0	0.06 - 0.1
	MRA	0.90-0.94	0.92-0.95	12.0-18.0	0.06 - 0.1
PT RC tear	MRI	0.67-0.74	0.93-0.94	11.2	0.4
	MRA	0.83	0.93	10.0 -11.9	0.2 – 0.28
Any RC tear	MRI	0.90-0.98	0.79- 0.90	5.0-9.0	0.03-0.1
	MRA	0.90	0.90	9.0	0.1

Adapted from (9, 273). FT = full thickness; PT = partial thickness; MRI = magnetic resonance imaging; MRA = magnetic resonance arthrogram

The sensitivity and specificity of MR in diagnosing labral tears has been reviewed. The authors found mean sensitivities of MRI, direct MRA, and indirect MRA to be 63.0%, 80.4%, and 74.2%, respectively. Mean specificities of MRI, direct MRA, and indirect MRA were 87.2%, 90.7%, and 66.5%, respectively (280). Sensitivity and specificity for the detection of full tears of the biceps tendon using non-contrast MRI has been shown to be 0.54 and 0.98 respectively, and for 0.27 and 0.86 respectively for partial tears (281). A recent study has shown that there were differences in inter-reader reliability for glenohumeral-cartilage lesions using non-contrast MRI. Inter-observer agreement was fair for the detection of humeral lesions (κ = 0.24) and moderate for glenoid lesions (κ = 0.41) (282). In the largest study to date evaluating the diagnostic ability of MRI for glenohumeral lesions, VanBeek et al. evaluated 84 shoulders and found a sensitivity and specificity for humeral lesions was 43% and 91% respectively, and 53% and 93% for glenoid lesions. The sensitivities and specificities for bursitis and signs of impingement have not been established.

2.7.1.4 The relationship between imaging and pain

Our understanding of the relationship between shoulder imaging pathology and symptoms is poor. Although there are studies demonstrating the presence of shoulder pathology in patients with symptoms (283, 284), shoulder pathology has also been found in asymptomatic individuals (81, 285). Bruyn et al showed that there was poor correlation between shoulder PROMS and ultrasound and MRI in a rheumatological population (286).

2.7.2 Imaging as an outcome measure in clinical trials

Imaging is used as outcome measures in clinical trials. Ultrasound and MRI is commonly used to measure severity or presence/absence of RC tendon pathologies and calcific tendinopathy (287-289). In one systematic literature review limiting its search to 6 orthopaedic journals, the use of ultrasound, MRI or CT with contrast has been reported in 65% of studies assessing rotator cuff tear and repair outcomes (287). In another review evaluating outcomes in the treatment of rotator cuff tear, only 28% of studies used evaluated tendon integrity using imaging tools (288). Radiographs have also been used to evaluate change in calcium deposit size following treatment for calcific tendinopathy (289).

2.8 Treatment of shoulder pain

Treatment of shoulder symptoms consists of non-surgical and surgical interventions. Non-surgical techniques include medication, physiotherapy and steroid injections. Other therapeutic options include barbotage, acupuncture and extra-corporeal shockwave therapy. Certain treatments are often tailored towards the specific pathology. For example, barbotage is often used for calcific tendinitis. Treatment for shoulder pain can be broadly categorised into non-surgical and surgical options.

2.8.1 Non-surgical

2.8.1.1 Physiotherapy

There are a large number of protocols and physiotherapy exercises (290). Physiotherapy encompasses a wide range of treatment modalities including postural control, increase range of motion, stretching and strengthening.

2.8.1.1.1 Types of exercises

Postural control involves training of the shoulder muscles, such as shoulder retraction or ensuring the trapezius remains relaxed during arm elevation (via feedback with the contralateral hand or in front of a mirror). Improvements of gleno-humeral motions use exercises such as pendulum exercises, where the arm is left to swing under the weight of gravity. Active assist exercises, for example with a cane or with the other arm supporting the affected arm, may also be employed. Progression of these exercises are generally dictated by comfort. Stretches can include posterior shoulder stretches, such as cross-body adduction or sleeper stretch (lying on affected shoulder with arm forward flexed 90^{o} and internally rotating shoulder). Anterior shoulder stretches can include placing the hands on the door and leaning forward. Finally, strengthening of the shoulder muscles include flexion, extension, internal and external rotation of the adducted arm, often against resistance (e.g. using an elasticated band). Push ups, rows (pulling elastic cord at shoulder height, with elbow flexed 90^{0}, aiming for scapulae to touch) and scaption (holding the arm 30^{o} forward, thumb up or down and raising and lowering the arm) exercises have also been advocated. The intended aim is to strengthen the RC and stabilise the scapula.

2.8.1.1.2 Dosing

Duration of exercises may also vary. Most authors recommend stretching from 15-30 seconds, 3 to 5 times with a 10 second rest between each stretch (290). Frequency of strengthening exercises are usually 3 sets of 10 repetitions with

a 60 second rest between sets. Some authors advocate increasing frequency after time, for example 3 sets of 10 in week one, then 3 sets of 15 in week 2 then 3 sets of 20 in week 3. Increasing the resistance of exercise bands may also be helpful. A recent review evaluated the contextual factors and prescription parameters of published exercise programmes for RC tendinopathy (291). The authors found the optimum number of repetitions of exercise and frequency was unclear, but higher number of repetitions result in better outcomes and three sets of exercises are better than two or one. The type of exercise in terms of pain production or pain avoidance did not seem significant, nor did supervised or home exercises. Exercises involving resistance did seem important, although the level of resistance was uncertain. Improvements in outcomes should be observed by 12 weeks.

2.8.1.1.3 Physiotherapy and shoulder exercises

There have been many systematic reviews on the role of physiotherapy in treating shoulder pathology. For subacromial pain syndrome, several reviews found home-based exercises were as effective as supervised exercises and additional manual therapy may be beneficial for RC therapy and impingement. Hanratty et al. found in a pooled analysis that exercise had a positive effect on RC strength in the short (6-12 weeks) and long term (>12 weeks) (292). The authors were only able to analyse the effect of exercise on pain in the short term, and found no significant effect (SMD 0.13 (95% CI -0.71, 0.45); p = 0.66). In another review, exercise (versus placebo) has been found to be effective in the short (≤ 3 months) and medium term (4-6 months), although no results were found for the long term (> 6 months) (293). Kromer et al. found physiotherapist-led exercise was more effective than no treatment at <6 months, with no long-term studies available (294). A different review found exercise to be effective for pain and function compared to placebo at ≥1 year (295).

Several reviews found only limited evidence to support the use of exercise in the treatment of subacromial pain syndrome (296-298). Although exercise was effective to some degree for improving pain and function in “subacromial

impingement", the heterogeneity of studies meant that firm conclusions could not be drawn.

Overall, physiotherapy may be beneficial in the short and medium term, although long term outcomes have yet to be conclusively shown.

In order to help clarify the role of scapula-specific exercises, there have been a review on scapula focused treatment for "RC related shoulder pain" (RC tendinopathy and impingement) (299). Interventions included scapular focused exercise therapy, scapular mobilisation and scapular taping. There was limited evidence on its effect on pain or function outcomes at 4-8 week follow-up, although these treatments did improve function in the short term only (< 6 weeks).

2.8.1.1.4 Manual therapy

Manual therapy includes joint mobilisation, as well as soft tissue mobilisation (effleurage, friction release, and kneading techniques). Manual therapy was superior to placebo and may be effective for subacromial pain when used in addition to exercises, compared to exercises alone, at <3 months (290, 295, 300). Other reviews found limited and conflicting evidence on the effectiveness of manual therapy in addition to exercise therapy for "impingement" (293, 301). In a recent Cochrane review, only one high quality trial was found comparing exercise and manual therapy with placebo for RC disease and found no significant difference but a higher level of adverse mild events (302). Another review found limited but favourable evidence on the use of mobilisation for RC pain and generalised shoulder pain (303). Other reviews found limited evidence on the effectiveness of manual therapy in isolation (295, 302).

Manual therapy may not be as effective as other treatments for adhesive capsulitis, although this was based on low quality studies (301, 304). Other authors have found low to moderate evidence supporting manual therapy for adhesive capsulitis when used as in addition to other therapies (303).

Overall, manual therapy may provide a short term benefit, although long term effects have yet to be shown.

2.8.1.1.5 Physiotherapy and other treatments

Combined treatments were better than single-intervention therapies (305). The authors used a network meta-analysis to simultaneously compare various treatment options. Compared to previous meta-analyses, this allowed comparison of each treatment against all other treatments. The use of exercise therapy with steroid injections, NSAIDS and hyaluronic acid showed a trend towards better outcomes, although the wide confidence intervals meant results were not significant.

Several reviews have compared physiotherapy treatment with surgery. In one review of 64 RCTs, exercise therapy was found to be as effective as surgery in the short (1 day to 3 months), medium (3 months to 1 year) and long term (≥ 1 year) (295). For RC disease, no differences have been shown between exercise with manual therapy and subacromial decompression in terms of pain, function, range of motion or strength at 6 and 12 months, or global treatment success at 4-8 years (302, 306). In a systematic review comparing physiotherapy to surgery for RC tears one RCT found no difference, whereas another found a significant improvement in the Constant score at 1 year for the surgical group (307). Overall, evidence suggests that conservative treatment is as effective as surgery in improving pain for shoulder “impingement” and RC disease. However, other outcomes such as function, speed of recovery, return to work and cost-effectiveness of therapies are important measures which have not been systematically reviewed.

2.8.1.1.6 Limitations of physiotherapy literature

There are several limitations inherent to all these reviews, which may explain conflicting findings. There was heterogeneity in exercise routine (type of exercises, frequency, intensity and duration), which would act as a significant confounding factor. Furthermore, the differences in nomenclature may imply

that different pathologies have been included under the same term. “Impingement” may not be a diagnosis but an actual symptom of a provocative test, which is produced by different pathologies such as bursitis, RC tears and tendinopathy. Differences in defining physiotherapy and manual therapy may also lead to variations in the inclusion criteria of reviews. Poor quality studies, variable length of follow-up, duration of pre-existing symptoms and lack of a detailed description of the exercise protocols used would contribute to variable findings.

The methodology for these reviews differed. For example, Hanratty et al. used PRISMA guidelines (292), whereas Kelly et al. used Physiotherapy Evidence Database (PEDro) scale (296) which focuses on the quality of reporting (rather than factors which influence bias). In addition, PEDro does not take into account timings of outcome or compliance with medication. Search strategies differed. For example, Hanratty et al. included English language papers only (292) . Desmeules et al. did not identify unpublished literature in their search or publish their search methodology, which could possibly introduce publication bias as well as selection bias (298). Several systematic reviews also included studies examining the effectiveness of exercise alongside other therapies, such as ultrasound, braces, electrotherapy and manual therapy (292, 294, 298). Disentangling the effects of exercise from other forms of treatment in current studies has therefore been difficult.

Overall, exercise and manual therapy may offer benefit to patients with shoulder pain in the short and medium term when compared to placebo, although long-term benefits are uncertain.

2.8.1.2 Steroid injections

Steroids are commonly used for the treatment of shoulder pain and can be taken orally or injected. Complications of this treatment could include infection, bleeding and may cause long term damage to tendons (308, 309)

An early review of steroid injections for non-specific shoulder disorders found, due to poor methodological quality, inconclusive evidence on the use of

injected steroids (308). Van der Sande et al. found conflicting evidence for the effectiveness of corticosteroid injections versus placebo for “subacromial impingement” in the short term (4 weeks) and long-term (12 weeks) (310). Another study found benefit of subacromial steroid injections in non-specific shoulder pain (311). Other reviews found for RC tendinopathy, subacromial injections can be effective for up to 9 months, with a possible dose effect (312, 313).

Buchbinder *et al.* found that oral steroids improved pain, function and range of movement in adhesive capsulitis, but not after 6 weeks (314).

The role of steroids compared to other therapies has been evaluated in adhesive capsulitis. A review found that there was a possible benefit of intra-articular steroid injection over placebo and benefit over physiotherapy in the short term (315). Other reviews found intra-articular and oral steroids lead to greater improvements in pain relief and ROM in the short (<3 months), medium (3-6 months) (316-319) (320) and the long term (316, 321, 322), although this was similar to other treatments such as manipulation under anaesthesia, hydraulic distention, and physiotherapists (316). Another review found that steroid injections improved pain, whereas physiotherapy improved ROM (316). In another recent review, 20mg or 40mg of triamcinolone injections delivered via either the intra-articular or subacromial route, provide significant symptom relief for 2 to 24 weeks in patients with adhesive capsulitis (319).

The role of steroids in combination with other therapies has been evaluated. Supervised strengthening and stretching was as effective as corticosteroid injection or multi-modal intervention for non-specific shoulder pain (323). One review found it was uncertain if steroids in combination with exercise and manual therapy improved function compared to steroid injections alone for RC disease (302). For adhesive capsulitis, steroids with physiotherapy may be more effective than physiotherapy alone in a 3-12 weeks period steroids (316, 322) or steroids alone (324).

Multiple injections (3-6) may provide benefit for up to 16 weeks (318). The efficacy of steroid injections may not be related to the site of injection (325).

Buchbinder et al. found that no difference in efficacy for varying doses of steroids for adhesive capsulitis (315). The timing of steroids may be important, as another review supported the use of oral steroids before manipulation (316).

Two systematic reviews have been undertaken to determine if image-guided or blind steroid injections improved patient outcome (326, 327). Soh *et al.* found that those receiving image-guided injections had statistically significant greater improvement in shoulder pain (non-specific) and function at 6 weeks after injection, based on 2 studies with a high risk of bias (326). Bloom *et al.* included 5 studies and were unable to establish any significant difference in pain, function, ROM or safety (327). Guided injections for adhesive capsulitis may be better than blind injections (317, 328).

Limitations with these reviews include inability to account for other clinically relevant factors such as additional medications, different injection techniques as well as heterogeneity of methodologies including definitions of pathologies (e.g adhesive capsulitis) for inclusion/exclusion criteria. Furthermore, analysis of studies differed. For example, when determining the differences between guided or blind injections, Soh et al. pooled change in scores from studies (326), whereas Bloom et al. pooled final scores (327).

Overall, steroid injections may benefit patients for the short-term, although its role in conjunction with other modalities is uncertain.

2.8.1.3 NSAIDS

There is generally a lack of evidence on the use of analgesics in the treatment of shoulder pain (310). There are possibly short term (3 or 6 weeks) benefit of NSAIDs (311), and conventional ibuprofen versus sustained release ibuprofen for “subacromial impingement” (310).

It is uncertain if manual therapy and exercise improves function more than oral NSAIDs alone in RC disease (302) or adhesive capsulitis at 3 weeks (304).

Oral NSAIDs were less effective in improving function at 4-6 weeks and no better for pain compared to steroid injections in patients with shoulder pain

(329) (330). Contrasting reviews found no evidence for steroid injection over NSAIDS or acupuncture in “subacromial impingement” (310) or RC disease (315). In an older review on the treatment of musculoskeletal pain, steroid injections in the shoulder were likely to be more effective than NSAIDs for RC tendinopathy (312) in the short term (<4 weeks) and possibly up to 9 months.

2.8.1.4 Psychosocial therapies

Psychosocial therapies have been used extensively for the management of other musculoskeletal pain, including back pain (331). Such interventions include cognitive-behavioural therapy and pain-coping aimed to improve self-management and alter behavioural and cognitive changes. The evidence for its use in shoulder pain is limited (332), with little scientific evidence for the effectiveness of multidisciplinary biopsychosocial rehabilitation (333). It has been suggested that psychosocial interventions in combination with other treatment modalities appear to confer additional benefit for all musculoskeletal pain presentations but there are conflicting ideas on the optimum specific treatment components, providers and settings.

2.8.1.5 Electrotherapies and other therapies

Electrotherapy modalities aim to reduce pain and improve function using electrical, sound, light, or thermal energies. This includes pulsed electromagnetic field therapy (PEMF), laser therapy, heat, glyceryl-trinitrate, acupuncture, extracorporeal shockwave therapy (ESWT) and therapeutic ultrasound. Ultrasound therapy delivers energy to deep tissue sites at frequencies of 1 or 3 MHz and intensities between 0.1 watts/cm^2 and 3 watts/cm^2 using a crystal sound head in either a pulsed or continuous manner. This modality supposedly increases tissue temperature and creates non-thermal physiological changes (e.g. cell permeability and cell growth) to promote soft tissue healing and muscle relaxation. Laser therapy generates a beam of light with a particular wavelength delivering energy to tissue. It aims to reduce pro-inflammatory cytokines and increase anti-inflammatory growth factors and cytokines. Variables such as dosage, wavelength, site and

duration of treatment may affect outcome. PEMF delivers pulses of low-frequency magnetic fields and aims to provide pain relief by influencing tissue generation and cell proliferation. ESWT is either focused or radial. Focussed ESWT creates high peak pressure waves at targeted tissue to induce denervation of pain receptors, phagocytosis, deposit fragmentation and neovascularization. This can involve low energy (L-FESWT) <.12mJ/mm or high energy (H-FESWT) >.12mJ/mm (334). High energy is often more painful (often requiring intravenous analgesia) and more expensive. Side-effects are relatively minor and include bruising and haemotoma formation. Radial ESWT involves the acceleration of a projectile by compressed air which transmitted radially from the applicator to the tissue.

For RC disease, a recent Cochrane review found low quality studies evaluating electrotherapies and the overall benefits of electrotherapy (laser, PEMF or ultrasound therapy) over other interventions is uncertain (335). Compared to placebo, PEMF may not provide benefit (335). There were benefits in the short term (<3 weeks) when using laser therapy compared to placebo. Laser therapy was found to be no more effective than placebo for tendinopathy in another review (189).

For calcific tendinitis, a combination of ESWT and needling was more effective than ESWT alone (336). Further meta-analyses showed that ESWT improved function, pain and calcification resorption over 6 months (336, 337), and H-FESWT showed greater improvement in function (Constant-Murley score) compared to L-FESWT at 3months, 6 months (174) and 1 year (338), as well as complete resolution of calcium deposits at 3 months (174). Another review found therapeutic ultrasound may have short-term (<6 weeks) benefits over placebo in people with calcific tendinopathy (335). There was moderate quality evidence that needling had similar effect to subacromial steroid injections (336). Needling has been found to improve function after 1 year and up to 10 years (338).

For “shoulder impingement”, one review found no benefit of low-level laser, EMF, ultrasound, acupuncture or taping in patients (295). There is conflicting evidence of laser therapy in “impingement” in the short term (≤3 months)

(293). Laser therapy alone or in combination has also been found to be effective in “impingement” and adhesive capsulitis in the short term (<3 months or not defined) (300, 316) and medium term (<6 months) (324). Other reviews have found conflicting evidence that PEMF therapy is effective compared to sham or placebo (293, 294). Ultrasound therapy is not effective compared to placebo, steroid injection or acupuncture (294, 311). Kromer *et al.* found that therapeutic ultrasound was not more effective than acupuncture in combination with home-based exercises in patients with impingement (294). One review found transdermal glyceryltrinitrate was effective for subacromial impingement up to 24 weeks (310). The quality of evidence was very low due to high risk of bias, lack of precision, lack of consistency and clinical heterogeneity. Heat therapy was found to be effective in the short term (≤3 months) compared to exercise therapy, although a combination of the two was more effective than control (293). No evidence was found for > 3 months.

For adhesive capsulitis, laser therapy delivered for 6 days may be beneficial for the short term (at 6 days) and the addition of exercise for 8 weeks may be beneficial in terms of short term pain (4 weeks) and function (4 months) when compared to exercise alone (339). Acupuncture in addition to exercises for adhesive capsulitis may be beneficial in the short term (<3 months) (316). Acupuncture did not offer any benefit to patients with adhesive capsulitis compared to other electrotherapies (324). Hyaluronic acid was not superior to steroids or physiotherapy and did not provide any additional benefits when used as an adjunct in adhesive capsulitis (340).

A Cochrane review found limited evidence for the use of acupuncture for shoulder pain (non-specific) or function in the short term (post-intervention) and at 4 months (341). Reviews have found that therapeutic ultrasound is not effective compared to placebo for shoulder disorders (293, 300, 311, 342).

There are several limitations to these reviews, including variations in the use of different devices, treatment protocols and energy levels. Furthermore, although there is a significant difference in outcome measures such as the Constant-Murley score.

In conclusion, there is conflicting evidence on the role of electrotherapies, and any benefit may be for a short-term only.

2.8.2 Surgical

Surgical options are often considered when conservative or minimally invasive therapies have failed. Surgical complications include infection, post-operative capsulitis and pain. General anaesthetics are used, which also carry significant risks. To date, there have been no randomised control trials comparing surgical treatment with no treatment, and further well designed studies are required (343).

2.8.2.1.1 RC tendinopathy and impingement

Surgery for RC tendinopathy and impingement often involves subacromial decompression (also known as acromioplasty), which involves removal of the acriomion or spurs, and can be done with open surgery or arthroscopically. A bursectomy alone or in combination with acromioplasty may also be done. For calcific tendinopathy, calcium deposits may be removed alongside an acromioplasty.

2.8.2.1.2 RC tears

The decision to operate on RC tears depends on many factors, including tissue quality. Muscle atrophy and fatty infiltration, two features seen on imaging such as MRI and ultrasound, may affect healing of RC tears (344). The size and number of tendons involved may also be an important consideration. Tears may also result in GHJ and ACJ abnormalities, which are additional considerations. Age and comorbidities could affect the healing process. Other considerations that would affect post-surgical rehabilitation and healing includes shape of tear, surgical approach and fixation method (e.g. single row, double row) (345).

Surgical options for partial RC tears include debridement, and larger tears may be sutured back to the original site onto the humerus. Larger tear repairs can involve tendon transfer, fascia implants or the use of synthetic material (345). Surgery can involve open repair, mini-open repair (arthroscopy using a larger incision about 2-3 cm, avoiding removal of deltoid from its insertion site as would be the case in an open repair) or arthroscopy (345). Several systematic reviews have shown that there is no significant difference in those with mini open repairs and arthroscopy (307, 346-349). Another review found no difference between open and arthroscopic surgery in the long term although in the short term, arthroscopic surgery had quicker recovery compared to open (350). In another review, the arthroscopic technique tended toward better efficacy than the open surgical technique (305).

2.8.2.1.3 Calcific tendinopathy

Reviews of surgery for RC tears, impingement, or calcific tendinopathy found no difference in pain compared to physiotherapy alone or in combination with steroids (220, 349, 351, 352). A systematic review found surgical removal of deposits for calcific tendinopathy, with or without subacromial decompression has been shown to improve function up to 7 years post-op (338). For subacromial impingement, there was no significant difference in pain or function between acromioplasty versus bursectomy alone (Donigan 2011 arthroscopic subacromial decompression). Acromioplasty has also been shown to not be cost effective when used in addition to a supervised exercise programme (353).

2.8.2.1.4 Long head biceps

Surgical repairs for LHB are indicated for tearing, instability, and tenosynovitis (354). Options for treatment include tenodesis (detaching LHB from superior labrum and re-attaching to humerus below shoulder) or tenotomy (releasing biceps from GH joint and allowing it to fall down the upper arm). The optimal choice of surgery remains unknown due to low quality studies (355-357), although tenodesis may have better functional and cosmetic outcomes (358).

2.8.2.1.5 Osteoarthritis

Shoulder replacement is often performed to manage severe OA. Surgical options include total shoulder replacement (TSR), stemmed or resurfacing hemiarthroplasty or reverse total shoulder replacement. A total shoulder replacement is usually considered if there is bone on bone OA with good RC. If the glenoid has intact cartilage or is severely deficient, this option is generally not considered, as the glenoid component is usually implanted with a bony cement. Hemiarthroplasty involves replacing the head of the humerus. A stemmed hemiarthroplasty involves replacing the head. This may be considered when OA only affects the humerus, or if a total shoulder replacement is not feasible. A resurfacing hemiarthroplasty involves replacing the head of the humerus only, with a cap-like prosthesis and no stem. This is often considered when there is a desire to preserve the bone (e.g. young patients). A reverse total shoulder replacement occurs when the glenoid and ball are reversed. This is usually considered in patients who have completely torn RC tears, as it allows the use of the deltoid, or in those with previous failed replacements. Variations in surgical procedure also include whether the glenoid component is cemented/uncemented and type of glenoid component (pegged or keeled). Total shoulder replacement may be better than hemiarthroplasty in terms of function, but had similar outcomes of pain, quality of life and adverse events (359-361).

2.8.2.1.6 Adhesive capsulitis

There are several surgical options for treating adhesive capsulitis. These include manipulation under anaesthesia (MUA), arthrographic distension (where fluid is injected into the shoulder) and capsular release. A review of RCTs found MUA offered no or less benefit than home therapy or arthrographic distension (324). Arthrographic distension with saline and steroids provides short-term (<12 weeks) improvements in pain, function and disability compared to placebo (362). There was no or limited benefit of arthrographic distension alone or in combination with steroids compared to

steroids alone, physiotherapy or manipulation (324, 362, 363). Distension with physiotherapy may be beneficial for the short term (<3 months) (316). Physiotherapy alone may improve symptoms of adhesive capsulitis, and so the addition of distension may not be beneficial. Capsular release may improve function and disability based on 2 case series (324). In a systematic review of non-randomised studies, there were minimal differences for arthroscopic capsular release instead of, or in addition, to manipulation under anaesthesia (364).

2.8.2.1.7 Instability

There are several surgical techniques for instability, dependent on the pathology (365). The Bristow-Latarjet procedure is a surgical technique for instability due to bone loss from the glenoid (from trauma or recurrent dislocations). There are variations on its technique, but generally the procedure involves transfer of the coracoid and its attached muscles to the front of the glenoid. It works by restoring the glenoid contact surface area; the transferred muscle stabilises the joint when the arm during movement by reinforcing the subscapularis and capsule; the capsule is surgically repaired (366). Other techniques include soft tissue repair of labral and capsular lesions e.g. Bankart repair (injury of the anterior-inferior glenoid labrum). Several reviews have shown that these surgical options reduce the risk of recurrence and re-dislocation (367, 368).

In summary, drawing conclusions on the efficacy of surgery and between surgical techniques remains difficult. Findings of the studies and reviews are articles are limited by low quality studies, small numbers, methodological heterogeneity, differences in quality assessment (Grant 2013), different outcome measures used and wide variations in follow-up. Limitations such as poor quality assessment and methodological weaknesses may make also findings unreliable and difficult to interpret (351). Overall, surgery for RC tears, impingement, calcific tendinopathy or adhesive capsulitis have not found differences in pain outcome when compared to physiotherapy.

2.8.3 Economic evaluation of treatment

Economic evaluation can include cost minimisation (where the outcome for different interventions are the same, therefore this method is used to determine which intervention is least costly), cost-effectiveness (where the outcomes vary, but are expressed in the same units, for example “healthy days" achieved through drug treatments of shoulder pain. This can then be expressed as cost per unit of outcome e.g. cost in £/healthy day), cost utility (allows for the comparison of interventions resulting in different outcomes. These outcomes are standardised into health utility measures e.g. quality adjusted life years (QALYs)) and cost benefit (where costs and outcomes are valued in monetary terms. Outcomes are converted to financial units by determining the individual’s willingness to pay for the result of treatment or their increased productivity) (369). A previous review on the economic evaluation of shoulder treatments has highlighted the paucity of good quality studies (370). Table 2.9 highlights the findings from good quality studies by Kuye et al.

Table 2.9 Summary of studies that met the six minimum health economic standards

	Mather et al. 2010	**Vitale et al. 2010**	**Van Til et al. 2006**	**Van den Hout et al. et al. 2005**	**Gereats et al. 2006**	**Buchbinder et al., 2007**	**Bruijn et al., 2007**	**McKenna et al. 2009**
Topic	Shoulder Arthroplasty	Rotator Cuff Repair	Chronic Shoulder Pain	Frozen Shoulder	Chronic Shoulder Pain	Frozen Shoulder	Chronic Shoulder Pain	Chronic Shoulder Pain
Analysis Type	Cost−Utility	Cost−Utility	Cost−Utility	Cost−Utility	Cost−Utility	Cost Utility and Cost Effectiveness	Cost−Effectiveness	Cost−Utility
Intervention and Comparators	Total Shoulder Arthroplasty (TSA) Hemiarthroplasty (HA)	Rotator Cuff Repair Doing Nothing	Percutaneous neuromuscular electrical simulation (P−NMES) Slings Anti−inflammatory injections	High−grade mobilization techniques Low−grade mobilization techniques	Behavioral graded exercise therapy (GET) Usual Care	Manual therapy and directed exercise Placebo	Education and Activation Program (EAP) Usual Care	1st Study. Trained general practitioners Untrained general practitioners 2nd Study Local anaesthetic injection (Lignocaine) Steroidal Injection (Cortisone)
Population	64−year−old patient	Patients between 40–80 years	Stroke victims with Hemiplegic pain	Patients who had suffered from adhesive capsulitis for at least a month	Patients with chronic shoulder complaints in the Netherlands	Patients over 18 years old who had pain and stiffness for	Patients older than 18 years old suffering from shoulder	Patients with shoul

		Rotator cuff tear verified on arthroscopic evaluation 12 or more month of failed non−surgical treatments				greater than three months and restriction of passive motion greater than 30 degrees in more than two planes of movement.	complaints that lasted up to three months	
Time Frame	Patient's Lifetime	52 weeks	24 weeks	52 weeks	12 weeks, 52 weeks	6, 12 and 26 weeks	26 weeks	52 weeks
Perspective	Societal	Societal	National Health Insurance Board	Societal	Societal	Societal	Societal	Societal
Costs Included	Direct Medical Costs	Direct Medical Costs	Direct medical costs	Direct medical costs, Direct non−medical costs and Indirect Costs	Direct medical costs, Direct non−medical costs and Indirect Costs	Direct medical costs, Direct non− medical costs and Indirect Costs	Direct medical costs, Direct non− medical costs and Indirect Costs	Direct medical costs and Indirect Costs
Source of Costs	National average Medicare reimbursement rates for the procedures in 2008 dollars.	Charges collected from patients medical records and then converted to costs using a cost to charge ratio.	Natural units obtained from patients and valued using pricing data from the Advisory Board for Healthcare Pricing the manufacturer prices and	Natural units gathered from patients with quarterly cost questionnaires and valued using Dutch reimbursement rates.	Cost diaries filled by patients and physiotherapist in natural units. Valued using the guidelines of the Dutch Health Care Insurance Counsel.	Patients filled out monthly cost diaries in dollar amounts.	Patients filled out a cost diary every six weeks in natural units. Valued based upon stated assumptions and standard reimbursement rates.	Patients filled out a questionnaire of natural units. Valued using national average unit cost estimate for 2005–2006.

			medical compass 2003					
Type of Sensitivity Analysis	One, 2− and 3−way sensitivity analyses performed on all variables	1−way analyses varying costs, QALYs and discount rates	Monte Carlo Simulation	Non−parametric bootstrapping	Alternative analyses using imputation of group mean for outliers	Repetition of analyses with calculation of bootstrap standard errors	Bootstrap Estimation	A sensitivity analysis was performed by removing productivity costs.
Results	TSA resulted in a higher number of average QALYs at a lower cost than HA. Authors concluded it was efficient.	The Rotator Cuff repair yielded a ratio of $3,091.90/QALY by use of the EuroQol. Authors concluded it was efficient.	P−NMES had an incremental cost− utility of €32,821/QALY over injections and €27,085 when compared to slings	Low−grade mobilization was significantly more expensive, and did not significantly affect the change in QALY.	GET had an incremental cost effectiveness ratio of €5,278 per unit of EQ−5D in a year follow− up. Authors concluded it was efficient.	No significant difference in cost, pain, function or quality of life.	EAP was not cost−effective due to the high costs.	Training GPS resulted in an incremental cost of effectiveness ratio of (ICER) £2,813 using the EQ−5D a year later. Authors concluded that training GPs was efficient. Lignocaine had an ICER of £122,000.

Adapted from (370)

A later study by Jowett et al. found there was no significant difference in costs or QALYS between injection plus exercise compared to exercise alone in patients with impingement, although overall healthcare costs were lower and QALYs were higher in the combined arm (371). In an RCT evaluating the cost-effectiveness of arthroscopic and open rotator cuff repair in patients aged ≥ 50 years with degenerative rotator cuff tendon tears there was no difference in treatment costs between open and arthroscopic surgery (307).

A review on the economic analysis of the management of adhesive capsulitis found that costs of injections were dependent on setting, deliverer and if guided or blind (324). The cheapest option was physiotherapist delivering treatment in a community setting and a rheumatologist in hospital was the most expensive. Guided steroids were most expensive. Arthrographic distension was estimated to cost approximately £114.84, dependent on the steroid used. Manipulation under anaesthesia cost an estimated £1446 and capsular release £2204, including rehabilitation physiotherapy. At 3 months, steroid alone may be more cost-effective than steroid plus physiotherapy or physiotherapy alone in terms of QALYs.

2.8.4 Current guidelines

There is no agreed consensus on the use of investigations and therapies for shoulder pain. Different national and international guidelines have been published and these will be outlined below.

2.8.4.1 Imaging guidelines in clinical practice

There is no consensus on the optimum imaging modality for individual shoulder disorders, or the role of radiographs, ultrasound or MRI in the shoulder pathway. Contributing factors to this variation in pathways may include costs, safety and availability of scanners, technicians and radiologists. In addition, the diagnostic ability of these imaging modalities has not been compared across all pathologies.

The American College of Radiologists have suggested the most suitable imaging modalities for suspected shoulder pathologies (see Figure 2.6) (253-255). In general, radiographs are often the first choice for patients > 40 years old with shoulder pain, followed by either MRI or ultrasound depending on the expected diagnosis, patient contra-indications, local resources and expertise. For patients with suspected RC lesions, impingement, biceps brachii abnormality, or subacromial-subdeltoid bursal abnormality, ultrasound is generally considered the next modality of choice, with MRI used when findings are equivocal (372). Patients with suspected labro-ligamentous lesions should be considered for MR.

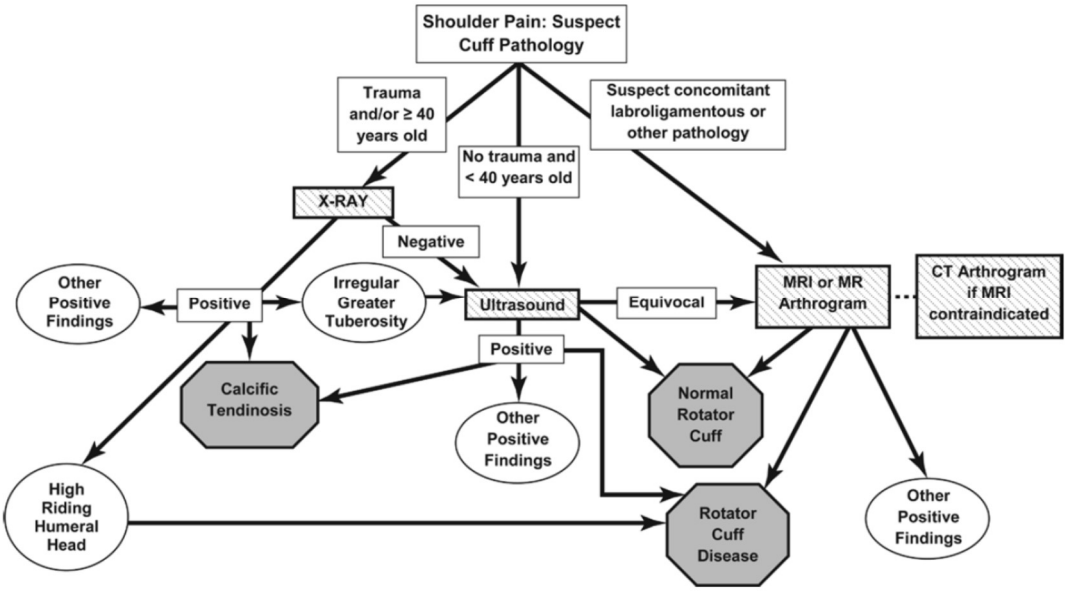


Figure 2.6 Diagnostic algorithm for painful shoulders with RC abnormality.

Taken from (372)

2.8.4.2 Using imaging to improve clinical outcomes

Further studies are required to determine the extent to which diagnostic tests on shoulder pain inform and affect patient management and outcomes (373). A report by the Academy of Medical Sciences has also highlighted the importance of rational diagnostic tests to improve patient care and reduce costs (374).

In a randomised control trial in the Netherlands, 129 patients presenting with acute unilateral shoulder pain had an ultrasound scan and after 2 weeks were randomised to usual care or treatment based on the ultrasound findings (375). At 1 year, the authors found no clinically significant difference in Global Perceived Recovery, EQ-5D, Shoulder Pain Score or Shoulder Disability Questionnaire between the groups. In addition, there was no significant difference in healthcare resource use (consultations, imaging, treatments). Unfortunately, this study was underpowered.

It has been shown that the inappropriate use of musculoskeletal imaging still exists. For example, recommendations that ultrasound should be used instead of MRI initially for RC tears are not followed (376). A barrier to rational testing is our limited understanding of the relationship between structure, symptoms and outcome measures. Other contributory factors to inappropriate use may include payment structure; defensive medicine; patient expectations; missed educational opportunities when inappropriate procedures are requested (377). Increasing the understanding of the relationship of imaging and shoulder symptoms will improve patient outcomes and resource allocation.

2.8.4.3 Treatment guidelines

In the UK, the British Elbow and Shoulder Society/British Orthopaedic Association have released guidelines on the management and onward referral of shoulder pain and frozen shoulder (see Figure 2.7) (378, 379), which has been adopted by various regions (380) and forms part of the basis for the NICE Clinical Knowledge Summary regarding the management of shoulder pain (381).

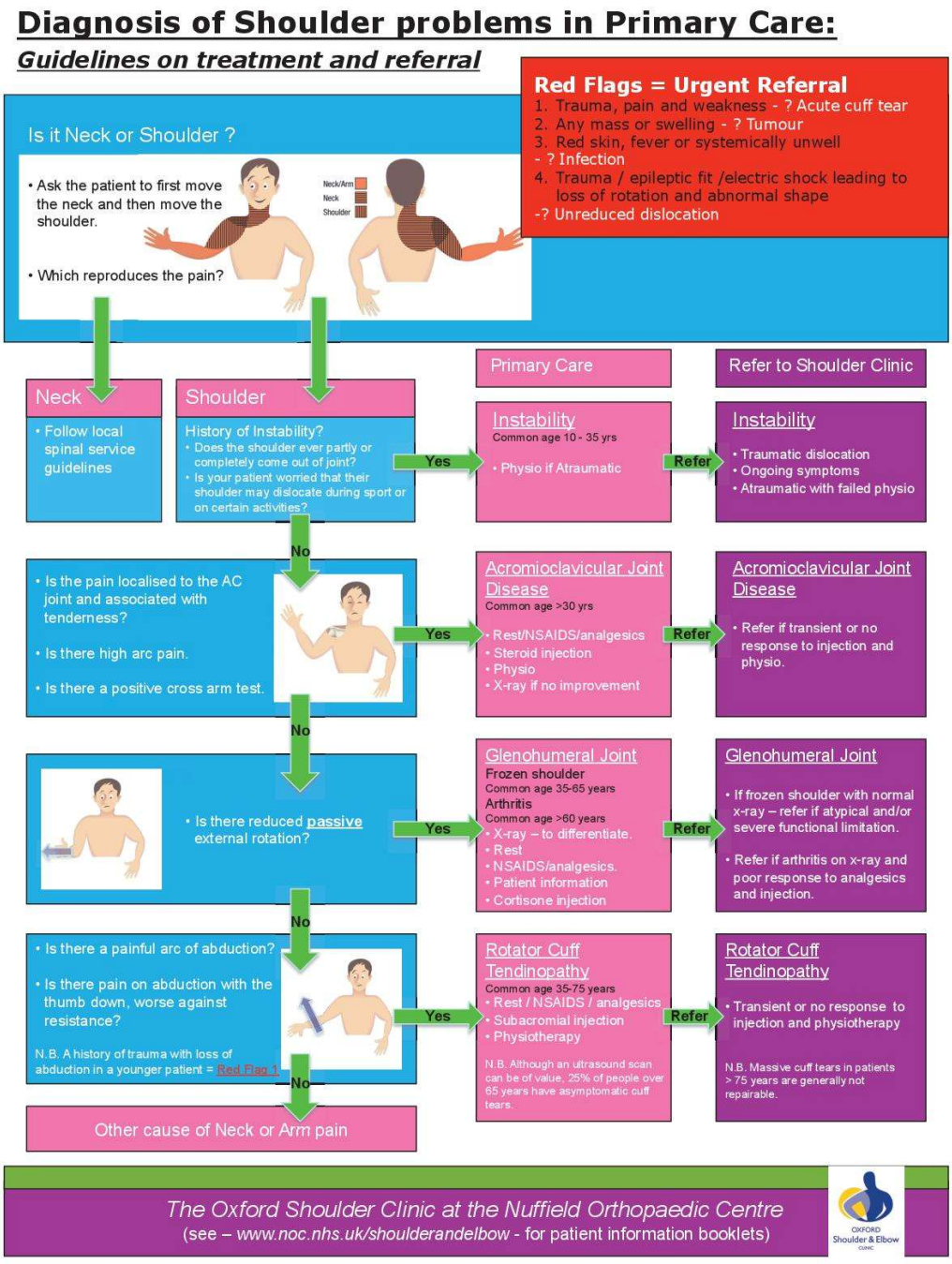


Figure 2.7 Guidelines from the British Elbow and Shoulder Society/British Orthopaedic Association

Taken from (378)

The New Zealand Guideline Group have also released recommendations in 2004 (382). For RC disorders, they initially recommend NSAIDs, steroid injections and supervised physiotherapy. Steroids for those with full RC tears should be considered in those not amenable to surgery. Referral to orthopaedics should be considered if no improvement in 6 weeks. For frozen shoulder, steroids with supervised physiotherapy, whilst avoiding vigorous early stretching, is recommended. For GH arthritis, activity modification, NSAIDs and physical therapy to maintain motion and strength, but not to aggravate the problem is recommended. If no improvement, referral is advised. For atraumatic instability, exercises should be prescribed.

The American Association of Orthopaedic Surgeons released guidelines in 2001 and a specific guideline in 2010 on the management of RC disorders, highlighting the strength of recommendations (383)

With regards to RC tears, the authors stated there was limited evidence on repairing RC tears in symptomatic patients, and inconclusive evidence on exercise, injections, NSAIDs, EMF, ultrasound, activity modification or ice and heat for RC tears or disorders. For RC disorders except tears, the authors found moderate evidence recommending NSAIDs, exercise. When patients underwent surgery for RC tears, there was limited or inconclusive evidence on the role of age, MRI tear characteristics or comorbidities (including diabetes or smoking). There was moderate evidence that routine acromioplasty is not required at the time of RC repair. There was inconclusive recommendations on arthroscopic, mini-open or open repair. Post-operatively, the type of exercise (active resistance, home or facility based, ROM) was inconclusive.

Recently, guidelines for the diagnosis and treatment of subacromial impingement has been published in the Netherlands (384). They advise that diagnosis should be made using a combination of clinical tests, with imaging used if symptoms persist > 6 weeks and non-operative therapies have failed. Ultrasound alongside conventional radiography should be the first line where possible, to exclude RC tears, OA and calcific tendinitis. Non-operative treatment should consist of rest with analgesia for 2 weeks, followed by

gradual activities. For severe pain, steroid injections should be considered. High-energy ESWT or barbotage can be considered for proven subacromial calcium deposits, although not in the acute phase. Exercise at low intensity and high frequency, focusing on eccentric movements are recommended. Muscle stretching and scapular stabilisation exercises should be considered. There is no convincing evidence that surgical treatment is more effective than non-surgical treatment. In those non-responsive to conservative treatment, a mini, mini-open, or arthroscopic bursectomy should be considered, as bursectomy + acromioplasty give similar results. Surgical treatment of calcific tendonitis is not recommended given that ESWT and barbotage may result in similar outcomes.

Recently, an algorithm for physiotherapy exercises was developed from a consensus-based process in Sweden (see Figure 2.8) (385). Recommendations for treatment were based on clinical findings and not structural pathologies, and involved active exercises, scapula-humeral control and mobilisation as indicated.

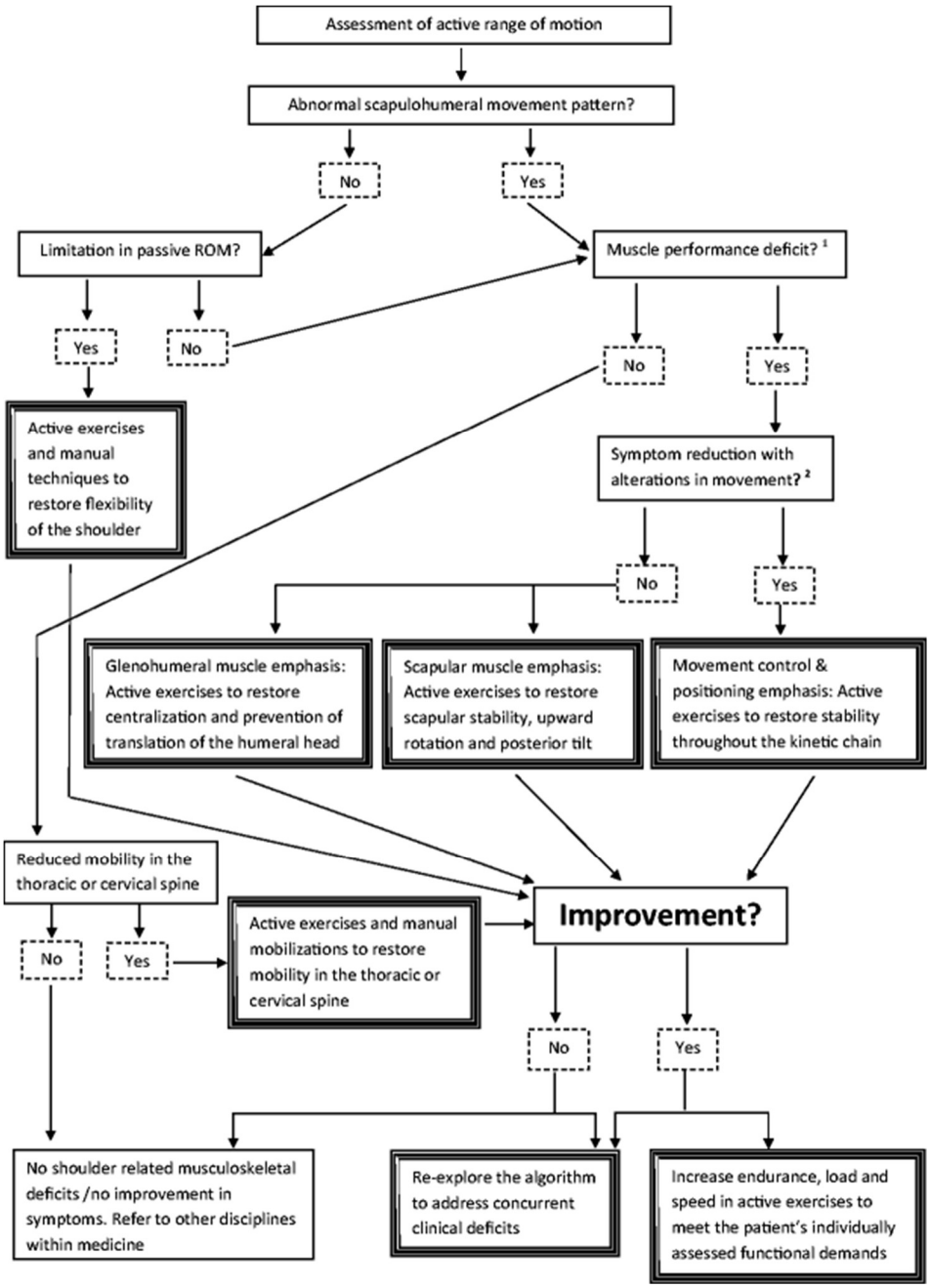


Figure 2.8 Assessment and treatment algorithm for a patient with shoulder pain.

[1]Muscle performance deficits may take the form of strength, strength ratio, active or passive length or recruitment pattern deficits. [2]Examples of methods to assess symptom reduction with alterations in movement: scapular assistance test; scapular retraction test; change of posture

Taken from (385)

The indications for surgical repair of RC tears remain uncertain. To assist with this, there have been published guidelines from a multidisciplinary group on the indications and limitations of surgery (386). The authors advise that surgery can be considered for painful, weak or disabling shoulder refractory to medical treatment (oral medication, injections, physiotherapy). For partial RC tears, repair of tears affecting over 50% of tendon thickness is recommended rather than debridement. The indications for tendon repair of full-thickness degenerative tears are symptomatic tears with healthy muscles (fatty cuff degeneration ≤stage 2), on a non-stiff shoulder in active and motivated patients. In those not amenable to tears (not reducible without tension or > stage 2 fatty degeneration), debridement of the muscle may be considered. If all other options fail, or there is a massive RC tear with pseudo paralysis, then a prosthesis may be considered. Furthermore, in patients with arthritis and RC tears, arthroplasty should be considered.

In summary, there is no international consensus on the optimum investigations and management of shoulder pain. Imaging is being increasingly used although its role in supporting management is uncertain. This may be a result of our lack of understanding of the relationship between pathology and pain. Variations in practice may also be due to a lack of understanding on the best therapies. Studies have shown that decisions regarding treatment utilisation may often be based on an individual practitioner's beliefs on efficacy, rather than an evidence based approach (311, 387).

2.9 Summary and over-arching hypothesis

Shoulder pain is a common condition and affects a large proportion of the worldwide population. It has a significant impact on quality of life, as well as a substantial economic impact in terms of healthcare utilisation, employment loss and compensation. The current management of shoulder pain has significant limitations: 50% of patients continue to have shoulder pain after 18 months. In order to help with the diagnosis and management of shoulder pain, imaging, and in particular ultrasound, is increasingly being used. However, the relationship between imaging and shoulder pain outcomes remains uncertain.

Understanding the predictive ability of ultrasound on medium-term shoulder symptoms is important to understand how this imaging tool can be used to improve the care of people with shoulder pain. Not all patients in pain necessarily require investigations or treatment and evaluating the relationship between pain and acceptable symptom state is also important to understand those who require interventions.

The over-arching hypothesis underlying this thesis was that aspects of the shoulder pain pathway can be improved through better utilisation of ultrasound and applying the concept of a PASS.

2.10 **Thesis aims**

The aims are to:

1. Understand the cross-sectional and longitudinal relationship of individual or groups of imaging pathologies to patient symptoms from the existing literature
2. Determine if people with shoulder pain can be classified into distinct groups from individual ultrasound pathologies
3. Determine the predictive ability for each newly-determined group and individual pathologies and 6 month outcomes, taking into account other factors including co-morbidities, activity and treatments received
4. Identify the factors affecting the PASS and if patients reporting PASS received different treatments

3 Chapter 3 - What imaging detected pathologies are associated with shoulder symptoms and their persistence? A systematic literature review

3.1 Introduction

In Chapter 2, the role of imaging modalities to accurately detect soft-tissue pathologies such as RC tears, tendinopathies and subacromial bursitis (273, 388), was described. Imaging has been shown to detect pathology more accurately than clinical examination and it is often used to aid the diagnosis of shoulder pain in clinical practice. Over time, imaging modalities have been increasingly used but despite this increase, the relationship between imaging findings and patient outcomes remains unclear.

The relationship between imaging-detected shoulder pathologies and clinical symptoms may be complex. Imaging studies have shown that pathologies exist in asymptomatic individuals (285, 389, 390), whereas other studies have suggested that certain features may correlate with pain (283, 284). A systematic review on the accuracy of imaging has highlighted that further studies are required to determine the extent to which diagnostic tests on shoulder pain ultimately inform patient management and affect outcomes (373). A report by the UK Academy of Medical Sciences has also highlighted the importance of rational, cost-effective diagnostic tests to improve patient care and reduce costs (391).

Therefore a comprehensive review of the literature was performed evaluating the cross-sectional and longitudinal association between shoulder symptoms and imaging.

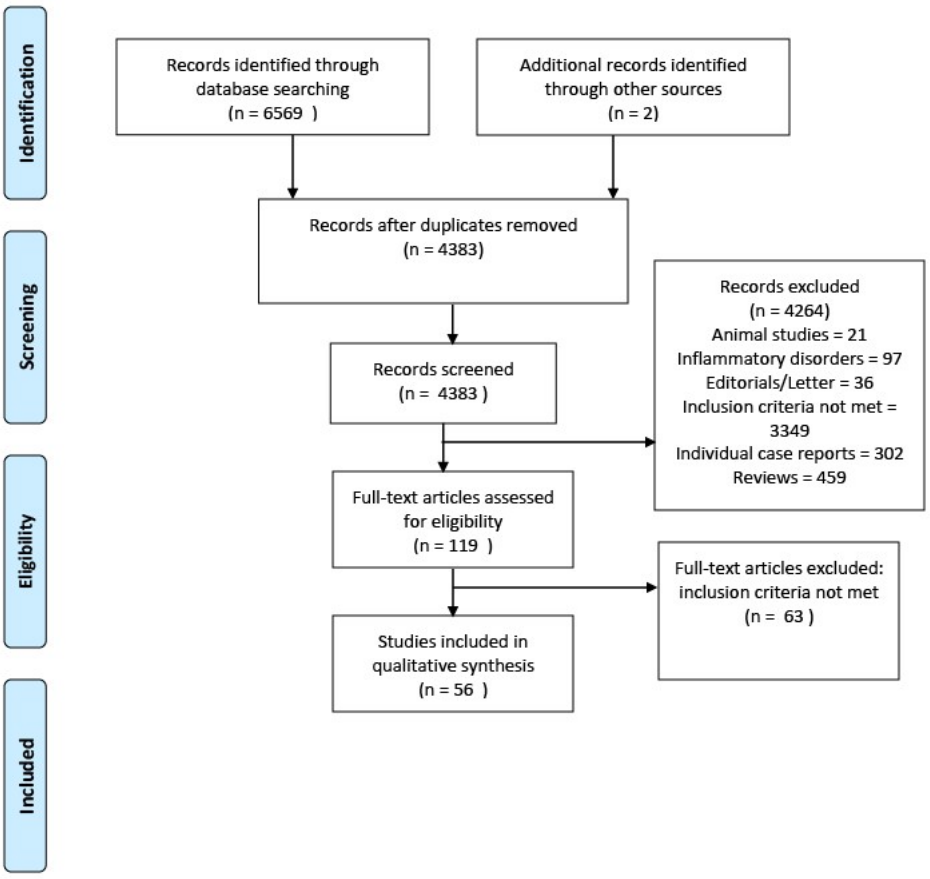
3.2 Aims

A systematic literature review of the literature to determine what imaging features are associated with symptoms and their progression, when common imaging modalities are employed. Imaging modalities included radiographs, ultrasound, CT, MRI and PET.

3.3 **Methods**

3.3.1 Search strategy and selection process

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) were followed and are described in Figure 3.1. A systematic literature search of Medline, EMBASE and the Cochrane library databases until April 2017 was performed. Grey literature and trial registries were searched including Open Grey, ClinicalTrials.gov and the World Health Organisation International Trials Registry Platform. A full description of the search strategy is presented in Figure 3.1.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Figure 3.1 PRISMA flow diagram

Table 3.1 Search strategy (1950 to April 2017):

1	exp SCAPULA/	32	exp SHOULDER IMPINGEMENT SYNDROME/
2	exp SHOULDER/	33	impinge*.ti,ab
3	exp HUMERUS/	34	exp TENDINOPATHY/
4	exp SHOULDER JOINT/	35	tendonitis.ti,ab
5	exp ROTATOR CUFF/	36	tendinitis.ti,ab
6	exp ACROMIOCLAVICULAR JOINT/	37	tendonopathy.ti,ab
7	exp CLAVICLE/	38	tendinopathy.ti,ab
8	scapul*.ti,ab	39	tenosynov*.ti,ab
9	acromio*.ti,ab	40	exp OSTEOARTHRITIS/
10	gleno*.ti,ab	41	osteoarth*.ti,ab
11	shoulder*.ti,ab	42	"rotator cuff tear*".ti,ab
12	humer*.ti,ab	43	"calcific tend*".ti,ab
13	rotator cuff.ti,ab	44	exp BURSITIS/
14	clavic*.ti,ab	45	burs*.ti,ab
15	subacrom*.ti,ab	46	frozen.ti,ab.
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15	47	shoulder.ti,ab.
17	magnetic resonance.ti,ab	48	46 AND 47
18	mr*.ti,ab	49	"frozen shoulder".ti,ab.
19	arthrogr*.ti,ab	50	"adhesive capsulitis".ti,ab.
20	exp ULTRASONOGRAPHY/	51	32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 48 OR 49 OR 50
21	ultraso*.ti,ab	52	exp SHOULDER PAIN/
22	exp TOMOGRAPHY/	53	pain*.ti,ab
23	ct*.ti,ab	54	function*.ti,ab
24	tomography.ti,ab	55	52 OR 53 OR 54

25	PET*.ti,ab	56	16 AND 31 AND 51 AND 55
26	positron*.ti,ab		
27	scintigraphy*.ti,ab		
28	exp RADIOGRAPHY/		
29	"x-ray".ti,ab		
30	radiograph*.ti,ab		
31	17 OR 18 OR 19 OR 20 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30		

Studies were included if they reported the relationship between structural abnormality on imaging and symptoms (cross-sectional) or progression/persistence of symptoms (longitudinal). Structures included RC tear, tendinopathy, subacromial bursitis, subacromial space and acromion. Outcome measures included pain or function measures. Exclusion criteria were post-surgical patients, systemic inflammatory conditions (such as polymyalgia rheumatica), neurological disease, chronic pain syndrome, fibromyalgia and non-human studies. There was no language restriction.

3.3.2 Data extraction

The citations identified by a preliminary search were screened by two reviewers (GT, PC) and for references not identified by the preliminary search. Discordance in opinion was resolved by a third reviewer (SK). Data extraction was performed by two reviewers (GT, PC). Papers meeting the inclusion/exclusion criteria were divided into longitudinal and cross-sectional papers and were evaluated for their relationship to shoulder symptoms, and if single or multiple pathologies were assessed. Extracted data included (a) inclusion criteria and population (b) patient number/controls, patient demographics (age, sex and body mass index) and study design (c) aims (d)

imaging feature (e) symptoms (f) if pathology is defined (g) results with or without adjustment for confounders (h) findings.

3.3.3 Quality assessment

The quality of each observational study was independently assessed by two reviewers (GT, PC), (see Table 3.2). A standardised quality scoring tool has previously been used to assess similar observational studies in musculoskeletal disorders (392, 393). This quality score was adapted for this SLR to assess the following components: (a) study population; (b) imaging feature; (c) pain or function outcome; (d) study design; and (e) analysis and data presentation. The main adaptation was changing the pain scoring criteria relevant to shoulder criteria (e.g. SPADI for item 12). A score of '1' or '0' was allocated for each question according to whether the study fulfilled the criteria or not respectively. Any discordance in opinion was recorded and where consensus could not be achieved a third reviewer (PGC) was consulted. Quality scores were converted to percentages of the maximum scores for each class of paper (cross-sectional, case-control or cohort study). A study was considered to be high quality if it exceeded or equalled the mean score in its class.

The quality scores for each study is in Table 3.3.

Table 3.2 Quality scoring criteria

Item	Criterion	CC	CH	CS
Study population				
1	Recruitment from the general population	1	1	1
2	Selection occurred before disease onset or at a uniform point. A uniform point was considered to be equal baseline grade of progression (e.g. Kellgren Lawrence grade) or an analysis within the same joint	1	1	1
3	Cases and controls drawn were from the same population	1		
4	Participation rate >80% for cohort studies (retrospective cohort studies score zero automatically)		1	
5	Sufficient description of baseline characteristics - must include age, gender and BMI (or height and weight)	1	1	1

Item	Criterion	CC	CH	CS
6	Baseline characteristics comparable between cases and controls - must include age, gender and BMI (or height and weight)	1		
Assessment of Imaging-detected risk factor or feature				
7	Risk factor / feature assessed with a standardised method (e.g. but not a subjective opinion of a radiologist)	1	1	1
8	Risk factor / feature assessment was identical (performed the same way) in the studied population(s)	1	1	1
9	Risk factor / feature was assessed prior to the outcome (pain or function). A score of zero was allocated if the methods did not describe this.	1	1	1
Assessment of outcome (pain or function)				
10	Outcome assessment was identical in the studied population(s)	1	1	1
11	Outcomes were assessed reproducibly (intraclass correlation coefficient > 0.81 with a standardised assessment). If multiple outcomes were measured the mean reproducibility score was used.	1	1	1
12	Outcome classification was standardised (e.g. the SPADI pain score but not a subjective opinion of a patient's pain)	1	1	1
Study design				
13	Prospective study design used		1	
14	Follow up time > 3 years	1	1	
15	Information provided on completers vs withdraws in cohorts (without prospective trial data cohorts automatically score zero)		1	
16	Outcome evaluators were blinded to feature (risk factor)	1	1	1
17	Analysis of relationship between feature and outcome was planned prospectively	1	1	1
Analysis and data presentation				
18	The frequency of most important outcomes were given	1	1	1
19	Appropriate analysis techniques used (statistical or comparative techniques)	1	1	1
20	Adjusted for at least age, BMI and gender	1	1	1
	Maximum Score	17	18	14

CC: case control, CH cohort (prospective and retrospective), CS: cross sectional

Table 3.3 Quality scores for each study

		Quality Scoring Criteria																					
No.	**US CROSS-SECTIONAL**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total	%
	Ardic 2006	0	0			0		0	1	0	1	0	1				0	1	1	1	0	6	43
	Brasseur 2004	0	0			0		0	1	0	1	0	0				0	1	1	1	0	5	36
	Cholewinski 2008	0	0			0		1	1	0	1	0	0				0	1	1	1	0	6	43
	Daghir 2012	0	0			0		0	1	0	1	0	0				0	0	1	1	0	4	29
	Chiou 2002	0	0			0		0	1	0	1	0	0				0	0	1	1	0	4	29
	Draghi 2015	0	0			0		0	1	0	1	0	0				0	1	1	1	0	5	36
	Fehringer 2008	0	0			0		0	1	0	1	0	1				0	1	1	1	0	6	43
	Hamid 2012	0	0			0		0	1	1	1	0	0				1	1	1	1	0	7	50
	Joensen 2009	1	0			0		0	1	0	1	0	1				0	1	1	1	0	7	50
	Keener 2009	0	0			0		0	1	0	1	1	0				0	1	1	1	0	6	43
	Keener 2010	0	0			0		0	1	0	1	0	1				0	1	1	1	0	6	43
	Le Goff 2010	0	0			0		0	1	1	1	0	0				0	1	1	1	0	6	43
	McMahon 2014	0	0			0		0	1	0	1	0	1				1	1	1	1	0	7	50
	Tracy 2010	0	0			1		0	1	0	0	1	0				0	1	1	1	0	5	43
	Wu 2010	0	0			1		0	1	0	1	1	0				0	1	1	1	1	8	57
	Yamaguchi 2006	0	0			0		0	1	0	1	0	0				0	1	1	1	0	5	36

		Quality Scoring Criteria																					
No.	**US LONGITUDINAL COHORT STUDY**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	total	%
	Chiou 2001	0	0		1	0		0	1	0	1	0	0	1	0	0	0	1	1	1	0	7	39
	Couanis 2015	0	1		1	0		0	1	1	1	0	0	1	0	1	0	1	1	1	0	10	56
	Desmeules 2004	0	0		1	0		0	1	1	1	1	1	1	0	0	1	1	1	1	0	11	61
	Keener 2015	0	0		1	0		0	1	0	1	0	1	1	1	1	0	1	1	1	0	10	56
	Mall 2010	0	1		1	0		0	1	1	1	1	1	1	0	0	0	1	1	1	0	11	61
	Saffran 2011	0	0		0	0		0	1	1	1	0	0	1	0	1	1	0	1	1	0	8	44
	Yamaguchi 2001	0	0		0	0		0	1	1	1	0	1	0	0	0	0	1	1	1	0	7	39

		Quality Scoring Criteria																					
No.	**PET CROSS-SECTIONAL**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	total	%
	Kim 2013	0	0			0		1	1	0	1	0	0				0	1	1	1	0	6	43
	Sridhiran 2017	0	0			0		0	0	0	0	0	0				1	0	0	1	0	2	14

		Quality Scoring Criteria																					
No.	**BONE SCAN CROSS SECTIONAL**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	total	%
	Koike 2013	0	0			0		1	1	0	1	1	1				1	1	1	1	0	7	50

	Clunie 1998	0	0			0		0	1	0	1	0	0				0	0	0	0	0	2	14
	Binder 1984	0	0			0		1	0	1	0	0	0				0	0	1	0	0	3	21

		Quality Scoring Criteria																					
No.	**X-RAY CASE-CONTROL STUDY**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	total	%
	Endo 2001	0	0	1		0	0	1	1	0	1	1	1		0		0	0	1	1	0	8	47

		Quality Scoring Criteria																					
No.	**X-RAY CROSS-SECTIONAL**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	total	%
	Kircher 2010	0	0			0		0	0	1	1	1	1				0	1	0	1	0	6	43
	Kircher 2012	0	0			0		0	1	0	1	1	1				0	1	1	1	0	7	50
	Mayerhoefer 2009	0	0			0		0	1	1	1	1	1				0	1	1	1	0	8	57
	Yamaguchi 2000	0	0			0		1	1	0	0	1	0				0	1	0	1	0	5	36

		Quality Scoring Criteria																					
No.	**X-RAYS COHORT STUDY**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	total	%
	Cho 2010	**0**	**0**		**0**	**0**		**0**	**0**	**0**	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**	**5**	**28**

		Quality Scoring Criteria																					
No.	**MRI CROSS-SECTIONAL STUDY**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total	%
	Ahn KY 2012	0	0			0		0	1	1	1	1	0				0	1	1	1	0	7	50
	Birtane 2001	0	0			0		0	0	0	1	0	1				0	1	1	1	0	5	36
	Curry EJ 2015	0	0			1		1	1	0	1	0	1				1	1	1	1	1	10	71
	Di Mario 2005	0	0			0		1	1	1	1	0	0				0	0	1	0	0	5	36
	Epstein R 1993	0	0			0		1	1	0	0	0	0				0	1	1	1	0	5	36
	Gill 2014	1	0			0		0	1	0	1	0	1				0	0	1	1	0	6	43
	Hodgson RJ 2012	0	0			0		1	1	0	1	1	1				0	1	1	1	0	8	57
	Jung 2013	0	0			0		0	0	0	0	0	0				0	0	1	0	0	1	7
	Kanatli U 2013	0	0			0		1	1	1	1	1	1				1	1	1	1	0	10	71
	Krief OP 2006	0	0			0		1	1	0	1	0	1				0	1	1	1	0	7	50
	Moses DA 2006	0	0			0		1	1	0	1	0	0				0	1	1	1	0	6	42
	Reuter 2008	0	0			0		0	1	0	1	0	0				0	1	1	1	0	5	36
	Song 2011	0	0			0		0	1	0	1	1	0				1	1	1	1	0	7	50
	Unruh 2014	0	0			0		0	0	1	1	0	1				0	1	1	1	0	6	43
	White 2006	0	0			0		0	0	0	0	0	0				0	1	1	1	0	3	21
	Williamson 1994	0	0			0		0	1	0	0	0	0				0	0	0	1	0	2	14

		Quality Scoring Criteria																					
No.	**MRI COHORT STUDY**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	total	%
	Moosmayer S 2013	0	1		1	0		1	1	0	1	0	1	1	1	0	1	1	1	1	0	12	67
	Moosmayer 2017	0	0		0	0		0	1	0	0	0	1	0	1	1	1	0	1	1	0	7	39
	Ertan 2015	0	0		0	1		0	0	0	1	0	1	0	1	0	0	1	1	1	0	7	39

No.	**MRI CASE CONTROL STUDY**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	total	%
	Frost P 1999	0	1	1		0	0	1	1	0	1	0	1		0		1	1	1	1	0	10	59
	Graichen H 1999	0	0	0		0	0	1	1	1	1	0	1		0		0	1	1	1	0	8	47
	Schweitzer M 1995	0	0	1		0	0	0	1	1	1	0	0		0		1	1	1	1	0	8	47

Meta-analysis was inappropriate due to heterogeneity in study populations and imaging modalities. A narrative analysis of the evidence for features and their associations with symptoms was provided based on the study design, adequacy of adjustment for covariates using a 'best evidence synthesis' approach (394). Comparisons were made for cross-sectional studies and longitudinal studies.

The research synthesis results were interpreted using the Grade of Recommendations Assessment, Development and Evaluation (GRADE) framework (395). GRADE is a systematic approach to enable judgements about quality of evidence. It was developed by the GRADE working group and is used to assess methodological flaws, consistency of results and generalisability of research results. The GRADE scoring system is calculated on points based on quality (e.g. follow-up, withdrawals, blinding); consistency (e.g. in populations, or outcomes); directness (e.g. generalisability of the reported results to population of interest); effect size. The quality of evidence is rated as high (≥4 points overall), moderate (3 points), low (2 points), and very low (≤1).

3.4 Results

3.4.1 Systematic literature search and selection

Following exclusion of duplicates, 4383 articles were included. 119 articles met the inclusion/exclusion criteria and were screened. In total, 56 papers were included (41 cross-sectional, 11 cohort, 4 case control). Imaging modalities included 25 ultrasound (47, 48, 284, 396-417), 24 MRI (35, 36, 283, 284, 414, 417-435), 12 radiograph studies (401, 404, 422, 425, 427, 433, 436-441), three bone scintigraphy (436, 442, 443), two PET (444, 445) and none CT. Of these studies, ten assessed associations with two imaging modalities (284, 401, 404, 414, 417, 422, 425, 427, 433, 436). Most studies included both genders; eight studies did not state the gender ratio involved (47, 411, 414, 431, 433, 436, 442, 445) and one included males only (408). The nomenclature for defining imaging pathologies varied between studies, and there was no standardised way of defining pathology (see Table 3.4). There was heterogeneity between study population.

Table 3.4 Definition of pathology

Pathology	Definitions
MRI defined partial rotator cuff tear	Incomplete tears are either intra-tendinous or partial. In intra-tendinous tears, the split is only within the tendon itself. In partial tears, some tendinous fibres on the articular or bursal surface are interrupted (16) Tear size was categorized into partial-thickness tear, <2 cm full-thickness tear, and ≥2 cm full-thickness tear (45) A partial tear was defined as T2 signal of defect was a fluid signal (49) The “bridging sign” , a band-like structure connecting cranial portion of the subscapularis tendon and anterior margin of the supraspinatus tendon through the subcoracoid and subacromial space with intermediate to low signal intensity in all sequences, which is associated with subscapularis tendon tear (52) Classification according to which surface of the tendon is involved and grades the severity of the tear according to its depth: grade 0, homogeneous signal and regular margins of tendon; grade 1, articular or bursal surface side lesion involving less than a quarter of the tendon thickness; grade 2, partial-thickness tear involving less than half the thickness of the tendon; and grade 3, partial-thickness tear involving more than one half of the thickness of the tendon with tenuous continuity but without full-thickness tear (54) The main criteria for partial-thickness tears were focal heterogenous hypoechogenicity and incomplete hypoechoic clefts. Secondary signs – including double cortex sign, pitting and irregularity of the bony surface of the greater tuberosity, and fluid in the biceps tendon sheath and the subdeltoid bursa – were used as diagnostic aids but were regarded as insufficient to make the diagnosis alone (41) A partial tear was a partial thickness defect on the coronal and/or sagittal images (58) The supraspinatus tendon was considered torn when there was increased signal within the tendon on both proton density and T2 weighted images, or when there was disruption and retraction of the tendon seen on any pulse sequence (62)
Ultrasound defined partial rotator cuff tear	Partial tear of supraspinatus tendon was defined as the presence of an anechoic or hypoechoic area, containing or not a central hyper- echoic core, only partly involving the thickness of the tendon at either the joint or above it (21)

	Partial rupture of subscapularis or infraspinatus tendon was defined as part of the tendon still attached to its insertion; thus, the echostructure of the rotator-cuff muscles was assessed (21) Rotator cuff integrity was evaluated according to the modified 5-grade Wiener and Seitz classification: Type III - area of cuff discontinuity at the inner or outer side of the cuff tendons; local loss of ‘‘anterior arc’’ of the cuff shape or major hypo-echoic area within the cuff. This type corresponds to partial full-thickness tear (23) A partial-thickness tear was recorded when there was minimal flattening of the bursal side of the rotator cuff or when a distinct hypoechoic or mixed hypoechoic defect was visualized in both the longitudinal and transverse planes (35) Tears measuring ≤15 mm were considered to only involve supraspinatus (or 1 tendon), tears that measured >15 mm but ≤30 mm were considered to be involving supraspinatus and infraspinatus and tears that measured >30mm in the transverse dimension were considered to involve supraspinatus, infraspinatus and part of teres minor (35)
MRI defined complete rotator cuff tear	A complete rotator cuff tear was defined as a focal, well-defined area of increased signal intensity on T1-weighted and T2-weighted images that ex- tended through the entire thickness of tendon. Complete tears are either focal (scoring as 1), subtotal (scoring as 2), or total (scoring as 3). Focal tears display a piercing tendon hole; in subtotal tears, only a few fibers are regularly inserted, whereas in total tears, all tendon fibers are torn and the stump is retracted under the acromion (16) Tear was categorized as full-thickness if tear ≥2 cm (45) Criteria adapted from Zlatkin et al: Grade 0 = normal; grade 1 = tendinitis; grade 2 = degeneration; grade 3 full thickness tear (48) Full-thickness tear, there was a tear evident from one side to other side of the tendon but not necessarily whole tendon, for a complete tear all fibres of the tendon were torn (49) Criteria for full-thickness tears included nonvisualisation of the rotator cuff, hypoechoic or anechoic discontinuity, and contour concavity of the superiorborder of the rotator cuff tendon (41) Measurement of tear size was made along a measuring line drawn between the edges of the tear (anterior-posterior plane) or between the lateral margin of the tear and the greater tuberosity (medial-lateral plane). Tears were classified into 3 groups according to tear size progression in the anterior-posterior plane: no to small progression (−5 to +9.9 mm), medium progression (10 to 19.9 mm), and large

	progression (≥20 mm) (44) A full thickness tear was categorized as a complete interruption of the tendon on the coronal and/or sagittal images (58) The diagnosis of a full-thickness rotator cuff tear was made when a high-signal-intensity, well-defined abnormality was seen in the rotator cuff with or without subacromial bursal fluid or retraction (59)
Ultrasound defined complete rotator cuff tear	The criteria of van Holsbeck and Introcaso for full thickness rotator cuff tears was used (with added scores): a discontinuity in the rotator cuff (scored as 1) and extension from the bursal to the humeral side of the rotator cuff (scored as 2) (16) A complete tear or rupture of the supraspinatus tendon was defined by one of the following criteria: (a) anechoic area through the entire thickness of the tendon; (b) a flat part of the superficial contour of the tendon; (c) a rotator cuff <2 mm thick or (d) no cuff visible (21) The diagnostic criterion for a complete rupture of the subscapularis or infraspinatus tendon was no visibility of the tendon at its insertion site (21) Rotator cuff integrity was evaluated according to the modified 5-grade Wiener and Seitz classification: Type IV - hypoechoic linear zone extending through the entire thickness of the cuff; segmental loss of convex cuff contour; the deltoid muscle may be found pushed into the cuff defect—to the degree where it is in contact with the humeral head; visualisation of the hyaline cartilage under- lying the cuff tendons ‘‘naked cartilage sign”. Type V: non-visualization of the rotator cuff tendons. Subdeltoid fascia and the deltoid muscle apposed to the contour of humeral head (23) The criteria of a rotator cuff tear included the following: (1) nonvisualization of the rotator cuff; (2) a focal hypoechoic cleft in the rotator cuff; (3) focal thinning of the rotator cuff; (4) focal depression of the rotator cuff; and (5) a focal heterogeneous, hypoechoic rotator cuff with a subdeltoid bursa (22) Full- thickness tears were classified by size (based on tear width or length, whichever was larger) as small (<10 mm), medium (10 to 30 mm) or large (>30 mm) (29) A full-thickness rotator cuff tear was recorded when the rotator cuff could not be visualized because of complete avulsion and retraction under the acromion or when a focal defect in the rotator cuff was created by a variable degree of retraction of the torn tendon edges (Safran 2011). A full-thickness rotator cuff tear was recorded when the rotator cuff could not be visualized because of

	complete avulsion and retraction un- der the acromion or when a focal defect in the rotator cuff was created by a variable degree of retraction of the torn tendon edges (35)
Arthrography defined rotator cuff tear	Rupture of the rotator cuff was considered to be present in an immediate flow of contrast medium from the shoulder joint into the subacromial/subdeltoid bursa occurred. With contrast medium present in the shoulder joint and subacromial bursa, the rotator cuff was clearly visible above the humeral head (65)
Capsulitis	Capsulitis was defined on arthrography as a marked reduction in joint volume (often under 5 ml) with loss of distensibility of the shoulder joint was found. Marked irregularity of joint outline and early lymphatic filling was also sometimes seen (65) Unilateral adhesive capsulitis is defined as ≥50 % loss of movement of the shoulder joint relative to the non-affected side in one or more of three movement directions (i.e., forward elevation, external rotation in 0° of abduction, or internal rotation). To determine joint capsule thickness, combined capsular and synovial thicknesses of the axillary pouch were obtained by measuring the widest portion of the capsule, which was determined based on the distance between the high signal fluid in the axillary recess and the outer border of the capsule in perpendicular direction to the capsular configuration on T2-weighted fat suppressed oblique coronal images. Gadolinium enhancement of the joint capsule in the axillary recess was assessed on T1-weighted fat-suppressed oblique coronal images and graded by the intensity and extent of the enhancement as follows: mild, subtle enhancement of the capsule with insufficient intensity; moderate, sufficiently strong enhancement of the capsule involving less than half of the capsule circumference; severe, sufficient enhancement involving over the half of the capsule circumference (15)
MRI defined Biceps Tendon Pathology	Biceps tendon lesions were classified as grade zero when the tendon had a normal shape and signal in all planes, grade 1 when shape abnormalities or signal abnormalities without discontinuity were present, and grade 2 when a discontinuity of the tendon was observed (54) Tendinopathy was categorized by abnormal signal intensity on short TE images without a defect in the tendon in fluid sensitive images (58) Normal fluid in the biceps tendon sheath was 1-2mm in thickness (59)
Ultrasound defined biceps tendon pathology	The location of the LHB tendon with respect to the intertubercular groove was considered normal when lying within the groove, in subluxation when it was situated beyond the medial margin of the groove, and in luxation when it was outside the groove (21)
MRI defined Tendon Pathology	Tendonosis was present if the proton density fat-saturated sequence signal was increased but the T2

	signal was less than that obtained if fluid was present (49) Rotator cuff tear based on the number of tendons involved; retraction of the rotator cuff tear in the coronal plane (minimal retraction, mid-humeral retraction, glenohumeral retraction, or retraction to glenoid); and the degree of muscle atrophy (56) In calcific tendinitis, classification and measurement of size of the calcium deposit and the measurements for the calculation of the acromion index were made at standardized true antero-posterior radiographs using digital X-rays with resolution of 0.1 mm. The deposits were classified according to Gärtner (appearance) and Bosworth (size) (68) For rotator cuff pathologies, especially the supraspinatus tendon, MRI findings were graded as normal, tendinosis, or a partial-thickness tear of the supraspinatus tendon (15) Zlatkin's MRI stages of SIS = stage 0 = normal tendon morphology and signal intensity; stage 1 = increased signal intensity without thinning irregularity or discontinuity; stage 2 = increased signal intensity with thinning irregularity; stage 3 = complete disruption of supraspinatus tendon (64) Tendon retraction in the coronal plane was classified in stages as described by Boileau et al. (45) The MRI classification was a modified version of the MRI staging system of Zlatkin et al: Type 1 showed increased signal intensity due to edema and inflammation of the tendon. Type 2 showed findings suggestive of fibrosis and tendinitis on MRI, in addition to the findings described for type 1. Type 2 was further subdivided into type 2a, in which there was involvement of the articular surface of the tendon, and type 2b, in which there was involvement of the bursal surface. Type 3 showed a partial tear of the rotator cuff tendon. Finally, type 4 showed a complete tear of the tendon (63) The rotator interval was assessed with respect to signal abnormality in the subcoracoid fat, which was considered to be present if there was a discrete focus of homogeneous low signal within the rotator interval on an oblique sagittal T1- weighted image. Subcoracoid fat obliteration was graded subjectively as absent, partial, or complete (15)
Ultrasound defined tendon pathology	Calcifications were identified as hyperechoic linear, round, or oval areas interrupting the US wave (21) The categorization of the phase of calcification as formative or resorptive was determined by the presence of symptoms; patients with acute onset of moderate or severe pain were classified as having calcification in the resorptive phase; otherwise, the calcification was classified as being in the formative

	phase (22) Tendon thickness was measured by the built-in calibrated callipers at predefined sites using osseous land- marks for exact positioning of the transducer longitudinally to the tendon. Thickness was measured on an imaginary line placed at 90◦ to the skin surface and drawn to the superficial and deep margins of the paratenon. The exact anatomical sites were determined by the deep anchor of the imaginary line; the base of the tuberculum majus plateau of the os humeri (28) Tear width describes the anterior-to-posterior dimension and tear length, the medial- to-lateral dimension. The tear area was calculated by multi- plying the tear width by the tear length. (30) Calcification of the rotator cuff was diagnosed if a hyperechogenic focus with or without acoustic shadow was found within the supraspinatus, infraspinatus or subscapularis tendon on ultrasound (31)
Radiography/bone isotope defined tendon pathology	The size of a calcific deposit was defined by multiplying the long axis by the short axis. The calcific deposits were classified into type I (sharply outlined and densely structured), type II (sharply outlined and inhomogeneous or homogenous with no defined border), and type III (cloudy and transparent in structure) (70) A diagnosis of a rotator cuff tear when at least 3 of these 4 criteria were met: (1) flattening of peribursal fat, (2) loss of actual rotator cuff tendon, (3) surface irregularity of the greater tuberosity, and (4) effusion of the subacromial bursa (72)
MRI defined Bursa Pathology	Mild subacromial bursitis had a sliver of fluid present or a small increase in T2 signal; moderate bursitis, clear fluid or thickening present; and severe bursitis, marked fluid distension and synovial thickening and/or the presence of rice bodies (49) Images were scored on a scale of 0-2 depending on the maximum thickness of enhancing tissue: 0, no abnormal enhancement; 1, up to 3mm thickness of enhancing tissue; 2, 3mm or more enhancing tissue (51) The criteria for subacromial bursitis was the presence of a fluid collection and enhancement in the subacromial bursa on oblique coronal T2-weighted images and oblique coronal fat-suppressed enhanced T1-weighted images (60)
Ultrasound defined bursa pathology	An effusion of subacromial–subdeltoid bursa (SSB) was defined as an anechoic lamina between the folds of the bursa. It was considered to be mild (lamina thickness <3 mm) or abundant (lamina thickness >3

	mm) (21) Subacromial–subdeltoid bursa thickness was considered to be abnormal when the hypoechoic lamina located between the deep hyperechoic lamina of the deltoid and the superficial hyper- echoic lamina of the supraspinatus was >2 mm thick. It was considered to be mildly thickened when this lamina was 2 or 3 mm, and markedly thickened when >3 mm (21) Effusion in the SASD bursa was evaluated by using a binary system (yes vs. no) (25) The patient was considered to present bursal effusion or bursitis if the width of the bursa exceeded 2mm (31)
Joint Effusion	A joint effusion was defined as an anechoic lamina partly, or completely surrounding the long head of the biceps tendon at the level of the intertubercular groove (21) A glenohumoral effusion was defined as a hypoechogenic area between the posterior labrum and the infraspinatus tendon (31) The glenohumeral joint effusion was scored on oblique coronal T2-weighted images using a modified MRI classification scheme developed by Schweitzer et al. as follows: 0, no joint fluid; 1, mild loculated fluid signal; or 2, extensive fluid signal (60) Glenohumoral Joint fluid was graded as follows: 0 =a thin intraarticular rim without distension of the recesses; 1 = either slight distension of the subscapularis recess, fluid in the biceps tendon sheath (>2mm thickness), or fluid in the axillary recess, which causes a U shape and is seen in more than one coronal oblique image; 2 = distension of two of these recesses; 3 = increased fluid I all three of these synovial structures (59)
Acromioclavicular Joint Pathology	ACJ arthritis severity was determined according to the degree of osteophytes, joint effusion, synovial thickening, bone edema and articular cartilage thinning (49) The criteria for osteoarthritis of the acromioclavicular joint was the presence of a fluid collection and enhancement in the acromioclavicular joint on oblique coronal T2-weighted images and oblique coronal fat-suppressed enhanced T1-weighted images (60)
Acromion Pathology	Bigliani et al. classified the morphology of the acromion according to the acromial under surface: flat, curved, hooked and convex.

	The intrinsic acromion angle was measured at the intersection of two lines: one joining the anterior and posterior margins of the acromial under surface, and the other running parallel to the longitudinal axis of the acromion. The acromio-humeral distance was measured in millimetres between the most caudal point of the acromial undersurface and the most cranial point of the proximal humeral epiphysis in the acromio-clavicular joint (46) Acromion was classified as flat (type 1), smoothly curved (type 2), or hooked (type 3). The acromions were classified according to their appearance on the T2 weighted MRI image obtained just lateral to the acromioclavicular joint (47) All shoulders were classified into one of three acromial shapes using the SOV. The Bigliani classification system was used. This system classifies the shape of the undersurface of the acromion as flat (type I), curved (type II), or hooked (type III). The SOV was also used to assess for the presence of an acromial spur. A spur was defined as a boney projection along the insertion of the coracoacromial ligament that showed an abrupt change in the curvature of the anterior edge of the acromion as described by Ogawa et al. The acromial index (AI) is a method to quantify the amount of lateral extension of the acromion relative to the humeral head. Described by Nyffeler et al, this calculation is done using the true anteroposterior radiograph (27) The acromion index (AI) was calculated as described by Nyffeler et al. by dividing the distance from the glenoid plane to the most lateral aspect of the acromion (GA) by the distance from the glenoid plane to the most lateral aspect of the proximal humeral head (GH) in the true anteroposterior view (68) Acromial shape was assessed on outlet view radiographs based on the illustrations by Toivonen et al and the criteria of Epstein et al. A flat acromion with no signs of anterior downsloping was classified as type I; an acromion with anterior downsloping in its midsection was classified as type II, and an acromion with downsloping in its anterior third as type III. If there was a bony spur on the anterior or anterolateral undersurface, the acromion was also graded as type III. AHD is considered pathological if the minimal distance between the dense cortical bone at the inferior aspect of the acromion and the subchondral lamina of the humeral head is ≤7 mm (55)
Rotator Cuff Tear progression/enlargement	A full-thickness cuff tear was considered to have enlarged if its size had increased by 5 mm in any dimension compared with baseline (39)

	A partial-thickness tear was considered to have enlarged when it had converted to a full-thickness defect, defined as a complete disruption of tendon continuity at the insertion (39) Substantial tear progression was defined as transformation of a partial-thickness tear into a full-thickness tear or a size increase of >5 mm in either the width or the length of a full- thickness tear compared with that at the time of enrollment (40) Increase in size in rotator cuff tear was defined as greater than 5mm on either longitudinal or transverse ultrasound views (42)
Labarum/ligament Pathology	Gleno-humoral joint cartilage damage was classified as mild if there were small areas of cartilage thinning (<50 mm thickness), moderate if areas of cartilage thinning were >50 mm or more extensive involvement of <50 mm areas of thinning and severe if there were larger areas of full cartilage loss. Glenoid labrum tears were deemed to be small if they were less than full thickness of the labrum and not displaced; large tears were full thickness (49). Maximal superior coracoacromial ligament (CAL) displacement was recorded from a measured line connecting the acromion and the coracoid process at the CAL attachment (34).
Muscle Atrophy	Atrophy of the supraspinatus muscle was assessed by the tangent sign as described by Zanetti et al (41) Atrophy of the supraspinatus muscle was assessed by the tangent sign as described by Zanetti et al. Fatty degeneration of the supraspinatus, infraspinatus, and subscapularis muscles was classified according to Goutallier et al. and Fuchs et al. The original five grades were dichotomized. Muscles showing no fat (grade 0) or only some fatty streaks (grade 1) were compared with those showing more than some fatty streaks but still more muscle than fat (grade 2), equal amounts of muscle and fat (grade 3), or less muscle than fat (grade 4) (41) To evaluate fatty degeneration of the rotator cuff muscles, the echogenicity and echotexture of each cuff muscle was examined with use of a 3-point scale as described by Strobel et al. The echogenicity was graded in comparison with the echogenicity of the overlying muscle (i.e., the deltoid for supraspinatus grading and the trapezius for infraspinatus grading). The echotexture was graded on the basis of the visibility of the central tendon and the normal muscular pennate pattern. The sum of the echogenicity and echotexture grades was calculated and used for data analysis (40) Fatty infiltration was determined based on the classification described by Goutallier et al, and classification of muscle atrophy was based on that by Warner et al. (45)

Calcific Plaque Morphology	The morphology of calcific plaque of the shoulder on HRUS was classified into 4 types, including arc-shape (echogenic arc with clear shadowing); fragmented (at least two separated echogenic plaques with or without shadowing) or punctuated (tiny calcific spots without shadowing); nodular (echogenic nodule without shadowing); and cystic types (bold echogenic wall with echo-free content) (22, 36) Calcific shoulder plaques were classified into four types on the basis of morphology, as previously described by Chiou et al 2001 (31)
Subacromial Space	The ultrasonographic measurement of the subacromial space was defined as the tangential distance between the humeral head and the edge of the acromion visible on the longitudinal sonogram as hyperechoic bony landmarks when the image was frozen. The measurement obtained therefore represents the AHD at the inlet of the sub- acromial space (38) For quantification of the subacromial space width, the minimal spatial acromiohumeral and claviculohumeral distances were determined by 3D Euclidean distance transformation (50)
Osteoarthritis	The degree of osteoarthritis was graded according to Samilson and Prieto by the size of the caudal osteophyte (grade I: <3 mm; II: 3–7 mm; III: >7 mm) (67) The presence of GHJ OA was determined using the Samilson-Prieto classification (49) For evidence of osteoarthritis, the presence of osteophytes was used, which were only considered present if they contained marrow (59)
Factors linked with impingement	The point of inter-section of the upper border of the scapular spine and the acromio-clavicular joint was defined as the outside point, and the medial end of the upper border of the scapular spine the inside point. The scapular upward rotation angle (SURA), that is, the angle of tilt between the scapular spine line and the horizontal, was adopted as the parameter of the upward rotational tilt. In order to evaluate the axial rotation tilt of the scapula, the distance between the scapular spine line and the upper border of the coracoid process was defined as the coracoid upward shift distance (CUSD) (66) The acromio-glenoid angle (AGA) was measured as described by Banas et al. This is the angle between the inferior outline of the acromion and the superior and inferior margins of the glenoid lab- rum.

	Supraspinatus-glenoid angle (SGA) was measured as described by Tetreault et al. on an oblique coronal image just posterior to the acromio-clavicular joint. This is the angle formed by the supraspinatus fossa and the labral outline of the glenoid on the oblique coronal image (53) Acromial index (AI) was measured as described by Nyff- eler et al. After obtaining a true A-P X-ray view, the measurement technique requires drawing three parallel lines and measuring the distances between those lines. The first line connects the superior and inferior osseous margins of the glenoid cavity and represents the plane of the glenoid surface. The second line is drawn tangential to the lateral border of the acromion, and the third line is drawn tangential to the most lateral part of the proximal humerus. The distance from the glenoid to the acromion is divided by the distance from the glenoid to the lateral aspect of the humeral head, and the resultant value is called the acromial index (53) Since the coracoacromial ligament (CAL) degeneration has been proposed as a well-known indicator of the subacromial impingement, it was used to assess the subacromial impingement. The degree of CAL degeneration was assessed arthroscopically according to Royal Berkshire Hospital Classification (RBHC) as described by Levy et al. This classification system categorizes the pathology into four different grades. Normal appearance of the CAL is accounted as grade 0, minor fraying as grade I, major fraying as grade II, and visualization of the bare bone under the CAL is accounted as grade III (53) The coracohumoral interval was defined as the interval between the coracoid process and the lesser tuberosity of the humerus was measured 3 separate times (33)
Glenohumoral Motion	The geometric center of the humeral head was found with the use of the center point of a “best- fit” circle positioned on the humeral articular surface. The superior and inferior end points of the glenoid articular surface were then marked to demarcate the glenoid line and the center point automatically determined by the software. A line drawn along the long axis of the humerus was compared with the glenoid line to calculate the glenohumeral angle. The perpendicular distance from the center of the humeral head to a perpendicular line drawn from the center of the glenoid line was calculated by the software for each arm abduction angle. The arm abduction angle was compared with the measured glenohumeral angle (69)

3.4.2 Summary of the methodological qualities of the studies included

Table 3.3 presents the results of the methodological quality assessment of the included studies. The mean (range) score was 48% (28%-67%) for cohort, 41% (7%-71%) for cross-sectional and 50% for (47% - 59%) case-control studies. 31 studies were high quality, and 25 were low quality. Six studies did not explain the statistical test used (407, 415, 419, 424, 430, 442). Nine studies did not define pathology.

The GRADE quality of evidence for the relationship for all imaging features/symptoms outcomes was ‘very low’ because of study limitations (risk of bias and observational study design), quality, inconsistency and indirectness.

3.4.3 Cross-sectional relationship between individual pathology features and symptoms

3.4.3.1 Rotator cuff tears

Sixteen studies evaluated the relationship of RC tears and symptoms (47, 48, 284, 400, 403, 404, 406, 418, 421, 422, 424, 426, 428, 430, 433, 443) (Table 3.5, Table 3.6,

Table 3.7). Nine evaluated the relationship with shoulder pain (47, 48, 284, 404, 406, 418, 422, 424, 443), four with shoulder disability (284, 403, 418, 426) and eight studies with symptoms using a composite pain and function score (400, 403, 406, 421, 422, 426, 428, 430).

RC tear was associated with pain in four ultrasound studies (47, 48, 284, 406), three MRI studies (284, 424, 433) and one bone scintigraphy study (443). These studies were unadjusted and the majority were of low quality. Larger RC tear size (mean size 22.7mm) was associated with pain in one low quality study (47). One study reported no association in RC tear size and symptoms, although in symptomatic tears >175mm^2, pain was correlated with tear size (404). Two high quality studies reported no association between RC tear size or location with pain, one of which was well-adjusted (418, 421). The type of RC tear (partial or full) was not associated with severity of pain (406).

RC tear was associated with disability in two high quality MRI studies (284, 426). RC tear was not associated with functional disability in one high quality ultrasound study (284) and two high quality, MRI studies, one of which was well-adjusted (418, 422). One study reported an association of RC tears with disability on MRI but not on ultrasound (284).

RC tear was associated with worse composite scores in two ultrasound studies (400, 406). There was no association between RC tears and composite scores in two ultrasound studies (403, 406) and five MRI studies (421, 422, 426, 428, 430) .

In summary, one high quality, well-adjusted paper, RC tears were not associated with pain or function (418). The other studies were of mixed quality, unadjusted and reported conflicting findings.

3.4.3.2 Tendinopathies

Eight studies evaluated tendinopathy and symptoms (284, 397, 402, 406, 421, 422, 430, 435) (Table 3.5, Table 3.6,

Table 3.7). Two evaluated the relationship with pain (406, 421), three with disability (284, 402, 422) and seven with both pain and disability (397, 402, 406, 421, 422, 430, 435). One high quality ultrasound study reported an association using measures of both pain and composite symptoms, although the authors did not separate those with tendinopathies from those with RC tears (406). In one high quality study, tendinopathy on MRI was not related to clinical shoulder impingement (pain only) (421).

One high quality ultrasound study reported a relationship between tendinopathies and disability (402). One high quality ultrasound study (284) and one high quality MRI (422) reported no relationship.

One ultrasound study reported a relationship between RC tendon thickness (≥0.8mm) and symptoms, which were undefined (402). One low quality MRI study found only a high stage tendinopathy, defined by complete disruption of supraspinatus tendon, was associated with symptoms (435). There was no association between RC thickness and symptoms of impingement (pain with functional impairment) between patients in one ultrasound study, but a significant difference in RC thickness of > 1.1mm was seen between affected and unaffected shoulder of the same patient ($p<0.01$) (397). Three MRI studies of mixed qualities (421, 422, 430) reported no relationship with tendinopathy and symptoms.

In summary, high quality but unadjusted studies found conflicting relationship between pain, disability and tendinopathy (284, 402, 406, 421, 422). No studies adjusted for covariates.

3.4.3.3 Subacromial bursal pathology

Ten studies (36, 48, 284, 398, 399, 405, 422, 425, 426, 432) evaluated the relationship between the subacromial bursa (SAB) and symptoms (Table 3.5, Table 3.6, Table 3.7).

Five mixed quality ultrasound studies (48, 284, 398, 399, 405) and two MRI studies of mixed quality (284, 432) reported an association between SAB and pain. In one study, peri-bursal fat and fluid and bursal thickness, but not bunching, was associated with

pain (398). One study reported an association with pain and SAB when seen alongside power Doppler within calcific deposits (405). One study reported the location of bursa pathology was important (432). One ultrasound study (284) and one MRI study (284) reported SAB effusion/thickening was associated with reduced function. Two high quality MRI studies reported no association (422, 425). One high quality MRI study reported an association between bursitis and symptoms (426). Two high quality MRI studies reported no relationship between SAB enhancement and composite score (36, 422).

In summary, two high quality, unadjusted studies found no relationship between shoulder symptoms and subacromial pathology (36, 425). No studies adjusted for covariates.

3.4.3.4 Osteoarthritis

Four studies of mixed quality (422, 430, 433, 438) evaluated the relationship between shoulder OA and symptoms (Table 3.5, Table 3.6, Table 3.7).

One low quality combined MRI and radiographic study reported an association between subacromial osteophytes in patients with impingement (433). One high quality x-ray study reported no relationship between ACJ or GHJ OA and pain (422) and another no relationship with GHJ space width (438). One radiographic study reported an increased size of osteophytes, but not joint space, was correlated to reduced range of movement (438). Two MRI studies of mixed quality reported no relationship between pain, function and ACJ arthrosis (422, 430).

In summary, one high quality, unadjusted study found no relationship with symptoms and features of ACJ or GHJ OA (422). There were no adjusted studies.

3.4.3.5 Calcification

Three studies evaluated the association between calcification and pain (48, 396, 405) and two studies evaluated the association with pain and function (422, 439) (Table 3.5, Table 3.6, Table 3.7).

Two ultrasound studies of mixed quality (396, 405) showed calcification was associated with pain and one low quality study found no association (48). Larger and fragmented calcifications (mean dimensions: longitudinal 1.64cm and transverse 1.39cm) were associated with pain (405), as was morphology and colour Doppler (396). Two high quality radiographic studies reported no association with pain or function (422, 439).

In summary, two high quality, unadjusted studies found no relationship with calcification and symptoms (422, 439). There were no adjusted studies.

3.4.3.6 Acromion pathology

Twelve studies (397, 401, 408, 419, 420, 423, 425, 427-429, 433, 439) evaluated the relationship between the acromion and symptoms (Table 3.5, Table 3.6, Table 3.7).

Two ultrasound studies (397, 408), three MRI studies (420, 423, 429), one radiographic study (439), two combined MRI and radiographic studies (425, 433) and one combined ultrasound and X-ray study (401) evaluated the relationship of the acromion and pain. One study radiographically evaluated the relationship with function (439). Two MRI studies (419, 428) and one combined MRI and x-ray study (427) evaluated the relationship with symptoms using composite score.

One high quality combined radiographic and ultrasound study (401) reported that acromial index (lateral extension of acromion relative to humeral head) was associated with pain, whereas two high quality radiographic studies (425, 439) reported no association with pain or function. Those with full thickness cuff tears had an increased prevalence of type 3 acromion compared to controls and patients with surgical impingement (420). No relationship existed between scapuloacromial angle (429), subacromial distance or acromion shape (433) and “impingement”. One MRI study in patients with clinical impingement reported a reduction in the subacromial space during activity (423) and another reported decreased coracohumeral distance (433).

One high quality, adjusted ultrasound study reported displacement in coraco-acromio ligament in symptomatic patients (408). A difference in distance (2.1mm) between the infero-lateral edge of acromion and the apex of the greater tuberosity of humerus was observed in affected shoulders in a high quality study (397). Two studies of mixed

quality reported an association with AHD and symptoms (419, 427) but another high quality study found no association (428). One study showed no relationship with acromial shape (427), whereas another was positively correlated to the intrinsic acromial angle (419).

In summary, high quality, unadjusted studies found conflicting results on the relationship between symptoms and acromial index (lateral extension of acromion relative to humeral head) (401, 425, 439) and acromial humeral distance (AHD) (427, 428). No relationship was found between scapuloacromial angle or acromion shape in high quality, unadjusted studies (427, 429).

3.4.3.7 Adhesive capsulitis

Six studies (35, 283, 436, 442, 444, 445) evaluated the relationship between adhesive capsulitis and pain (Table 3.5, Table 3.6, Table 3.7).

Two high quality MRI studies reported enhancement of the joint capsule in the axillary recess and rotator cuff interval was associated with pain intensity (35, 283). One MRI study showed capsular thickening was associated with decreased external rotation (283). Two PET studies of mixed quality showed increased uptake of 18F-FDG in rotator cuff interval, anterior joint capsule, or axillary recess (444, 445). One low quality bone scintigraphy study reported no difference (442). One low quality study using bone scintigraphy and x-rays showed increased technetium uptake but no association between passive range of movement or recovery (436).

In summary, high quality, unadjusted studies have shown imaging features associated with symptoms in adhesive capsulitis (35, 283, 444).

3.4.3.8 Other features

Several studies evaluated other pathological imaging features. None of these were adjusted. Radiographically, one high quality study showed reduced upward and axial rotational tilts of the scapula was impaired in shoulder pain (437). There was no relationship in abnormal scapular planar glenohumeral motion measured using x-rays in patients with RC tears and pain in a low quality study (440). One high quality MRI study reported the presence of glenohumeral effusion was not related to pain (431).

One high quality radiographic study found in symptomatic patients with full RC tears >175mm^2, pain was correlated with humeral migration (404). One low quality study reported an association between the absence of subacromial fat in patients with impingement (433). One high quality study reported no association between acromio-glenoid angle, supraspinatus-glenoid angle and pain (425). Glenoid labral tear was associated with disability on MRI in a high quality study (284). In another high quality MRI study, glenoid labrum tears or cartilage damage was not associated with pain or functional impairment (422). In one high quality ultrasound study, coracohumeral interval is narrower in symptomatic shoulders (407).

Table 3.5 Cross-sectional ultrasound scans

Author	Patient and study characteristics	Findings	Quality score
Ardic 2006 (284) # Brasseur 2004 (48) # Chiou 2002 (396) * Cholewinski 2008 (397) #	Clinically suspected SIS Secondary care 58 patients/no controls 13 males; mean age 55.5 years Tennis players from French veteran championship of the Roland Garros Tennis Open 150 consecutive patients/contralateral shoulder 85 men; mean age 55 Shoulder calcification on radiographs Population NR 94 patients 42 male; average age 57 years Clinical SIS Orthopaedic outpatients 57 patients /unaffected contralateral shoulder/36 asymptomatic volunteers 23 males; mean age 56 years	SAB effusion/hypertrophy correlated with shoulder extension pain (r=-.04 p= 0.03) Complete supraspinatus tear correlated with pain on internal (r =0.4, P =0.04) and external rotation (r=0.3, p=0.02) Subacromial bursa effusion/thickening was correlated with restricted shoulder internal rotation (r= -0.4, p=0.02) After applying logistic regression was found that only glenoid labral tear and bursal effusion/hypertrophy on MRI were determinants of shoulder disability SAB effusion or thickness >2 mm associated with pain (p<0.001) A complete supraspinatus tendon tear occurred significantly more frequently in players with current pain and those with former pain (p<0.05) No relationship between calcification and pain Significant difference between the morphology of the calcific plaques and the clinical symptoms (p<0.01) (non–arc-shaped calcifications had more severe symptoms) High-grade colour doppler had significantly increased severe symptoms (p < .01) Difference in distance (3.3mm) between acromion and the AGT of humerus in affected joints and controls, and 2.1 mm in comparison to the contralateral unaffected joint (p=0.001). Significantly reduced AGT distance in affected joints (P<0.001) RC thickness not statistically significant between affected and control but was significant between affected and unaffected shoulder of same patient (1.1mm) (p<0.001).	43 36 29 43

Daghir 2012 (398) # 	Clinical SIS Recruited from university hospital 22 patients /23 healthy 10 male; mean age 52	Bursal fluid thickness significantly greater in SIS when measured using the short-axis supraspinatus view only (p<0.006) Peribursal fat was significantly thicker in all patients than controls on the long-axis subscapularis view only (p=0.036) SAB dynamic bunching not associated with SIS symptoms (p=0.41)	29
Draghi 2015 (399) * 	US of shoulders Radiology Department 1105 consecutive pts/none 600 males; mean age 52 years	Effusion in the SASD bursa is associated with shoulder pain independent from the underlying pathology (p<0.01)	36
Fehringer 2008 (400)	Patients >65 years from orthopaedic lower limb clinic 104 patients / number not specified (those without RC tears and not seen physician) 53 male; mean age 71.4 years	Mean Constant scores were lower for those with full thickness tears than for those without after adjusting for age and sex (p=0.0003) For those without tears, odds of having a SST score of 9 or greater were 0.22 times those with tears (P <.0001).	43
Hamid 2012 (401) * 	Asymptomatic RC tears Population NR 216 patients /47 (no rotator cuff tear) (43 people with no rotator cuff tear was used as a control for AI) 128 males; average age 64.8 years	Acromion index associated with the pain (p=0.02) No significant difference between acromion spur and pain Presence of an acromial spur, regardless of size, was highly associated with a full-thickness rotator cuff tear, even after adjusting for age, sex, and hand dominance (OR, 3.05; 95% CI, 1.42-6.52)	50
Joensen 2009 (402) # 	Clinical diagnosis of tendinopathy General practice and physiotherapy outpatients 64 patients /64 asymptomatic contralateral side 28 males; mean age 47.5 years	For symptomatic side, maximal pain-free isometric force (≤10N), tendon pain pressure (≥0.6kg) and tendon thickness (≥0.8mm) significantly different compared to asymptomatic side (p<0.001)	50
Keener 2009 (404)	Unilateral shoulder pain related to rotator cuff disease Background population not stated 62 (symptomatic side)/98 (asymptomatic side)	Humeral migration is related to tear size in symptomatic patients with a critical size of tear >175mm^{2}related to humeral migration (p=0.01) Proximal humeral migration was greater in the shoulders with a symptomatic tear (p=0.03)	43

#	Background population not stated 32 males; mean age 60.6	No difference in VAS between small and large RC tears in the symptomatic group; no significant difference in RC tear size between the asymptomatic and symptomatic shoulders In the symptomatic group with full RC tears >175mm^2, VAS is correlated with tear size (r= 0.70, p=0.001) and humeral migration (r=0.68, p=0.002)	
Keener 2010 (403) * 118 males; mean 62.1 years	Symptomatic RC tear and contralateral asymptomatic RC tear Orthopaedic department patients 196 patients /54 (intact RC)	RC tear (partial or full) associated with a clinically insignificant loss of shoulder function No differences were seen in functional scores between different sizes of full-thickness RC tears	43
Le Goff 2010 (405) *	Calcific tendonitis on X-ray Rheumatology outpatient 57 consecutive patients/24 (asymptomatic calcific tendonitis) 19 men; mean age 51 years	Power doppler within the calcific deposit and widened SAB (>2mm) associated with pain (p<0.005) Larger (p=0.0015) and fragmented (p=0.01) calcifications were associated with pain	50
McMahon 2014 (406) #	Elite athletes participating in 2005 Senior Olympics >60 years old 141 patients /no controls 58 men; median age 70	Increased odds of pain VAS score with RC abnormality (tear or tendinopathy) (OR 8.0 95% CI 1.0–62.5) Pain not associated with types of pathology (full or partial RC tear) ASES and DASH not related to US findings	36
Tracy 2012 (407) #	Clinical suspicion of coracoid impingement Population NR 7 patients/19 (asymptomatic) 6 males; mean age 55.9 years	CHI is significantly narrower in symptomatic shoulders than in asymptomatic volunteers (p<0.001)	43
Wu 2010 (408) #	Clinical suspected SIS High school players 10 patients /16 (asymptomatic)	Significant displacement found in CAL in symptomatic patients (mean 3.0mm) (p=0.017)	57

	10 males; mean age 16.7 years		
Yamaguchi 2006 (47) # 	Unilateral shoulder pain Population NR 58 patients /no control Gender distribution not stated; average 62.8 years	In patients with bilateral RC tears, increased size may be associated with pain ($p<0.01$) (mean size for asymptomatic = 17.4mm vs 22.7mm symptomatic)	36

Table 3.6 Cross-sectional MRI scans

Author	Patient and study characteristics	Findings	Quality score
Ahn KY 2012 (283) #	Clinical adhesive capsulitis. Orthopaedic Surgery Department patients 97 patients /no control 47 males; mean age 56yrs	Thickening of joint capsule in axillary recess associated with decreased ER in males, in their non-dominant arm (r^2=0.34 p<0.05). Gadolinium enhancement of the joint capsule in axillary recess correlated with pain intensity (OR 0.78 95% CI 0.62-0.97; p<0.05) No significant correlation between subcoracoid fat obliteration of the rotator interval or supraspinatus pathology and shoulder ROM or pain	50
Ardic 2006 (284) #	Clinically suspected SIS Secondary care patients 59 shoulders 13 males; mean age 55.5 years	Severity of disability correlated with SAB effusion (r=0.4, p=0.03) and labral tear (r=0.5, p=0.02) Labral tears associated with pain (r=0.8, p<0.001) and disability (r =0.6 p=0.02) SAB effusion associated with disability (r=0.5, p=0.03) Restricted movements associated with RC tears	43
Birtan 2001 (435) #	SIS (defined by improvement to local anaesthetic injection) 86 patients 48 male Average age 51.6	Stage 3 tendinopathy significantly associated with worse score (p<0.05)	36
Curry EJ 2015 (418) *	RC tears Orthopaedic and physiotherapy clinics 67 patients/ no controls 37 males, 58%>60 yrs	Pain & function status were not associated with tear size/thickness, fatty infiltration and muscle atrophy	71
Di Mario 2005	Clinical SIS	Impingement syndrome is positively correlated to intrinsic acromial angle and negatively correlated to acromio-humeral distance	36

(419) # 	Background population not stated 74 patients with SIS/no controls 47 males, mean age 49yrs		
Epstein R 1993 (420) # 	Surgically proven SIS Surgically proven RC tears. Background NR 30 SIS (6 men, mean age 39) / 35 cuff tears (25 men, mean age 58)/56 controls (26 males, mean age 36)	Patients with RC tears had increased prevalence of type 3 acromion compared to control, and in impingement group ($p<0.001$).	36
Frost P 1999 (421) # 	Clinical SIS Population NR 42 patients / 31 controls 25 males; mean age 47.5 years;	No association between supraspinatus pathology and pain	59
Gill T 2014 (422) # 	Current shoulder pain, history of shoulder pain & no history of shoulder pain. General population in Australia 30 in total: 10 Current shoulder pain, 10 history of shoulder pain & 10 no history of shoulder pain 12 males; mean age 64.8 years	No significant differences in shoulder pathologies and those with/without pain	43
Graichen H 1999 (423) # 	Clinical SIS Population NR 10 patients /10 controls 5 males, 39-64yrs,	A significant decrease in the width of the subacromial space compared with that of the healthy contralateral side during activity ($p<0.05$)	47
Hodgson RJ 2012	RC tears Primary care referrals to the shoulder	No link between pain & bursal enhancement (OR = 20.44, 95% CI = 0.03–22347.73, p = 1.00).	57

(36) * 	ultrasound service 18 with pain/15 without pain 5 males; mean age 55.4yrs		
Jung 2013 (424) *	Arthroscopic confirmed full-thickness tear of the subscapularis tendon Orthopaedic referrals 29 patients/no controls 11 males; mean age 64.5 years	Patients with the “bridging sign” had longer duration of shoulder pain (no statistical significance given)	7
Kanatli U 2011 (425) *	Clinical SIS Orthopaedic department 44 patients / no controls Patients scheduled for shoulder arthroscopy 20 males, mean age 54.1	No correlation between radiological measurements and severity of acromial impingement	71
Krief OP 2004 (426) #	Mainly pain in deltoid region after the failure of non-inflammatory therapy and a rehabilitation program Patients referred by sports medicine clinicians or orthopedic surgeons 1075 patients / no controls 47% male, mean 52yrs	The presence, size, and location of full-thickness RC tears did not influence the level of disability or pain The global disability was statistically linked to partial-thickness tears involving the superficial and deep surfaces of the supraspinatus tendon ($p < 0.01$, $R^2 = 0.350$), to the presence of bursitis ($p = 0.01$ $R^2 = 0.337$), but not other RC or biceps pathology	43
Mayerhoefer 2009 (427) #	Clinical SIS failed to response to treatment for >6months Orthopaedic department 47 patients /no controls 33 males; mean age 51.7 years	The Constant score was correlated with AHD ($r = 0.39$ for XR and 0.41 for MRI, $p< 0.01$) but not with acromial shape. Patients with an AHD <7 mm on MRI had significantly lower Constant scores than those with an AHD >7mm (mean difference, 18.5; $p<0.01$)	57

Moses DA 2006 (429) #	Patients with surgically diagnosed impingement and instability Secondary care 27 GH instability, no impingement; 18 shoulder impingement, no tear; 21 impingement with tear/no controls 48 males, mean age 29	No difference in scapula position between instability, impingement with tears or impingement without tears	42
Reuter 2008 (430) #	Symptomatic or non symptomatic athletes Ironman Triathletes 16 patients/7 (asymptomatic)/17 non-athletes 11 males; average age 39 years	No statistical difference in prevalence in RC tendinopathy/tears or ACJ disease	36
Schweitzer M 1995 (431) *	Criteria and background population not defined 208 patients with mixture of shoulder pathology/17 Sex ratio NR; mean age 47yrs	GH fluid not associated with focal tenderness, joint pain or impingement	47
Song 2011 (35) #	Clinically diagnosed adhesive capsulitis Patients attending radiology department 35 patients /45 14 males; mean age 50.1 years	Thicker joint capsule in the axillary recess and thicker enhancing portion of the axillary recess and the RC interval associated with adhesive capsulitis ($p<0.001$)	50
Unruh 2014 (428) #	Symptomatic RC tears Enrolled by surgeons involved 450/ no controls Full thickness cuff tears 49% male, mean age 62	Longer duration of symptoms does not correlate with more severe cuff disease. Duration was unrelated to weakness, decreased ROM, tear size, fatty atrophy, muscle retraction AHD or validated outcome measures	43

White 2006 (432) *	Patients with full thickness RC tears Population NR 35 patients /36 asymptomatic 22 males; mean age 41	Mean SAB thickness in symptomatic individuals significantly higher than in asymptomatic in RC tears (3.3mm vs 1.3mm respectively $p<0.05$) and fluid in symptomatic patients located in the anterior quarter of the humerus or anterior to the humerus	21
Williamson 1994 (433) # 	Clinical diagnosis of impingement syndrome, based on relief of symptoms after lidocaine injections Population NR 41 Participants with impingement syndrome/ 40 patients with shoulder instability used as controls Sex ratio NR; mean age 39	Absence of subacromial fat, presence of a supraspinatus tear, subacromial osteophytes, and a decreased coracohumeral distance observed in impingement compared to shoulder instability groups	14

Table 3.7 Cross-sectional x-ray, PET and bone scans

Author	Patient and study characteristics	Findings	Quality score
Binder AI 1984 (436) (x-ray) *	Clinical adhesive capsulitis Population NR 42 had x-rays/40 controls Patients with capsulitis, age & sex not documented	No association was found between the passive range or its recovery and the findings on plain x-ray	21
Endo 2001 (437) (x-ray) #	Clinically diagnosed chronic SIS Orthopaedic outpatient clinic 27 patients/7 controls 14 male; mean age of 57.5 years	Upward and axial rotational tilts of scapula impaired in shoulder pain ($p<0.05$)	47
Gill T 2014 (422) (x-ray) #	Current shoulder pain, history of shoulder pain & no history of shoulder pain. General population in Australia 30 in total: 10 Current shoulder pain, 10 history of shoulder pain & 10 no history of shoulder pain 12 males; mean age 64.8 years	No significant differences in shoulder pathologies and those with/without pain	43
Hamid 2012 (401) (x-ray) *	Asymptomatic RC tears Orthopaedic department 216 patients / 47 (contralateral asymptomatic RC intact side) 128 males; mean age 68.4 years	Acromion index associated with the development of pain ($p=0.02$) No significant difference between acromion spur and development of pain Presence of an acromial spur, regardless of size, was highly associated with a full-thickness rotator cuff tear, even after	50

		adjusting for age, sex, and hand dominance (OR, 3.05; 95% CI, 1.42-6.52)	
Kanatli U 2011 (425) (x-ray) *	Clinical SIS Orthopaedic department 44 patients / no controls 20 males; mean age 54.1	No correlation between radiological measurements and severity of acromial impingement	71
Keener 2009 (404) (x-ray) #	Unilateral shoulder pain related to rotator cuff disease Background population NR 62 (symptomatic side)/98 (asymptomatic side) 32 males; mean age 60.6	Humeral migration is related to tear size in symptomatic patients with a critical size of tear >175mm^2 related to humeral migration (p=0.01) No difference in VAS between small and large RC tears in the symptomatic group In groups with ≥175mm^2 tear, there was a correlation between VAS and migration (r=0.68, p=0.002) and VAS and the tear area (r=0.70, p=0.001) pain and tear area predictors of humeral migration (overall model r^2=0.63, p=0.0006), with the tear area to be the single most important (r^2=0.63, p=0.01).	43
Kircher 2010 (438) (x-ray) *	"Advanced" OA of the shoulder Background population NR 120 patients /no control 64 males; mean age 64.9 years	Increasing size of osteophytes is correlated to reduced active and passive range of movement :flexion (r=−0.203, p=0.026; r=−0.254, p=0.026, respectively), abduction (r=−0.197, p=0.032; r=−0.270, p=0.017), external rotation (r=−0.243, p=0.008; r=−0.338, p=0.002) and internal rotation (r=−0.243, p=0.008; r=−0.245, p=0.030) Joint space width **not** associated with pain or ROM	43
Kircher 2012 (439) (x-ray) *	Calcific tendinitis on radiographs Orthopaedic department 109 patients /no control 46 males; mean age 48.2	No association or correlation between acromion index/calcium deposition and pain or function	50
Mayerhoefer 2009 (427) (x-ray)	SIS Orthopaedic department	The Constant score was correlated with AHD (r=0.39 for XR and 0.41 for MRI, p< 0.01) but not with acromial shape	57

#	47 patients /no controls 33 males; mean age 51.7 years	Patients with an AHD <7 mm on MRI had significantly lower Constant scores than those with an AHD >7mm (mean difference, 18.5; p <0.01)	
Williamson 1994 (433) (x-ray) #	Clinical diagnosis of impingement syndrome, based on relief of symptoms after lidocaine injections Background population NR 41 Participants with impingement syndrome/ 40 patients with shoulder instability used as controls Sex ratio NR; mean age 39	Subacromial osteophytes, but not sclerosis and cysts, observed in SIS group vs control	
Yamaguchi 2000 (440) *	Full thickness RC tears Population NR 10 painful shoulders/10asymptomatic tears/10 normal volunteers 5 males with painful shoulders Age range 20-29 years (mean age not given)	Although RC tears demonstrated abnormal GH kinematics, there was no relationship with symptoms	36
Kim DH 2013 (PET scan) (444) #	Patients diagnosed with Adhesive capsulitis in musculoskeletal pain clinic 22 shoulders in 21 patients, 40 shoulders in 20 patients (control group) 9 males; 59.3yrs,	Specific patterns of uptake in the rotator interval, ACJ or axillary recess may be related to adhesive capsulitis. Increased uptake of 18F-FDG in RI, AJC, or AR compared to controls and contralateral shoulder (p<0.001)	43
Sridharan 2017 (445) *	Adhesive capsulitis Population not documented 15 patients with confirmed adhesive capsulitis /109 controls Patients with capsulitis, age & sex not documented	Significant association with PET-positivity and AC was significant (Fisher's exact, p=0.001).	14
Binder AI 1984 (436) (Bone scan) *	Clinical adhesive capsulitis Population not documented 38 had bone scans/40 (similar age/sex no symptoms)	No association between technetium uptake and duration of symptoms, initial severity, or recovery.	21

	Patients with capsulitis, age & sex not documented	Significantly increased technetium uptake in symptomatic shoulder compared to contralateral asymptomatic shoulder or controls (p<0.001)	
Clunie 1998 (442) (Bone scan) #	Unilateral shoulder pain: either clinically diagnosed SIS or adhesive capsulitis Recruited from Rheumatology clinic 12 subacromial impingement; 4 adhesive capsulitis/16 controls (contralateral asymptomatic side) Age & sex NR	No difference in Tc-HIG distribution between symptomatic vs asymptomatic shoulders	14
Koike Y 2013 (443) (Bone scan) #	Symptomatic cuff tears Secondary care hospital 28 symptomatic tear, 26 asymptomatic cuff tear/20 no tear (controls) 14 males; mean age 62	Shoulders with a symptomatic rotator cuff tear showed higher radioisotope uptake on bone scintigraphy than those with an asymptomatic tears, or shoulders without tears (p=0.02)	50

3.4.4 Longitudinal relationship between individual shoulder features and symptoms

3.4.4.1 Rotator cuff tears

Six ultrasound studies evaluated the relationship between RC tears and symptoms (412-417) (Table 3.8, Table 3.9). Five studies evaluated the relationship between RC tears and pain persistence or progression (412, 413, 415-417), three with function progression (412, 413, 417) and four with symptom progression using composite scores (412, 414, 415, 417).

In four studies of mixed quality, an increase in RC tear size was associated in the incidence of pain (412, 413, 416, 417), although this was not shown in two other studies (414, 415). Two high quality, unadjusted studies showed function worsened with increasing RC tear (412, 417). An increase in RC tear size and tear type from partial to full thickness was associated with the incidence of symptoms measured using a composite score (412), although this did not reach statistical significance in two other studies of mixed quality (414, 415).

Overall, the high quality studies suggested that increasing size of tears was associated with symptom incidence (412, 413). These studies were unadjusted.

3.4.4.2 Tendinopathies

One low quality, unadjusted MRI study reported patients with tendon oedema and inflammation were more likely to achieve complete recovery with conservative treatment compared to those with fibrosis or tears (p=0.038) (Table 3.8, Table 3.9). (434).

3.4.4.3 Subacromial bursa pathology

One high quality, unadjusted ultrasound study found pain was associated with SAB thickness one week after a marathon swim (p=0.032) (Table 3.8, Table 3.9) (410).

3.4.4.4 Calcification

One low quality, unadjusted ultrasound study showed vascularity and shape was associated with resorption of the calcium deposit and improved pain ($p<0.001$) (409). One low quality, unadjusted radiographic study reported no association between calcium deposition and progression of pain or function (Table 3.8, Table 3.9) (441).

3.4.4.5 Other features

One high quality, unadjusted ultrasound study reported a reduction of the AHD narrowing on abduction correlated with improvement of symptoms (Table 3.8, Table 3.9) (411). The rate of progression to advanced fatty muscle degeneration on MRI and long head of biceps on ultrasound was associated with an increased odds of symptom incidence measured using a composite score in a high quality, unadjusted study (414) but not in another study (413). One study reported no relationship between the incidence of pain and progression of fatty degeneration (413). Another low quality, unadjusted study found supraspinatus atrophy was associated with worse strength and composite scores (417).

3.4.5 Studies exploring multiple pathologies

Only one, low quality, unadjusted study examined the association of combined pathologies with pain (399), and reported effusions in the SAB were associated with shoulder pain independent of the underlying pathology (399).

20 out of 56 studies evaluated more than one pathology, but the majority did not examine a combination of pathologies: eight ultrasound studies (eight cross-sectional (48, 397, 399, 406, 407); one longitudinal (413)); nine cross-sectional MRI studies (35, 283, 421, 422, 426-428, 430, 433) one X-ray study (439); and two combined MRI and ultrasound studies (284, 414).

Table 3.8 Longitudinal ultrasound scans

Author	Patient and study characteristics	Findings	Quality score
Chiou 2001 (409) *	Radiographic calcific tendinosis Recruitment population NR 100 patients /no control 52 males; average age 60	Higher vascularity significantly associated with spontaneous resorption and improvement of symptoms (p<0.001) Those with arc-shaped calcific plaque were less likely to resolve spontaneously	39
Couanis 2015 (410) *	Swimmers intending to complete an unassisted channel crossing and between 18-65 years 22 patients /no controls 15 males; mean age 37.27 year	SAB thickness is significantly correlated with kilometres swum in the pool in the preceding week (p=0.05) SAB thickness associated with pain 1 week post swim (p = 0.032), but not prior to race Significant differences in pain between those with severe and normal (p=0.004), mild (p=0.008) or moderate RC tendinopathy (p=0.012)	56
Desmeules 2004 (411) #	Clinically diagnosed SIS Primary care and physical therapy units 7 patients /13 controls Sex ratio NR; average age 44 years;	No difference between AHD and WORC (p=0.06) Reduction of AHD narrowing on abduction correlated with improvement of WORC post rehabilitation (r=0.86; p=0.01)	61
Keener 2015 (412) *	Symptomatic RC tear and contralateral asymptomatic RC tear Orthopaedic department 224 patients /36 (no RC tears) 112 men; mean age 62 years	RC tear enlargement (>5mmm or change in tear type) associated with a greater risk of pain development (p<0.05) Baseline SST (p < 0.05) and ASES (p < 0.05) scores worsened with advancing tear type Shoulders with new pain had a significant decline in function from baseline (p < 0.05) Greater risk for pain development associated with advanced final tear type (partial or full thickness) (p < 0.05).	56

Mall 2010 (413) *	Asymptomatic RC tear Population NR 44 patients/55 (asymptomatic RC tears) 30 males; mean age 63.3 years	The size of a full-thickness rotator cuff tear increased significantly in those who developed pain (median area increase of 31mm^2 p=0.006). Larger RC tears on enrolment were more likely to develop pain Function decreased with onset of pain Pain development in asymptomatic RC tears is not associated with progression of fatty degeneration of the rotator cuff muscles No significant differences were seen in GH kinematics and the onset of pain	61
Moosmayer 2013 (414) *	Asymptomatic tears or patients with contralateral shoulder pain Orthopaedic outpatients 50 asymptomatic shoulders Age and sex ratio NR	Tear size increase not associated with the development of symptoms (p>0.05). Increased odds of development of symptoms with new biceps tendon pathology (OR 7.5; 95% CI, 1.3 to 42.5; p=0.02)	67
Moosmayer 2017 (417) *	Patients reviewed by a single orthopaedic surgeon in a Norwegian secondary care centre 49 patients 30 males; average age 61 years	Large RC progression resulted in worse Constant, ASES, strength and VAS scores (p<0.05)	39
Saffran 2011 (416) *	Non surgically treated patients with full thickness RC tears <60 years old Secondary care hospital 51 patients 28 males; mean age 54 years	Patients in considerable pain at follow-up had an increase in tear size >5mm (p=0.002) No correlation was found between the appearance of new rotator cuff tears in the follow-up ultrasound and pain at the time of the follow-up	44
Yamaguchi 2001 (415) *	Asymptomatic RC tears in patients with symptomatic contralateral RC tears Population NR 23 had ultrasound scans/no control 22 males; average age 69.8 years	Reduced function with increased pain (p<0.05) No statistical significance shown between pain and function and tear progression (no statistical test undertaken)	39

Table 3.9 Longitudinal MRI scans and x-ray

Author	Patient and study characteristics	Findings	Quality score
Ertan 2015 (434) (MRI) #	"SIS" without RC tears between March 2002 and August 2005. Patients recruited from outpatients clinic 63 patients:3 groups of shoulder pain: no recurrence; relapsing course; chronic shoulder pain 28 males; mean age 48 (range 28-74 years)	Patients with type 1 changes on MRI (p=0.038), have higher shoulder examination scores at the first evaluation are more likely to achieve complete recovery with conservative treatment	39
Moosmayer S 2013 (414) (MRI) *	Full thickness asymptomatic RC tears Orthopaedic outpatients 50 asymptomatic shoulders Age and sex ratio NR	Progression of muscle atrophy increased odds of symptom development - not statistically significant (OR 4.0 [95% CI, 0.84 to 19.1]; p=0.08) Increased odds of symptom development with progressive RC fatty degeneration OR, 13.1 [95% CI, 1.4 to 122]; p=0.02)	67
Moosmayer 2017 (417) *	Patients reviewed by a single orthopaedic surgeon in a Norwegian secondary care centre 37 patients 30 males; average age 61 years	Worse Constant score, ASES and muscle strength in those with supraspinatus atrophy	39
Cho 2010 (441) *	Treated calcific tendinitis Secondary care 87 patients /no controls 18 males; mean age 53.2 years	VAS, Constant score, UCLA scale and ROM improved irrespective of calcification location, deposit type or size	28

Key: ACJ = acromion clavicular joint; AHD – acromio-humeral distance; AGT = apex of the greater tuberosity; AI= acromion index; ANOVA = analysis of variance; ASES score = American Shoulder and Elbow score; BPI = Brief Pain Inventory; BT = biceps tendon; CAL = coraco-acromial ligament; CDUS = colour Doppler ultrasound; CHI = coracohumeral interval; CSA = critical shoulder angle; DASH = disabilities of the arm, shoulder and hand score; F/U = follow up; GH = glenohumeral; NR = not reported; OA = osteoarthritis; OP = outpatients; RBHC = Royal Berkshire Hospital Classification; RI = rotator interval; ROM = range

of motion; RC = rotator cuff; SAB = subacromial bursa; SA = subacromial; SAS = subacromial space; SF-36 = 36-Item Short-Form Health Survey; SIS = subacromial impingement syndrome; SPADI = shoulder pain and disability index; SST = Simple Shoulder Test; US = ultrasound; WORC = Western Ontario Rotator Cuff Index; VAS = visual analogue score WUSPI = Wheelchair users' shoulder pain index;

* studies imaging features as independent variables and symptoms as dependent variable

studies symptoms as independent variables and imaging features as dependent variable

3.5 **Discussion**

This systematic review is the first to comprehensively examine the relationship of imaging features with shoulder symptoms. The majority of studies reported conflicting results.

The majority of studies evaluated single shoulder pathologies. RC tendons contain nociceptors and it would be rational to expect that as tear size increased, patients would be more likely to report pain and functional impairment. However, studies evaluating RC tears reported conflicting results, and the majority of studies were unadjusted and of low quality. A cross-sectional, high quality, adjusted study did not find any association with symptoms, although in high quality, unadjusted longitudinal studies, increasing size of tears was associated with symptom incidence. Inflammation may also be a possible cause of pain. The relationship between imaging and adhesive capsulitis was only evaluated in cross-sectional studies. Although these studies were unadjusted, enhancement of the joint capsule on MRI and increased uptake of 18F-FDG in the rotator cuff interval, acromio-clavicular joint or axillary recess on PET may be associated with symptoms. There were conflicting results on RC tendinopathy, SAB pathology and calcific tendinopathy and symptoms. These studies were unadjusted and of mixed quality and therefore further high quality studies are required to determine if any relationship exists.

It has been previously shown that numerous pathologies commonly co-exist in the same symptomatic individual, although most studies in this review did not compare multiple pathologies with symptoms (446). Only one unadjusted, low quality study, evaluated shoulder pain with multiple pathologies in this review, and the authors found SAB effusion may be associated with pain.

In nine of the 56 studies, the pathologies being studied were not defined, and multiple studies used varying definitions for the same pathology. These differences in nomenclature have further added to the confusion in diagnosing and treating shoulder pain (373). Standardising the definition of pathologies is an important aspect of understanding their relationship to symptoms.

Variations in definitions may lead to the inclusion or exclusion of pathologies and result in different outcomes. Furthermore, basic definitions are important to allow standardised scoring and therefore evaluation of outcomes. There was also heterogeneity between study populations and this may be a reason for conflicting findings.

Structure-pain relationships are complex. There is the possibility that there may be no relationship between imaging findings and symptoms, and imaging findings need to be considered as part of a wider pain construct. Other factors which may be associated with musculoskeletal symptoms include age, gender, body mass index, activity, mental health and central sensitisation (447). Only six studies adjusted for age and gender when evaluating the relationship between shoulder pain and imaging (36, 47, 283, 400, 401, 426), and none adjusted for psychological factors. Other adjustments included occupation (426), arm dominance (283, 401, 426) and co-morbidity (283).

3.6 Limitations

There were several limitations to this work. Observational studies were rated relative to the overall mean quality scores, which may have artificially rated studies as high quality. However, the distribution of quality scores indicated a broad range of quality, with a range of 14-71%. In this review, there was no threshold for the minimum number of patients to be included in each study. A previous review evaluating imaging features and knee pain excluded articles if fewer than 20 patients took part in a study (393). This threshold for that review was arbitrarily chosen and reflects an absence of guidelines on how to exclude studies with low participant numbers. Inclusion of studies with lower number of participants may contribute to imprecise findings, especially in the context of a heterogeneous population. In this review, however, all studies that satisfied the inclusion criteria were included in order to provide an overall conclusion.

The analysis involved associations of imaging features with PROMS, such as SPADI or Constant Score. As described in Chapter 2, some PROMS have undergone extensive psychometric tests. Other scores, such as the Constant

Score, have not been evaluated in the context of reliability, responsiveness and validity. There may therefore be measurement bias in some of the studies included.

For this systematic review adjustment for age, gender and BMI denoted an association that was ‘well-adjusted’ for the covariates of shoulder pain and function. However, as described in Chapter 2, there are many other co-variates, such as co-morbidities and occupation that may contribute to shoulder symptoms and its persistence. Therefore, when describing imaging feature association with shoulder symptoms and their persistence, the lack of adjustment for these for these covariates may result in residual confounding.

Publication bias could not be assessed with a funnel plot as there were insufficient results for odds and relative risk ratios. Meta-analysis was not performed due to the heterogeneous nature of the measures of the features and pain or function outcomes.

3.7 **Conclusion**

In conclusion there were conflicting results on the association of imaging features with shoulder symptoms and its persistence. The existing evidence was very low in quality based on the GRADE. There was no significant association between most imaging features and symptoms amongst high quality, cross-sectional studies. There was low-quality evidence that enhancement of the joint capsule on MRI and increased uptake on PET was associated with symptoms in adhesive capsulitis. Based on high-quality longitudinal studies, enlarging rotator cuff tears was associated with an increased incidence of symptoms.

Numerous pathologies commonly co-exist in the same symptomatic individual, although only one study in this review compared multiple pathologies with symptoms. This study was unadjusted and of low quality.

Currently, shoulder imaging is increasingly used for assessment of shoulder symptoms. Despite this rise, its relationship with symptoms and its role in informing management remain unknown. Understanding the relevance of

imaging-detected pathologies and their role in the shoulder management pathway is essential to improving care and reducing costs. Therefore, there is a large unmet need for high quality, adjusted, prospective studies evaluating the role of multiple imaging pathologies and other extrinsic factors to understand the role of imaging in shoulder pain care pathways.

This systematic review highlights the need for greater information on the relationship of multiple imaging pathologies and shoulder symptoms. There is very little evidence describing how a combination of shoulder pathologies contribute to shoulder symptoms and their persistence. This unmet need will be addressed in the following Chapters.

4 Chapter 4 - A retrospective cohort study to determine if groups of imaging detected pathologies exist and if these groups differ in their outcomes

4.1 Introduction

In Chapter 3, the systematic literature review identified the need for further studies to evaluate the role of multiple pathologies in shoulder symptoms. This Chapter describes a retrospective study evaluating multiple pathologies in 3000 ultrasound scans and their relationship with patient reported outcome measures and treatments.

As discussed in Chapter 2, the clinical diagnosis of shoulder pathologies remains difficult, with evidence suggesting poor levels of reliability and reproducibility amongst clinicians when examining for shoulder pain (38, 448). Recent qualitative research has also shown uncertainty amongst GPs in diagnosing the causes of shoulder pain (449). Ultrasound can offer accurate detection of pathology and in the context of the reported diagnostic uncertainty it is unsurprising its use is increasing. From 2001-2009 in Australia, there was a fourfold rise in shoulder ultrasound (450). The number of primary care referrals for shoulder ultrasound scans in a UK regional centre tripled to 3000 from 2007 to 2015 (451)(451). However, it is still unclear how information from ultrasound relates to treatment and long-term outcomes (452, 453).

It has been suggested that the identification of subgroups within a population would allow appropriately targeted therapy to increase treatment success (8). For patients with shoulder pain, the lack of satisfactory treatment outcomes may be due to the assumption that all patients are similar in all important variables. The identification of subgroups for treatment have often focussed on single variables, but this single factor may not account for a clinically meaningful proportion of the variance in outcome. Outcomes could possibly be the result of an interaction of multiple factors, and the identification of subgroups may therefore enable optimised therapies. Subgrouping in other

musculoskeletal conditions, such as lower back pain, has helped to provide improved patient outcomes in a cost effective way (447, 454).

Shoulder pain may have complex aetiologies and pathologies often do not occur in isolation; some may respond to particular therapies better than others, which could complicate assessment of efficacy if they co-occur. Therefore, understanding patterns of shoulder pathology may help us to target therapies more effectively. Given the uncertainty in clinical diagnosis, it seems reasonable to examine the potential of pathology-based diagnosis using ultrasound. If ultrasound cannot identify groups of patients who will achieve different outcomes, either in the current care pathway or in trials of targeted therapies, there would be limited justification for its continued use in this patient group.

As a first step to understand the importance of a pathology-based classification, I aimed to determine whether distinct clusters of ultrasound-defined pathologies exist, and whether there is any evidence that these have implications for long-term clinical outcomes.

4.2 **Aims**

The hypothesis relevant to this Chapter is that unobserved subgroups result in clustering of ultrasound detected pathologies.

The aims of this Chapter are:

- To describe the population referred to the single tertiary care centre for an ultrasound scan of their shoulder from primary care
- To determine if groups with different patterns of imaging detected pathologies exist
- To determine if these groups differ in their outcomes

4.3 **Methods**

The Shoulder Pain Study (Shoulder - PAST) was carried out with ethical approval from the North East - Newcastle & North Tyneside 1 Research and Ethics Committee (15/NE/0115) and given Research and Development permission from Leeds Teaching Hospitals Trust (R&I number RR15/091 (173654W/Y)).

4.3.1 Patients

Ultrasound reports were retrieved for consecutive primary care patients referred to a single centre radiology department in Chapel Allerton Hospital, Leeds, UK for a scan of their shoulder. A sample size of 3000 patients was selected, based on the estimated annual referrals from primary care and patients were included if they had scans that occurred between 2012-2013. As discussed in Chapter 2, approximately 50% of patients were expected to have pain 18 months on from their initial presentation, thus contacting patients who were first scanned more than 18 months prior was intended to provide the most accurate estimate of outcomes included in the questionnaire. Inclusion criteria were: aged over 18 years old; referred by primary care; referred for shoulder pain; and attending for their first ultrasound scan. Patients were excluded if they had previous surgery or were not referred from primary care. A list of eligible patients and their details was obtained from the radiology information technology team. Further information at the time of referral, such as duration of pain prior to referral, was identified by the clinical details written on their referral card and the electronic patient records.

In our centre, local primary care guidelines advise that patients are referred from primary care for an ultrasound scan of their shoulder if they have moderate-severe painful abduction, have not improved after physiotherapy, or have suspected acromio-clavicular joint pain. However, clinical experience of the broad range of symptoms and signs presenting raises questions about adherence to these recommendations and may further highlight discrepancies in clinical evaluation of shoulder pain.

4.3.2 Ultrasound scans

Data from a single shoulder per patient was utilised and where identifiable, the first symptomatic shoulder was included. Eligible patient records were examined to identify the first ultrasound scan for a selected shoulder, even if the first scan fell outside the collection dates. Information of the pathologies detected on the shoulder scan was obtained from the electronic results server. Scans were undertaken by musculoskeletal radiologists and sonographers. Previous work has shown that inter-rater reliability for shoulder pathologies between two of the radiologists is substantial (all Kappas>0.6) for full thickness rotator cuff tear, calcification, impingement and tendon abnormalities (455). The following features were documented as present or absent: bursitis, impingement, calcific tendinitis, ACJ degeneration, glenohumeral osteoarthritis, adhesive capsulitis, biceps tenosynovitis, RC tendinopathy and full or partial RC tear. The definitions used by the department for these pathologies are in Table 4.1 below.

Table 4.1 Ultrasound reporting definitions for shoulders

Pathology	Definitions
RC Tears	Record foot print tears as partial thickness if articular surface not involved
Bursal thickening	Bursal effusion or synovitis >0.5mm
Dynamic subacromial impingement	Bunching of the bursa lateral to the coraco-acromial ligament during active abduction in the absence of rotator cuff tear.
Calcific tendinitis	Diagnosed in the presence of globular calcific deposition, exclude linear entheseal calcifications.
ACJ pathology	Diagnosed in the presence of osteophytosis or synovitis, effusion, joint malalignment and bone cortex irregularity.
GHJ OA	Diagnosed by the presence of marginal osteophytosis at the cartilage bone junction or humeral articular cartilage thinning.
Adhesive Capsulitis/ frozen shoulder	Diagnosed in patients with limited passive external rotation possibly with a

	small LHB effusion and thickening of the coracohumeral ligament compared to the contra-lateral side in the absence of any features of OA.
Biceps tenosynovitis	Non-displaceable or non-fully compressible hypoechoic thickening of the long head of biceps tendon sheath with or without power Doppler signal of evidence of tendonopathy (see 9) or thinning of the long head of biceps tendon.
Tendinopathy	Hypoechogenicity or heterogeneity with thickening of the rotator cuff tendons compared to the other rotator cuff tendons of the ipsilateral or contralateral shoulder.

After discussion with the sonographers, impingement was assumed to be present if there was a full-thickness RC tear, even if impingement was not reported. Other pathologies were assumed to be absent if not reported. Other details recorded included age at time of scan, gender, whether an injection was given on the day of the scan (documented on the electronic results server) and, where available, duration of pain.

4.3.3 Questionnaire

A postal questionnaire was sent to all eligible patients scanned in 2013. A second wave of questionnaires was sent to those that had not replied after 4 weeks. In order to maximise the rate of survey response, I sent out questionnaires in two waves, as the first questionnaire can often by misplaced by the patient. In a large-scale survey of disablement, which was sent to 25 000 households in the Calderdale area, the response rate to the first wave of questionnaires was 57%, which increased to 73% after a second wave of questionnaires was sent (1). I employed similar strategies to maximise the response rate, such as minimising the length of the questionnaire whilst maintaining readability, as well as including a stamped addressed return envelope alongside the questionnaire.

The data collected included key variables which may be associated with shoulder pain, as outlined in Chapter 2: demographics (age, sex, height and

weight) ((65) (53)).; characteristics of pain (if pain was still present and how long they have had pain for) [(63)]; self-reported comorbidities (61); previous injuries since or before ultrasound scan; other joints affected (55); activity as measured by the Marx shoulder activity scale (130). Previous treatment (injections, physiotherapy or surgery) was included to determine if any identified groups received different therapies.

The primary outcome was SPADI. This outcome measure was chosen as it has been shown to be feasible and have good construct validity, reliability and is responsive, as discussed in Chapter 2. EQ-5D-5L was included in order to evaluate if health status differences existed between any identified groups.

Returned questionnaires were matched to the ultrasound findings. This was done by allocating a unique identifiable number to each patient with an ultrasound report and documenting this number on the front corner of the questionnaire sent to the patient. Patients were also offered the opportunity to decline participation by completing a form which was included alongside the posted questionnaire.

4.4 **Statistical analysis**

Latent class analysis (LCA) was performed on ultrasound pathology findings. Latent class analysis is a form of structural equation modelling and is an unbiased method used to identify subgroups within a population: in this case people who share a distinct pattern of shoulder pathology. A ‘latent’ variable is the opposite of an observed variable (a variable measured by a researcher, such as height or weight), and may be referred to as a factor or construct. Latent variables are therefore inferred (via a mathematical model) from observed variables. This latent variable is usually discrete. The ‘class’ is characterised by a pattern of conditional probabilities that indicate the chance that these variables take on this latent value.

LCA is a model in which individual cases can be classified based on their pattern of responses using a probabilistic approach. The accuracy of the classification can be improved and bias can be eliminated in the analysis by including covariates such as age and gender.

Each of the pathologies recorded during the scan, coded as present (2) or absent (1), was included in the model, together with covariates age and sex. A rho prior value of 1 was set to stabilise estimates.

The optimum number of latent classes can be identified (assessed for best fit) using different methods including Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), 'consistent' AIC (CAIC), adjusted-BIC (a-BIC), entropy, G2, the proportion of 1000 random seeds associated with the best model and the bootstrap likelihood ratio test (BLRT). Lower values of AIC, BIC, CAIC, a-BIC and G2 are desirable, whilst higher values of entropy and solution stability are preferred. Solution stability was calculated as the proportion of 1000 random seeds that were associated with the best model. Previous work has shown that BLRT may be a better test to correctly identify the number of classes, although BIC may also be suitable (456). The BIC value has been demonstrated to be the best performing of the available information criteria, and is preferred over (AIC), consistent AIC or adjusted BIC [1]. BIC is also used for sparse data. Sparse data often occurs when the number of observed variables or the number of categories of these variables is large, as is the case in this study. BIC also takes parsimony into account i.e. BIC defines the optimal subgroups that explains the most variance and with the simplest specification. A lower BIC indicates a better model fit than a higher BIC. BIC also takes parsimony into account, thereby defining the optimal subgroups that explains the most variance and with the simplest specification.

Initial models used two hundred random starts to investigate whether the optimum number of classes was stable and to identify the optimum seed for the final model. Missing data were assumed to be missing at random (MAR) and for patients with missing pathology scores the model estimates were adjusted to include only the observed items (full information maximum likelihood).

The maximum posterior probability of membership (i.e. probability of membership observed across the different classes) was used to determine the most likely class membership for each patient. Patients were then assigned to the classes (hereafter groups) on this basis. For each group the corresponding

mean posterior probability was calculated to give an indication of the accuracy of group assignment.

Groups identified via LCA were then compared for age, sex, duration of pain (determined from the initial ultrasound scan referral, if documented), steroid injection given (according to the initial scan record), and the presence of each pathology. These details were also compared between patients who completed the questionnaire and those who did not, to check for responder bias. Questionnaire responses were compared between the pathology groups using quantile, Poisson or binary logistic regression, according to the outcome type, adjusting for age and sex. Appropriate checks were made that the data satisfied the test assumptions. Analyses used Stata v13.1.

The identification of subgroups can be done by other means instead of LCA. Cluster analysis is another statistical method to identify subgroups. This involves examining multivariate data to uncover clusters of homogenous observations. Different methods of cluster analysis exists, including hierarchical clustering and k-means clustering. Cluster analysis involves initially creating a distance of between individual points (such as a Euclidian distance in K-means cluster analysis). The underlying subgroup structure is then determined by optimising the intra-subgroup (within-cluster) variability of individual distance measures whilst maximising the inter-subgroup (between-cluster) variability. For example, for K-means cluster analysis (also known as a centroid model), the user chooses the number (*K)* of clusters and selects variables to define these clusters. Each cluster is randomly positioned at a point in the variable space and the variables are assigned to the nearest K clusters using Euclidean distance. Within-cluster means are then calculated and the clusters are re-positioned at this centroid point. The process is continued until convergence. K-means clustering has been used to identify homogeneous subgroups of patients with spinal cord injury pain (457).

There remains several limitations with cluster analysis: this includes the needs for there to be a similar metric for variables (e.g. distance rather than gender and marital status); there is no statistical criterion to choose number of clusters; and one cannot classify respondents with missing data.

Regression analysis has also been used to identify patients likely to respond to certain treatment. Regression analysis is a statistical approach of identifying subgroups working backwards from an outcome, such as response to treatment. This enable the identification of clinical characteristics most likely to respond to that therapy. For example, in order to identify patients with lower back pain who respond to manual therapy, Flynn *et al.* identified individual variables from history, examination and patient reported outcome measures. The authors then tested for the univariate association with success or non-success to treatment (458). The positive likelihood ratio was then calculated. Prediction variables were identified and inputted into a step-wise logistic regression equation to determine predictors. This differs from LCA as it works backwards from an outcome, and does not identify groups from the multiple variables.

The use of LCA is able to overcome these limitations. Its advantage over cluster modelling includes the ability to handle missing data better; better manage variables of mixed measurement types (such as dichotomous, ordinal and interval scales); and there are more formal criteria to make decisions on the number of clusters (459).

In a head to head comparison comparing cluster analysis with LCA methods, the use of the LCA methods offered the best combination of sensitivity to subgroups, ease of application and presentation of results (460). Artificial datasets with known subgroup memberships were also used to test the ability of these statistical analyses to correctly identify subgroups. All methods correctly did this.

In another comparison, LCA substantially outperformed K-means cluster analysis, when using data with known group membership (459).

4.5 **Results**

To identify 3000 eligible ultrasound scans, 3035 referral cards were reviewed. Reasons for exclusions were: 6 scans were technically difficult and the operator was therefore unable to identify all pathologies; 9 scan results were inaccessible on the results server; 17 were referred for soft tissue lumps only

and not for shoulder symptoms; 3 had guided procedures without diagnostic scan and therefore no report was provided.

4.5.1 Ultrasound pathology findings

In the 3000 patients selected the mean age was 54.6 years and 52% were female (Table 4.2). For 8 patients impingement could not be assessed due to difficulty in moving the patient's arm; impingement status was set to 'missing' for these patients. The most common pathologies were subacromial impingement (69%) and bursitis (68%), followed by ACJ degeneration (40%), tendinopathy (36%), calcific tendonitis (12%), biceps tenosynovitis (7%), glenohumeral osteoarthritis (6%), adhesive capsulitis (3%).

Table 4.2 Demographics and ultrasound findings in patients included in the full scan review, and those sent a questionnaire

	Full scan review n=3000	Questionnaire recipients (2322)	Responders n=777	Non-responders n=1545
Age, years: mean (SD)	54.6 (15.1)	54.1 (15.1)	56.4 (13.8)	53.0 (15.6)
Female: %	52%	52%	54%	51%
Pain duration, months: median (IQR)	5 (3, 9), n=1165	5 (3, 10), n=868	5 (3, 10), n=292	5 (3, 9), n=576
Steroid injection at time of scan: %	33%	31%	37%	28%
RC tear: %	26%	24%	27%	23%
Full thickness RC tear: %	19%	18%	20%	17%
Bursitis: %	68%	71%	72%	71%
Impingement: %	69% (/2992)	68% (/2314)	71% (/776)	67% (/1538)
Calcific tendinitis: %	12%	12%	14%	12%
ACJ degeneration: %	40%	45%	48%	43%
Glenohumeral OA: %	6%	5%	5%	6%
Adhesive capsulitis: %	3%	3%	4%	3%
Biceps tenosynovitis: %	7%	9%	9%	9%
Rotator cuff tendinopathy: %	36%	38%	40%	37%

4.5.2 Latent class analysis

The LCA suggested four or five groups existed (for full details see Table 4.3). The BIC, CAIC, a-BIC and entropy showed similar levels for the 4 and 5 class solution, although slightly favouring the 5 class solution. The overall proportion of 1000 random seeds associated with the ML model favoured the 4 class model. AIC, G^2 and BLRT favoured the five class solution.

Table 4.3 Model fit and stability measures for solutions with 2 to 6 classes

Number of classes	df	AIC	BIC	CAIC	a-BIC	Entropy	G^2	Solution %	BLRT p-value
1	502	655.3	2709.3	2718.3	260.7	1.00	2637.3	100	-
2	492	1771.2	1885.3	1904.3	1824.9	0.95	1733.2	35	0.010
3	482	853.4	1027.6	1056.6	935.4	0.87	795.4	100	0.010
4	472	495.9	730.1	769.2	606.3	0.77	417.9	100	0.010
5	462	419.0	713.3	762.3	557.6	0.78	321.0	85	0.010
6	452	410.5	764.9	823.9	577.4	0.75	292.5	50	0.180

Table 4.4 and 4.5 describes the 4 class and 5 class solution. Following a discussion with an expert group of shoulder surgeons (two consultants), rheumatologists (one consultant and one registrar) and radiologists (two consultants) at Leeds Teaching Hospitals NHS Trust, it was felt that the four class solution most closely resembled what was seen in clinical practice and therefore I retained the four group solution. Based on the patterns of pathology in each group, we interpreted that they represented: bursitis with limited inflammation elsewhere (group 1); bursitis with extensive inflammation (group 2); RC tears (group 3); limited pathology (group 4) (Table 4.4).

Group 1 was the largest (43%; Table 4.4); the other three groups each represented approximately 20%. The groups were similar in gender balance or duration of pain prior to the first scan. Patients in group 4 were the youngest; 42% had no pathologies recorded, and a further 42% had just 1 pathology

reported (Figure 4.1). In group 4, mean age was similar to group 1; all patients in group 1 had bursitis but few had tendinopathy or ACJ degeneration. In group 2, on average 20 years older than groups 1 and 4, almost all patients had bursitis, RC tendinopathy and ACJ degeneration, and a quarter had biceps tenosynovitis. Patients in group 3 were the oldest on average; all had RC tears, which were full-thickness in the majority. Patients in this group had the highest rate of glenohumeral osteoarthritis, as might be expected for their age, but a smaller proportion had ACJ degeneration compared to group 2. Nearly all patients in group 3 had impingement; however, comparatively few had bursitis compared to groups 1 and 2.

Table 4.4 Demographic characteristics and ultrasound pathology findings in each of four pathology groups

	Bursitis (limited inflammation) n=1280	Bursitis (extensive inflammation) n=595	RC tear n=558	Limited pathology n=567
% of sample	43	20	18	19
Age, years: mean (SD)	47.6 (11.5)	64.2 (10.5)	69.1 (11.2)	46.1 (13.5)
Female: %	54	52	51	46
Pain duration, months*: median (IQR)	5 (3, 10)	5 (3, 9)	5 (3, 9)	4 (3, 8)
Steroid injection at time of scan: %	44	37	13	26
RC tear (y/n): %	2	24	100	6
Full thickness RC tear: %	1	13	86	<1
Bursitis: %	100	94	30	7
Impingement: %	88	65	91	6
Calcific tendinitis: %	14	18	5	9
ACJ degeneration: %	26	83	54	15
Glenohumeral OA: %	<1	10	16	2
Adhesive capsulitis: %	<1	3	<1	12

Biceps tenosynovitis: %	<1	25	10	2
Rotator cuff tendinopathy: %	23	92	24	20
Probability of membership: mean	0.88	0.80	0.89	0.93

*n=507; 198; 233; 227

Table 4.5 Five class solution from latent class analysis

	Bursitis (limited inflammation) n=1291	Inflammation (impingement) n=448	Inflammation (no impingement) n=306	RC tear n=523	Limited pathology n=432
% of sample	43	15	10	18	14
Age, years: mean (SD)	46.8 (11.2)	64.0 (10.1)	65.0 (10.6)	69.0 (11.3)	43.1 (11.9)
Female: %	54	54	45	52	48
Pain duration, months*: median (IQR)	5 (3, 10)	5 (3, 9)	5 (3, 10)	5 (3, 9)	4 (3, 8)
Steroid injection at time of scan: %	44	33	41	12	23
RC tear (y/n): %	3	26	20	99	6

(FT tear: %	1	20	-	90	<1
Bursitis: %	98	100	57	28	<1
Impingement**: %	86	98	<1	95	3
Calcific tendinitis: %	14	16	18	5	8
ACJ degeneration: %	23	91	65	52	7
Glenohumeral OA: %	<1	7	13	17	<1
Adhesive capsulitis: %	<1	2	9	<1	12
Biceps tenosynovitis: %	<1	30	9	9	<1
Rotator cuff tendinopathy: %	23	85	77	21	16
Probability of membership: mean	0.88	0.80	0.75	0.90	0.91

*n=515; 106; 151; 219; 174 **n=1287; 446; 305; 522; 432

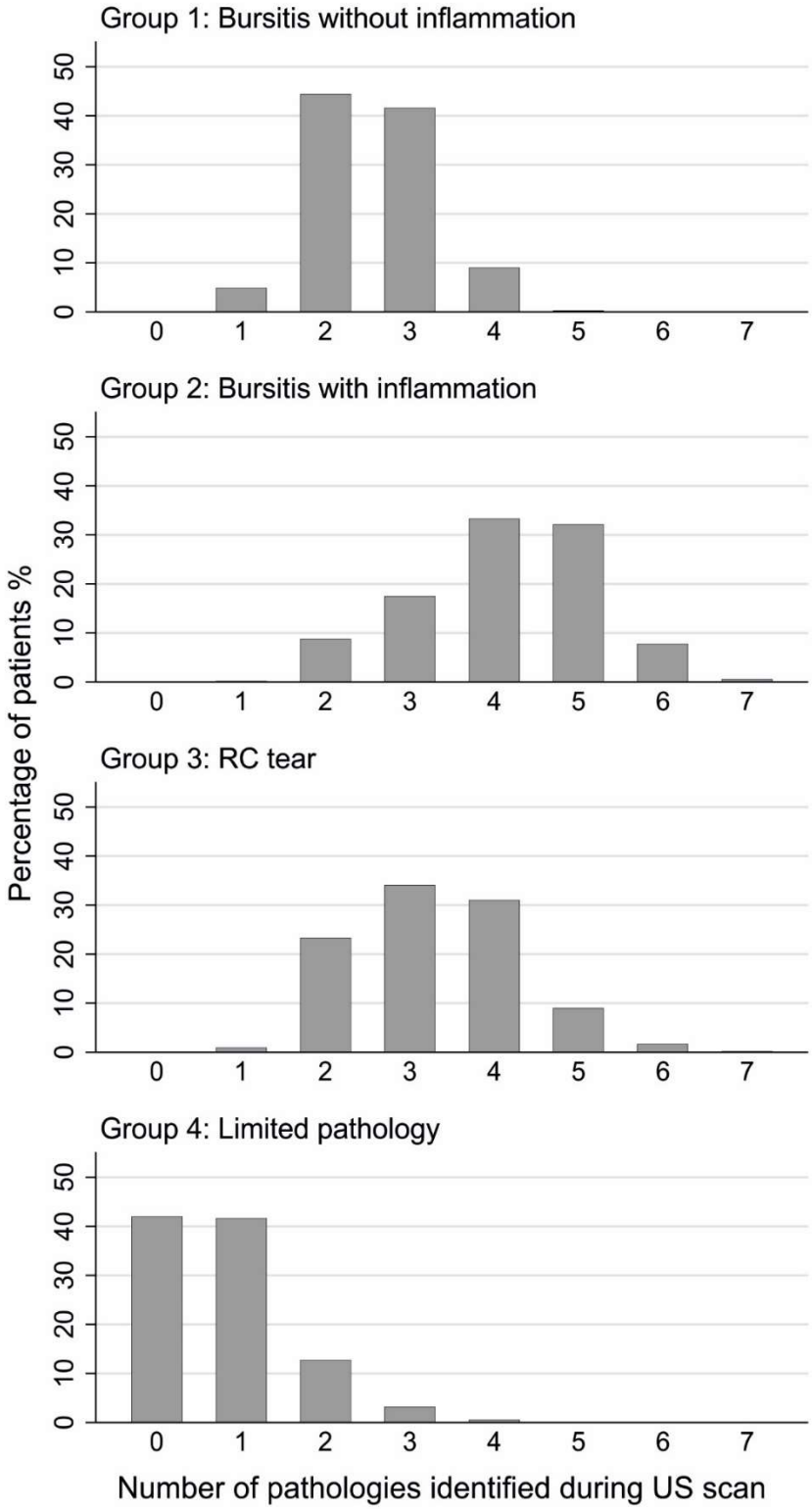


Figure 4.1 Pathology count by group

4.5.3 Patient questionnaire findings

A postal questionnaire was sent to all eligible patients scanned in 2013 (n= 2322). Of these patients, 777 completed questionnaires (33%); I received replies from a further 233 (10%) who declined to participate. Responders and non-responders were similar in gender balance, age and ultrasound pathology findings (Table 4.2). Some respondents reported a diagnosis of rheumatoid arthritis (RA) (n=87). Ultrasound findings did not show intra-articular synovitis in the RA-reporting group. Re-running the LCA in questionnaire respondents who did not report having RA (n=690 out of a total of 777 respondents) resulted in very similar results to the full (n=3000) LCA (Table 4.6).

Using the four group solution, the patients who returned the questionnaire were generally assigned to the same groups they had been assigned to when the LCA was run in the full cohort (exact agreement over group assignment in 87% of cases); the five group solution was almost exactly the same as the four group solution for groups 1-3, but a limited number (n=17) of patients with adhesive capsulitis were moved from group 4 to form a separate group. I opted to retain the four class solution to avoid overfitting the data at this stage.

Table 4.6 Comparison of 4 group solutions obtained in questionnaire respondents without RA (n=690)

	Re-calculated group excluding RA				
Original group	1	2	3	4	Total
1	238	13	0	40	291
2	3	160	0	14	177
3	0	9	113	0	122
4	8	0	0	92	100
Total	249	182	113	146	690

Questionnaires were completed by 30%, 36%, 34% and 25% of patients in groups 1-4 respectively. Older patients were more likely to respond; there were no differences in adjusted response rate between groups [probability of response in group 1=0.31 (0.28, 0.34), group 2=0.33 (0.29, 0.37), group 3=0.30 (0.26, 0.35), group 4=0.28 (0.23, 0.32); chi-sq=3.04, p=0.386].

Questionnaire results for all respondents are presented in Table 4.7; 67% still experienced pain at a median (IQR) 25 (22, 29) months since their scan. Ultrasound findings by group (restricted to questionnaire respondents) are in Table 4.8. Follow-up duration was similar in the four groups (Table 4.10). Between 63 (groups 1&2) and 77% (group 3) of patients reported persistent pain at follow-up.

Table 4.7 Questionnaire results from all respondents, excluding those reporting rheumatoid arthritis (n=690)

	All respondents	N with data
Age, years: mean (SD)	56.0 (13.7)	690
Female: %	54	690
Smoker: %	39	635
Comorbidity count: median (IQR)	1 (0, 2)	553
Painful sites count (including target): median (IQR)	3 (1, 6)	690
Follow-up, months: median (IQR)	25 (22, 29)	684
Had shoulder fracture before scan: (%)	1	671
Had shoulder dislocation before scan: (%)	1	672
Had breast/shoulder cancer before scan: (%)	<1	671
Had major injury to target shoulder before scan: (%)	9	670
Had shoulder fracture since scan: (%)	<1	669
Had shoulder dislocation since scan: (%)	<1	668
Had breast/shoulder cancer since scan: (%)	<1	667
Had major injury to target shoulder since scan: (%)	3	670
Had physiotherapy since scan: (%)	62	630
Had injection since scan: (%)	67	639
Had >1 injection since scan: (%)	29	629
Had surgery since scan: (%)	22	620
Still has shoulder pain: (%)	66	673
If still in pain:		
Pain duration, months: median (IQR)	24 (12, 36)	366/442
Has pain free periods: (%)	73	435/442
Experiences pain on moving in a certain way: (%)	91	435/442
If not still in pain:		
How long since last had pain, months: median (IQR)	12 (6, 18)	175/231
How long did pain last, months: median (IQR)	10 (4, 18)	198/231
Symptoms at time of questionnaire (all respondents):		
SPADI pain: median (IQR)	36 (6, 64)	678
SPADI difficulty: median (IQR)	18 (0, 46)	674
SPADI total: median (IQR)	28 (5, 53)	672
Shoulder activity score: median (IQR)	6 (3, 10)	640
EQ5D health index score: median (IQR)	0.8 (0.6, 0.8)	648
EQ5D VAS: median (IQR)	75 (60, 90)	681

EQ5D anxiety or depression (>0): (%)	33	663
Depression reported in comorbidity list: (%)	16	628
Difficulty standing from sitting (>1): (%)	17	674

*Date of questionnaire completion missing **In patients who still had shoulder pain

Table 4.8 Ultrasound findings for the four pathology groups restricted to patients who responded to the survey (n=690)

	Bursitis (limited inflammation) n=291	Bursitis (extensive inflammation) n=177	RC tear n=122	Limited pathology n=100
% of sample	42	26	18	14
Pain duration, months*: median (IQR)	6 (3, 10)	5 (3, 10)	5 (3, 8)	4 (3, 8)
Steroid injection at time of scan: %	46	42	14	31
RC tear: %	1	27	100	8
Full thickness RC tear: %	<1	16	76	-
Bursitis: %	100	97	28	3
Impingement: %	86	68	92	8
Calcific tendinitis: %	14	16	5	18
ACJ degeneration: %	28	88	57	16
Glenohumeral OA: %	<1	8	13	-
Adhesive capsulitis: %	<1	3	<1	17
Biceps tenosynovitis: %	2	22	13	1
Rotator cuff tendinopathy: %	23	95	20	17
Probability of membership: mean	0.86	0.81	0.89	0.94

*n=118; 60; 57; 35

Table 4.9 Questionnaire outcomes summarised by pathology group, excluding those reporting rheumatoid arthritis (n=690)

	Bursitis (limited inflammation) n=291	Bursitis (extensive inflammation) n=177	RC tear n=122	Limited pathology n=100
% of sample	40	39	33	42
Age, years: mean (SD)	49.9 (11.1)	64.8 (9.2)	67.1 (10.4)	47.5 (12.6)
Female: %	63	45	47	55
Smoker: %	40	39	33	42
Comorbidity count: median (IQR)	1 (0, 2)	2 (1, 2)	2 (1, 3)	1 (0, 2)
Painful sites count (including target): median (IQR)	3 (1, 6)	3 (1, 7)	3 (1, 6)	2 (1, 4)
Follow-up, months: median (IQR)	26 (23, 29)	26 (22, 29)	25 (23, 29)	24 (21, 26)
Had shoulder fracture before scan: (%)	2	2	<1	1
Had shoulder dislocation before scan: (%)	1	-	4	1
Had breast/shoulder cancer before scan: (%)	<1	-	-	-
Had major injury to target shoulder before scan: (%)	7	8	18	3
Had shoulder fracture since scan: (%)	<1	1	-	1
Had shoulder dislocation since scan: (%)	<1	-	-	-
Had breast/shoulder cancer since scan: (%)	<1	<1	-	-

Had major injury to target shoulder since scan: (%)	1	2	7	1
Had physiotherapy since scan: (%)	65	62	59	58
Had injection since scan: (%)	76	67	48	61
Had >1 injection since scan: (%)	33	30	22	24
Had surgery since scan: (%)	23	21	28	16
Still has shoulder pain: (%)	63	63	77	64
If still in pain:				
Pain duration, months: median (IQR)	24 (12, 36)	21 (12, 36)	25 (12, 36)	24 (18, 36)
Has pain free periods: (%)	70	77	72	77
Experiences pain on moving in a certain way: (%)	91	93	92	85
If not still in pain:				
How long since last had pain, months: median (IQR)	12 (6, 17)	13 (12, 20)	12 (6, 18)	12 (10, 20)
How long did pain last, months: median (IQR)	9 (3, 15)	9 (5, 18)	12 (12, 18)	6 (4, 12)
Symptoms at time of questionnaire:				
SPADI pain: median (IQR)	34 (4, 62)	26 (2, 62)	48 (18, 66)	32 (6, 64)
SPADI difficulty: median (IQR)	13 (0, 45)	14 (0, 43)	30 (10, 54)	9 (0, 38)
SPADI total: median (IQR)	24 (3, 52)	21 (3, 51)	41 (15, 59)	25 (5, 49)
Shoulder activity score: median (IQR)	6 (3, 10)	6 (3, 10)	5 (3, 9)	7 (4, 11)

EQ5D health index score: median (IQR)	0.8 (0.6, 0.8)	0.7 (0.6, 0.8)	0.7 (0.5, 0.8)	0.8 (0.7, 0.8)
EQ5D VAS: median (IQR)	80 (55, 90)	80 (60, 90)	75 (60, 80)	80 (70, 90)
EQ5D anxiety or depression (>0): (%)	34	30	40	29
Depression reported in comorbidity list: (%)	17	14	18	14
Difficulty standing from sitting (>1): (%)	16	20	21	10

Data was not available for all outcomes for all survey responders; see Table 4.10 for numbers of patients with data available

Table 4.10 Numbers of patients with data available for each survey item, by pathology group

	Bursitis (limited inflammation) n=291	Bursitis (extensive inflammation) n=177	RC tear n=122	Limited pathology n=100
Smoker:	270	161	108	96
Comorbidity count: median (IQR)	238	135	88	92
Painful sites count (including target): median (IQR)	291	177	122	100
Follow-up, months: median (IQR)	289	177	121	97
Had shoulder fracture before scan:	288	171	116	96

Had shoulder dislocation before scan:	288	170	118	96
Had breast/shoulder cancer before scan:	288	169	118	96
Had major injury to target shoulder before scan:	282	172	119	97
Had shoulder fracture since scan:	284	171	116	98
Had shoulder dislocation since scan:	286	168	116	98
Had breast/shoulder cancer since scan:	284	169	116	98
Had major injury to target shoulder since scan:	284	168	119	99
Had physiotherapy since scan:	260	159	115	96
Had injection since scan:	274	160	110	95
Had >1 injection since scan:	274	160	110	95
Had surgery since scan:	252	169	109	90
Still has shoulder pain:	287	171	117	98
If still in pain:				
Pain duration, months: median (IQR)	153/181	87/108	70/90	56/63
Has pain free periods:	176/181	108/108	89/90	62/63
Experiences pain on moving in a certain way:	179/181	107/108	88/90	61/63
If not still in pain:				
How long since last had pain, months: median (IQR)	84/106	47/63	20/27	24/35
How long did pain last, months: median (IQR)	92/106	54/63	21/27	31/35

Symptoms at time of questionnaire:				
SPADI pain: median (IQR)	287	170	121	100
SPADI difficulty: median (IQR)	282	171	121	100
SPADI total: median (IQR)	282	169	121	100
Shoulder activity score: median (IQR)	271	162	111	96
EQ5D health index score: median (IQR)	271	168	114	95
EQ5D VAS: median (IQR)	287	174	121	99
EQ5D anxiety or depression (>0):	276	171	117	99
Depression reported in comorbidity list:	270	155	106	97
Difficulty standing from sitting (>1):	282	175	118	99

The most commonly-reported painful sites other than the target shoulder were lower back (36%), neck (33%) and knees, either ipsi- (27%) or contralateral (24%) to the target shoulder (Figure 4.2). Adjusted estimates of the number of painful sites were highest in group 2 (mean 4.2) and lowest in group 4 (mean 3.0; Table 4.12).

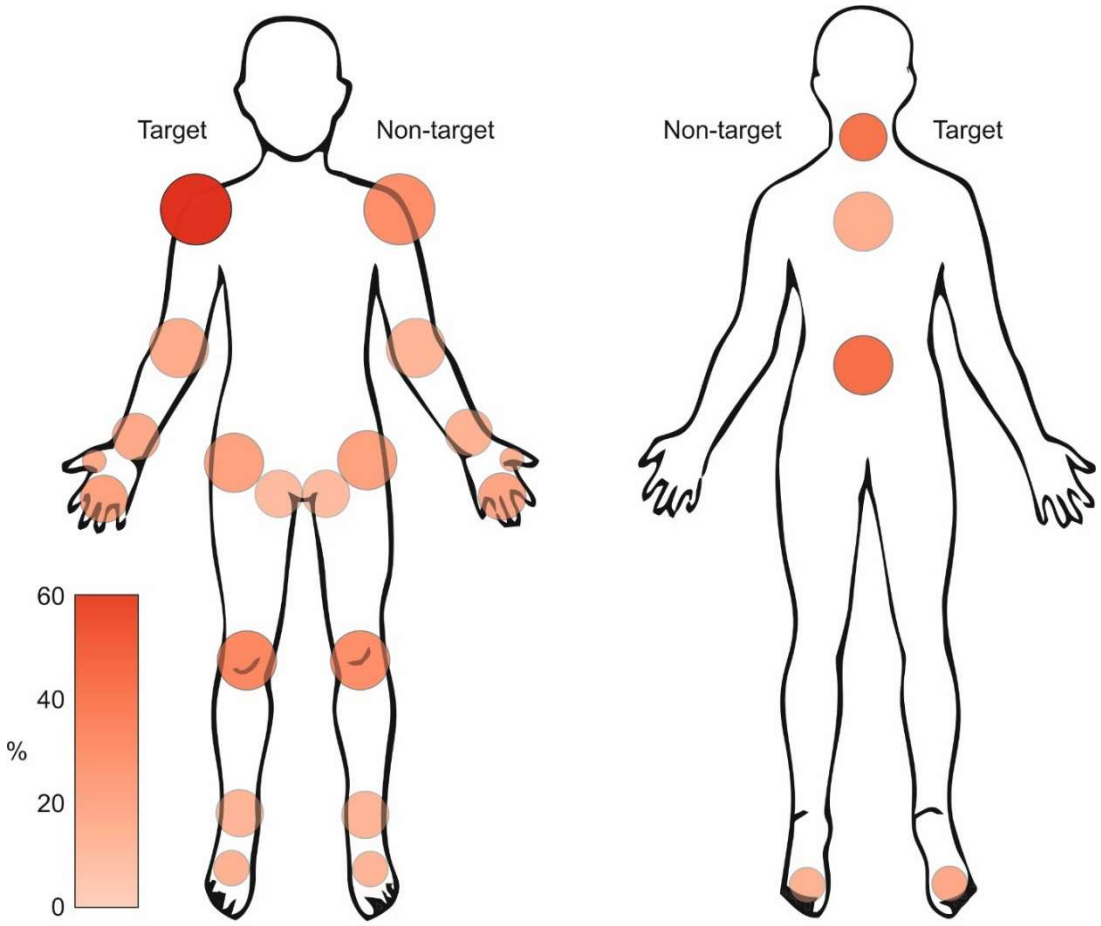


Figure 4.2 Joints reported to be painful at the time of the survey, according to whether or not they were on the same side as the target shoulder

There was descriptive evidence that treatment differed according to presence of certain individual pathologies (see Table 4.11).

Table 4.11 Therapies received according to the presence of individual ultrasound-detected pathologies

		Steroid injection (at scan)	Steroid injection (since scan)	Physiotherapy	Surgery
Number with data		690	639	630	620
RC tear		45	72	62	19
Absent		14	50	63	32
Present					
Bursitis		22	53	59	22
Absent		43	72	63	22
Present					
Impingement	Absent	46	72	60	17
	Present	33	64	63	24
Calcific tendinitis	Absent	38	67	61	21
	Present	36	67	72	31
ACJ degeneration	Absent	38	67	65	23
	Present	37	67	59	22
GHJ OA	Absent	38	67	62	23
	Present	19	57	60	11
Adhesive capsulitis	Absent	38	67	62	23
	Present	33	68	59	9
Biceps tenosynovitis	Absent	37	67	62	22
	Present	43	64	60	21
Other tendinopathy	Absent	36	66	60	22
	Present	39	69	65	22

All values in the table are %

There were clear differences in treatment at the group level for steroid injection ($p<0.001$) and surgery ($p=0.015$) (Table 4.12). Those in group 1 (bursitis with limited inflammation) were the most likely to have had steroid injection(s) (adjusted probability 76%) while those in group 3 (RC tears) were least likely (49%). Patients in group 3 were the most likely to have had surgery (35%); surgery was least likely in the limited pathology group (14%). In patients with bursitis, those in group 3 were less likely to have a steroid injection at time of scan than those in groups 1 & 2 [estimated probability of injection (95% CI)

group 1=0.48 (0.41, 0.54); group 2=0.41 (0.33, 0.49); group 3=0.20 (0.06, 0.33); chi-sq=8.6, p=0.014]. Adjusted rates of physiotherapy did not differ between groups.

Groups differed in the severity of their reported symptoms. Group 3 (RC tears) were more likely to still have pain at follow-up (Table 4.12) and they reported the highest levels of SPADI pain; a similar trend was seen for SPADI difficulty scores (Table 4.9 and Table 4.12; Figure 4.3). These trends were not explained by the higher rate of surgery in group 3; those who had surgery reported lower scores [adjusted difference in median total score (95% CI) -19 (-38, 0); z=-1.98, p=0.048]. The differences in total SPADI by surgery were negligible for group 1 [-8 (-22, 5); z=-1.23, p=0.220] and group 2 [0 (-17, 17); z=-0.04, p=0.965]. In contrast, in group 4 total SPADI was substantively higher in the patients who had surgery [25 (-1, 51); z=1.89, p=0.059].

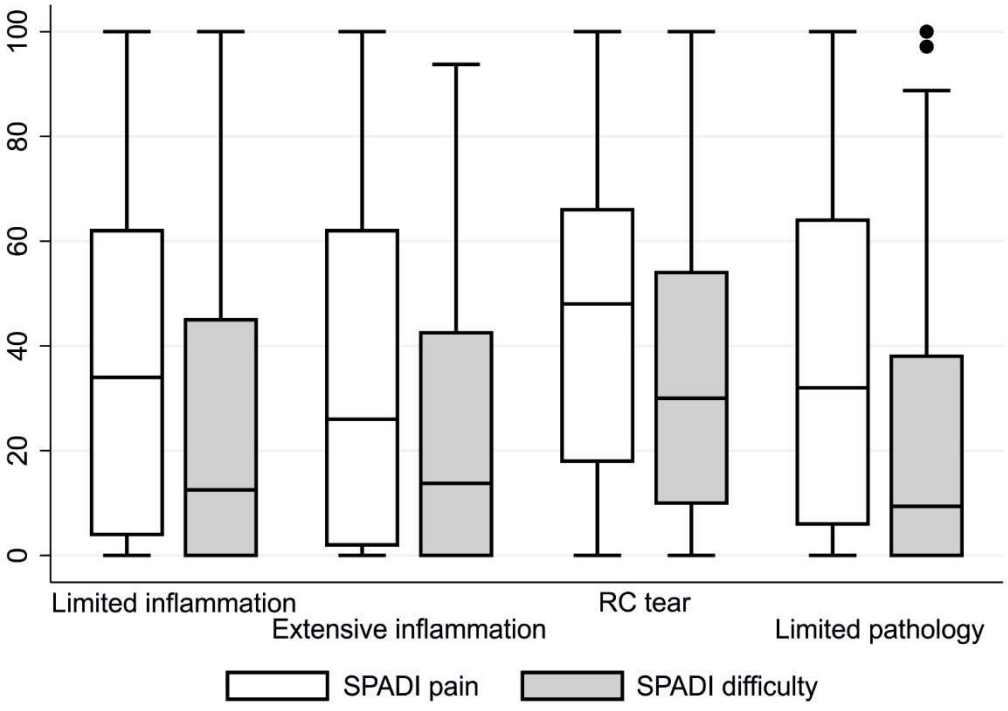


Figure 4.3 SPADI boxplot

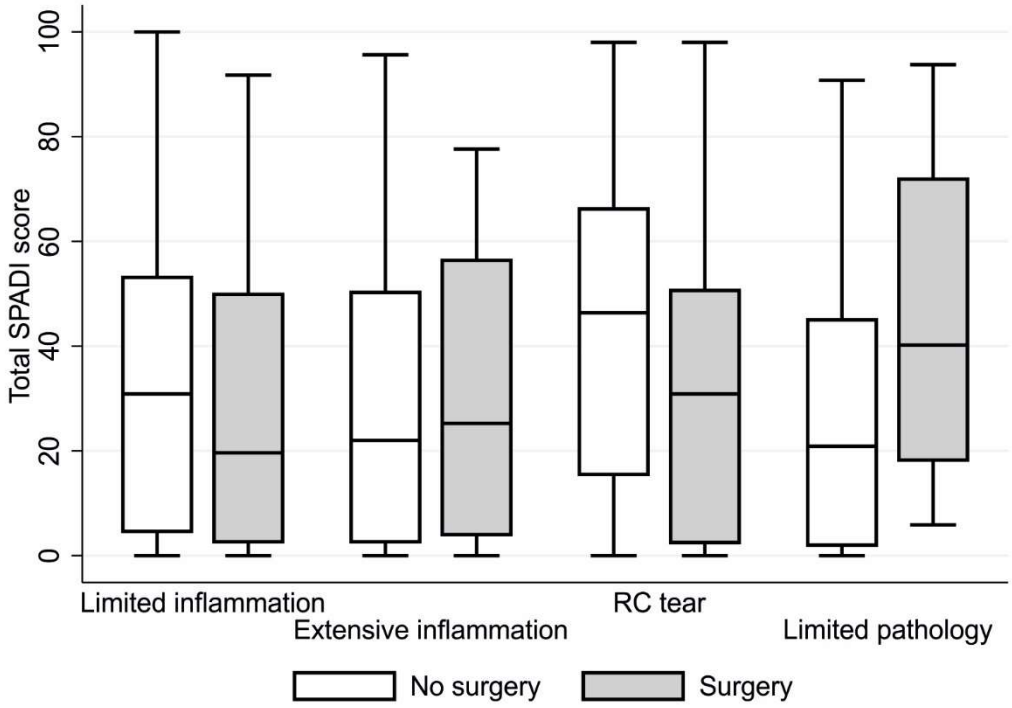


Figure 4.4 Total SPADI scores according to whether patient had surgery between scan and survey

Patients in group 4 who had surgery were more likely to report a diagnosis of depression than those who had not (adjusted probability (95% CI) 0.40 (0.15, 0.66) vs. 0.09 (0.02, 0.15), while surgery was not associated with depression in the other groups (interaction effect group X surgery chi-sq=9.4, p=0.025). However, the nature of the association between symptoms, surgery and depression cannot be determined in this cross-sectional study.

There were no substantive age- and sex-adjusted differences between the groups in shoulder activity level, EQ5D index score, EQ5D health VAS score, the number of comorbidities reported, or the odds of reporting difficulty standing from sitting.

Table 4.12 Age- and sex-adjusted comparisons between pathology groups for key outcomes, excluding those reporting rheumatoid arthritis (n=690)

	Bursitis (limited inflammation)	Bursitis (extensive inflammation)	RC tear	Limited pathology	Test result, *P* value
Number of painful sites*	4.0 (3.7, 4.2)	4.2 (3.9, 4.6)	3.6 (3.3, 4.0)	3.0 (2.6, 3.3)	X^2=29.0, p<0.001
Steroid injection at time of scan	0.49 (0.42, 0.55)	0.40 (0.32, 0.47)	0.12 (0.06, 0.18)	0.34 (0.24, 0.44)	X^2=40.1, p<0.001
Steroid injection since scan	0.76 (0.70, 0.81)	0.67 (0.69, 0.75)	0.49 (0.39, 0.59)	0.63 (0.52, 0.73)	X^2=20.3, p<0.001
Physiotherapy	0.59 (0.53, 0.66)	0.67 (0.60, 0.75)	0.67 (0.58, 0.76)	0.53 (0.43, 0.63)	X^2=5.0, p=0.171
Surgery	0.19 (0.15, 0.24)	0.25 (0.18, 0.33)	0.35 (0.25, 0.46)	0.14 (0.07, 0.21)	X^2=10.5, p=0.015
Pain at follow-up	0.59 (0.53, 0.65)	0.68 (0.61, 0.75)	0.81 (0.74, 0.88)	0.60 (0.50, 0.70)	X^2=17.3, p<0.001
SPADI pain**	29 (22, 36)	32 (23, 41)	51 (40, 62)	28 (17, 40)	$F_{(3, 672)}$=4.0, p=0.008
SPADI difficulty**	15 (10, 20)	19 (12, 25)	31 (23, 39)	11 (3, 20)	$F_{(3, 668)}$=4.1, p=0.006

SPADI total**	23 (18, 29)	25 (18, 32)	42 (34, 51)	20 (11, 29)	$F_{(3, 666)}$=5.3, p=0.001

*Adjusted mean (95% CI) presented **Adjusted median (95% CI) presented

All values in the table are adjusted probability of the outcome (95% CI) unless otherwise stated.

4.6 Discussion

This study has demonstrated, for the first time, clustering of ultrasound pathologies into four groups. These groups reported different treatments and to some extent had different age and sex-adjusted outcomes at 2 years; however, due to the low questionnaire completion rate, the longitudinal results need to be interpreted with caution.

As discussed in Chapter 2, there is limited evidence-base on the role of imaging in the shoulder pain care pathway and there is conflicting guidance on the use of ultrasound in the shoulder pain pathway (372, 382). Although the diagnosis and management of many common painful musculoskeletal problems generally does not require imaging as part of routine care, the uncertainty in clinical evaluation, poor patient outcomes and increasing use of ultrasound supports critical evaluation of the usefulness of a pathology-based classification. Evidence from a recent pragmatic randomised trial reported no difference in patient perceived recovery between those with ultrasound tailored treatment and usual care groups (461). However, in that study, ultrasound guided treatment was targeted at individual pathologies, and it would be interesting to see if outcomes would differ using our novel pathology based classification.

The clinical validity of the pathology groups identified in this study will require further evaluation in future studies. Conceivably patients with just one pathology may respond differently to treatment compared to patients in whom the same pathology co-occurs with other pathologies. While we were unable to examine the efficacy of different treatments, different patterns of treatment were reported. Group 1 was most likely to receive steroid injections. Steroid treatment may help with subacromial bursitis in the short-term (462), which may explain the treatment in this group. Groups 1 and 2 may represent a spectrum; group 2 are older and if we were to follow patients similar to those in group 1 over time, their patterns of shoulder pathology may eventually resemble group 2. Group 3 was the oldest group, confirming previous studies

that have shown RC tears increase in prevalence with age (463). They were less likely to receive steroid injections, even if they had concurrent bursitis, and more likely to undergo surgery. Steroid injections may impede tendon repair and RC tears offer a surgical target, which may explain this variation in treatment. Group 3 also had the highest level of current pain and functional impairment. Surgical repair techniques of RC tears vary and surgery has shown conflicting results in improving outcomes in patients with shoulder pain (464-466). My data suggests that those who had surgery reported lower levels of pain and functional impairment. Group 4 was the youngest group and a smaller proportion of these patients reported having surgery, because fewer had detectable pathologies present. Group 4 also had the lowest levels of pain and functional disability of all the groups.

Many in group 4 (42%) had no pathology; some of these patients may have improved at the time of scan. Another explanation is that other pathologies were present that ultrasound could not detect. Ultrasound is as sensitive and specific as MRI in detecting RC disorders (273) but further work is required to understand its sensitivity and specificity in detecting other pathologies such as calcific tendinopathy. Furthermore, pathologies such as labral tears require MRI for identification (467, 468). In addition, imaging-detected pathologies may not correlate with clinical findings. In this study, 16% of patients without detectable pathology received steroid injections at the time of their scan; many reports documented that this was after discussion with the patient, and in some cases because clinical impingement was suspected even though this was not confirmed by the scan. A further explanation could be that the pain may be referred from other regions, such as the neck. The cause of chronic pain is multifactorial, and other features apart from imaging pathology play a role in characterising pain. Psychological factors such as fear-avoidance, depression and poor quality of life can result in worse pain, function and perceived recovery outcomes (95, 469). Ultrasound detected pathologies have previously been reported in asymptomatic individuals and further work is required to understand what factors result in the development and progression of symptoms in these individuals (452, 463, 464, 470).

4.7 **Limitations**

There are a number of limitations to this study. This study was undertaken in a single centre, which means that these findings may not be necessarily translatable to other populations. However, my sample size was large and the demographics of included patients seem similar to other large community cohorts (2, 471). The scans performed by the radiologists and sonographers in our department may also differ from other centres; although the scans are performed using a standardised procedure (472), local protocols and interpretations of pathology may differ. Although the radiographers in this study followed a standardised method of performing ultrasound scans of shoulders (472), standardised reporting of all pathologies was not routine so if pathology was not documented, it was assumed absent. It is possible that some pathologies may not have been reported, especially if lesions that are considered more severe or clinically relevant are primarily reported. Impingement was assumed in all patients with complete RC tears, although this was not reported in all cases. This may have implications on the ultrasound groupings. The existence of a putative fifth group, which only represented 2% of the sample, should be confirmed in a prospective study with tighter inclusion criteria and standardised reporting of pathology. This will be discussed in Chapter 5. Group 3 had the highest level of glenohumeral OA but a lower frequency of ACJ degeneration; the latter finding may be a result of non-standardised reporting, although it may also be an artefact introduced as a result of the groupings formed from LCA. There was no control group, limiting the interpretation of pathologies and symptoms.

Our local care pathway recommends that patients over the age of 65 with shoulder pain undergo a radiograph of their shoulder, which may result in a channelling bias as patients with radiographic OA may not receive an ultrasound. In this study, local recommendations suggested that patients were referred for an ultrasound scan if they have moderate-severe pain and not responding to physiotherapy, which could have led to selection bias in our

cohort. However, it would seem that this group will likely be typical of shoulder pain patients requiring investigation in potential future care pathways. The patient questionnaire was retrospective, raising the possibility of recall bias. Only 33% completed the questionnaires, therefore there is potential for selection bias. However, my work suggests that completers and non-completers were very similar in demographic characteristics and pathology findings. This was a retrospective study, so we were unable to explore inter-reader reliability, especially in partial RC tears, where a recent review has shown that ultrasound has some difficulty in diagnosing this pathology (273). Previous work has shown that for most shoulder pathologies, the inter-rater reliability for two of the present sonographers was acceptable (455).

Although I looked at associations between baseline pathologies and outcomes, the absence of baseline clinical data means I could not evaluate the predictive value of ultrasound. As discussed in Chapter 2, there have been previous attempts at identifying predictors of outcomes in people with shoulder pain (473-477). Pain characteristics such as worse baseline pain, duration of pain, concomitant psychological complaints, other concomitant musculoskeletal problems and repetitive shoulder action resulted in worse outcomes (92, 474, 476, 477). Existing prognostic models to improve shoulder pain management have yet to be validated and assessed for clinical utility (476, 478). There are very few studies evaluating the prognostic role of ultrasound in shoulder pain: one suggested that the absence of subacromial bursa pathology may be a predictor of excellent outcomes at 3 weeks (473). A prospective longitudinal study with baseline data using my classification system may help understand the predictive value of ultrasound. This will be discussed in Chapter 5.

The prognostic value of a pathology-based classification needs to be established before consequent treatment pathways can be explored. Treatment may act as a mediator to the outcome of interest, SPADI. The lack of baseline data and therefore inability to measure change prohibits the analysis of treatment as a mediator. In addition, it would be difficult to understand the role of physiotherapy, steroid injections or surgery in an

observational study as there is marked heterogeneity in treatment, such as dose, frequency, type (of steroid or exercises prescribed by physiotherapy) and surgical technique.

4.8 **Conclusion**

This study demonstrates, for the first time, that patients undergoing ultrasound scans for shoulder pain can be grouped according to pathology patterns. My data suggests these groups may receive different treatment and have different outcomes. This preliminary data supports further exploration of the potential benefits of a pathology-based classification for shoulder pain.

5 Chapter 5 - A prospective cohort study to confirm groups of imaging detected pathologies exist and understand how these groups differ in their outcomes

5.1 Introduction

As discussed in Chapter 2, shoulder pain is common and 51% of affected individuals continue to have pain 6 months later. This may be a result of the inability to identify subgroups which would allow for targeted therapies and treatment success. Understanding patterns of imaging-detected shoulder pathologies may be one method of identifying subgroups. Ultrasound has high sensitivity and specificity for rotator cuff (RC) disorders, including RC tears and inflammatory pathologies such as bursitis. In Chapter 4, I undertook a retrospective cohort study demonstrating groups of ultrasound pathologies in the shoulder existed, and these groups may have different outcomes. However, this was a retrospective study lacking baseline data and standardised reporting.

This Chapter describes a prospective study evaluating 500 patients who attended for their first ultrasound scan of their shoulder, and explores outcomes for each group.

5.2 Aims

This Chapter aimed to:

1. Confirm preliminary findings from Chapter 4 that people with shoulder pain can be classified into distinct groups according to ultrasound pathology, once standardised reporting has been introduced and other relevant covariates are included
2. Determine if accurately-detected inflammation could predict medium-term outcomes in pathology-based groups or individual pathologies
3. Explore response to steroid injection, used for its anti-inflammatory effects, in patients with and without ultrasound-detected inflammation in different groups at 2 weeks.

4. Explore the response of steroid injections in patients with bursitis, with and without RC tears.

5.3 Methods

The (Leeds Observational Cohort Ultrasound Study) LOCUS study was carried out with ethical approval from North East - Newcastle & North Tyneside 2 Research Ethics Committee (16/NE/0108) and given Research and Development permission from Leeds Teaching Hospitals Trust (R&I number RR16/128 (201260).

5.3.1 Study design and study population

I conducted a prospective, observational study on 500 community-based patients referred by their primary care practitioner for a routine ultrasound scan of their painful shoulder from October 2016-December 2017. Scans were performed in a single radiology unit in England.

Patients received ultrasound-guided corticosteroid injections at their ultrasound appointment according to GP request and ultrasound findings. Patients received subsequent therapies according to usual care.

Inclusion criteria were: age > 18 years old, ability to provide informed consent, first ultrasound scan at recruitment (determined by clinical records). Patients were excluded if they had an inflammatory arthritis, previous fracture/dislocation of the affected shoulder, previous surgery on the affected shoulder, a steroid injection or physiotherapy for the target shoulder within the prior 6 weeks, complex regional pain syndrome or were referred for reasons other than suspected mechanical shoulder pain.

5.3.2 Data collection

Patients completed a paper questionnaire at baseline (clinic visit) and 6 months (via mail). Data collected included age, gender, body mass index (BMI), disease duration prior to scan, currently in pain (yes/no), co-morbidities and other joints affected. Outcome measures included Shoulder Pain and

Disability Index (SPADI), Oxford Shoulder Score (OSS), Pain-DETECT, quality of life (EQ-5D-5L), Hospital Anxiety and Depression Scale (HADS), Brief Illness Perception Questionnaire, Pain Self Efficacy Questionnaire (PSEQ) and Brophy & Marx shoulder activity scale (SAS). Guidelines for shoulder problems recommend treatment of either physiotherapy, corticosteroid injections, analgesics (including NSAIDs) or surgery (378). These treatments were recorded prior to initial scan at baseline and treatments received during the study were collected at 6 months. Analgesia use was recorded at the end of the 6-month follow-up period. To verify analgesia use, repeat prescriptions for analgesia (NSAIDS and opioids) were identified from primary-care electronic medical records (479).

At the 2 week time-point, patients were asked to complete a SPADI. At 3 months, patients were asked about treatments received since baseline: analgesia, physiotherapy, injections, or surgery. Both 2 week and 3 month data were collected via telephone or email.

Scans were performed using GE LOGIQ E9 machines at the Radiology Department at Chapel Allerton Hospital, Leeds, UK. To ensure comprehensive and consistent reporting, the Radiology Department undertook a consensus session where definitions for ten ultrasound pathologies and standardised scanning examination and reporting for these pathologies were agreed (table S1). The decision to include the selected pathologies was based on previous work, where the most frequently reported pathologies were identified (265). Pathologies were reported as present/absent. Three consultant radiologists, two specialist trainees, and three senior sonographers undertook scanning.

To avoid recruitment bias, quota sampling was used in four categories: gender (male/female) and age (younger/older split at the median); target proportions of patients falling into these categories have been determined from the retrospective study described in Chapter 4.

In order to maximise the response rate at 6 months, strategies such as minimising the length of the questionnaire whilst maintaining readability, as well as including a stamped addressed return envelope alongside the questionnaire were employed.

Patients with no ultrasound-detected pathologies were invited to attend a research clinic for clinical evaluation within 4 weeks. This clinic involved a consultant shoulder surgeon and rheumatology registrar. Information collected at this clinic were a standardised proforma agreed upon by musculoskeletal specialists, which included history, examination and SPADI.

Table 5.1 Ultrasound pathology definitions

Pathology	Definition
RC Tears	Record foot print tears as partial thickness if articular surface not involved
Bursal thickening	Bursal effusion or synovitis >0.5mm
Dynamic subacromial impingement	Bunching of the bursa lateral to the coraco-acromial ligament during active abduction in the absence of rotator cuff tear
Calcific tendinitis	Diagnosed in the presence of globular calcific deposition, exclude linear entheseal calcifications
ACJ pathology	Diagnosed in the presence of osteophytosis or synovitis, effusion, joint malalignment and bone cortex irregularity
Glenohumeral OA	Diagnosed by the presence of marginal osteophytosis at the cartilage bone junction or humeral articular cartilage thinning
Adhesive Capsulitis/ frozen shoulder	Diagnosed in patients with limited passive external rotation possibly with a small LHB effusion and thickening of the coracohumeral ligament compared to the contra-lateral side in the absence of any features of OA
Biceps tenosynovitis	Non-displaceable or non-fully compressible hypoechoic thickening of the long head of biceps tendon sheath with or without power Doppler signal of evidence of tendinopathy or thinning of the long head of biceps tendon
Tendinopathy	Hypoechogenicity or heterogeneity with thickening of the rotator cuff tendons compared to the other rotator cuff tendons of the ipsilateral or contralateral shoulder

5.4 Statistical analysis

5.4.1 Sample size

The primary objective was to determine the change in SPADI for the different ultrasound-based groups and individual pathologies from baseline to 6

months. Latent class analysis (LCA) identified the groups. Regression analyses compared outcomes between the groups and compared the response to corticosteroid injections in patients with bursitis, with and without RC tears.

For the Bayesian Information Criterion (BIC) to accurately identify the number of classes present, the sample size was calculated to be n=500. This was deemed sufficient as the LCA included <10 categorical outcomes and there was assumed to be an unbalanced, complex structure as was the case in the in Chapter 4 (456).

Rules of thumb for linear regression analysis require 50 + 8m patients, where m is the number of independent variables (480). Analysis from the study in Chapter 4 suggested there would be 4 or 5 groups present. Assuming 4 dummy variables to capture the groups, and to include 17 covariates including baseline value of outcome, this would require 218 patients.

Due to the large number of covariates, there is the potential for over-fitting. Using the PEAR technique, which aims to maximise precision efficacy (PE) in future samples, assuming R-squared=0.40 and requiring PE to be at least 75% this would require a total sample size of 286 patients.

To meet all of our objectives 500 patients were required at baseline for the LCA,. Although a study evaluating the response rates for surveys in 1607 studies found an average overall response rate to be 48.3% (481), we included a tolerance for drop-out of up to 40% for the longitudinal analyses.

5.4.2 Latent Class Analysis

Latent class analysis, as previously described in Chapter 4, was undertaken to confirm the groups. In order to eliminate bias in the analysis, membership to the latent classes were identified using all the covariates. All independent variables and outcomes included in imputation and analysis models were included. This ensured that the association between the latent classes and each of the covariates is maintained. If these co-variates are not used in the classification model, but used in the analysis, then relationship estimates may

be attenuated (underestimated) (482). Furthermore, attenuation may increase as the strength of the true relationship also increases.

Each of the pathologies recorded during the scan, re-coded as 1=absent or 2=present, was included in the model. . For LCA, partial and full RC tears were combined i.e. coded RC tear present. Initially models were run without covariates, with 1000 random seeds and with a varying number of classes from 1 to 6. Model fit statistics (AIC, BIC, CAIC, a-BIC, entropy, G2 and the proportion of 1000 random seeds associated with the best model), as discussed in Chapter 4, were used to identify the optimum number of classes present. We also performed bootstrapped likelihood ratio tests (BLRT) to compare the fit between nested solutions.

Although the LCA model itself can be used to reconstitute groupings based on all of the pathologies entered into the model, to obtain a parsimonious list of pathologies that could be used to classify future patients, a chi-square automated interaction detection (CHAID) algorithm was then used to classify patients into the pathology groups based on their individual pathology profile, allowing the minimum node size prior to splitting to be n=20 and after splitting to be n=10. This was performed separately in each imputed dataset; the most commonly selected pattern was then applied to all imputed datasets and agreement was checked descriptively against the pathology group assignment from LCA within each dataset.

5.4.3 Rasch analysis

Prior to latent class analysis, all questionnaires except the EQ5D were assessed for fit to the Rasch model (483). For scales that fit this model the raw, ordinal scores can be transformed to a linear, interval level scale for parametric analysis.

For an ordinal scale to fit the Rasch model it must satisfy certain criteria (483): uni-dimensionality (i.e. it measures one construct); internal consistency; invariance of items (i.e. the ratio of levels of impairment captured by the items, across any items, remains the same across the ability of respondents and is therefore sample independent); appropriate ordering of categories (i.e. the

probability of the patient using successively higher score categories increases with the level of the underlying pain or functional impairment); no differential item functioning (DIF) (i.e. for a given level of underlying pain or functional impairment, no differences in the observed scores between subgroups of the sample such as males and females); independence of items (i.e. the response to one item does not influence the response to another item on the measure). A Rasch analysis permits diagnostic assessment of items and of these criteria to guide development of the scale e.g. omission of item response categories and guide amendment or omission of items themselves.

The Rasch model is based on the relationship between item difficulty and person ability. It is a probabilistic form of the Guttman scale. The Guttman scale follows a deterministic pattern with a strict hierarchical ordering of items, whereby if a person affirms an item, then all items below that level of difficulty should also be affirmed. The Rasch probabilistic model relaxes this to state that if an item is affirmed, then there is a high probability that all items below that level of difficulty will also be affirmed.

For the Rasch-transformed SPADI, the logit scores were transformed to match the original 0-100 scaling. The testlet approach was used, as previously described (484). The HADS was found to fit the Rasch model as a total score, indicating that the anxiety and depression subscales could be combined into one over-arching domain of psychological distress. Prior to Rasch analysis the brief illness perception questionnaire (IPQ) (which is intended as a suite of single-indicator health outcomes as opposed to items in a single scale) was investigated using exploratory factor analysis, which revealed that 5 items were loaded by one factor but 3 were loaded by another factor. The three items were reverse-coded with respect to the others which may have been responsible for this apparent multidimensionality. The five items loading onto one factor were assessed for fit to the Rasch model and were found to fit; the Rasch-transformed estimates from these five items are referred to as the brief IPQ in the rest of the analysis.

For SPADI and OSS, which were to be examined longitudinally, the scale was shown to be invariant over time by selecting a single time-point per patient

such that the sample was balanced over the three visits. A test for DIF by visit was then performed in this restricted sample.

For all scales, observations were restricted to the baseline visit to assess fit to the model; estimates for subsequent visits (where appropriate) were then obtained having anchored the data to the baseline model. Fit to the model was assessed in terms of: item-trait interaction test (acceptable if $p>0.05$), Cronbach's alpha (minimum 0.7), individual item fit (acceptable if Bonferroni adjusted item chi-square $p>0.05$, absolute fit residual <2.5), differential item functioning (acceptable if analysis of variance main effect Bonferroni adjusted $p>0.05$ for both items for age, sex and shoulder side, or, if $p<0.05$, effect size for difference in person estimates before and after splitting for DIF <0.2).

5.4.4 Missing data

To address missing covariate data, multiple imputation by chained equations (MICE) was used to impute 20 complete datasets, results from which were combined according to Rubin's rules. Imputation models included each of the individual pathology indicators (coded 0=absent, 1=present), duration of symptoms, patient-reported physiotherapy and number of injections received prior to baseline, difficulty standing from sitting, using arms to rise from a chair, injection received at time of US scan, EQ5D-5L (Index score and VAS), SPADI, OSS, pain self-efficacy questionnaire (PSEQ), brief IPQ, the Hospital Anxiety and Depression Scale (HADS), the painDetect scale and patient acceptable symptom state (coded unacceptable=0, acceptable=1).

Baseline characteristics (using available data) were also compared between patients who completed the questionnaire and those who did not, to check for responder bias.

5.4.5 Comparisons between pathology groups identified via LCA

Baseline characteristics and post-baseline treatment received were compared descriptively between the pathology groups using linear, quantile, or logistic regression (binary or ordinal), according to the outcome type, to estimate

means, medians or proportions. This was necessary because pathology group varied across imputations.

To predict SPADI at 2 weeks and 6 months, multivariable linear regression was used. An interaction term was added to investigate whether response to steroid injection at 2 weeks differed between pathology groups. In a subgroup analysis of patients with bursitis, an interaction term was added to show whether response to steroid injection at 2 weeks differed according to whether an RC tear was also present. Interactions were tested at a two-sided 10% level of significance. All other analyses were conducted at the two-sided 5% level of significance. Appropriate checks were made that the data satisfied the test assumptions. Analyses used Stata v14.0.

5.5 **Results**

500 patients were recruited at baseline (52% female, mean age 53.6 years). Following Rasch transformation of SPADI, there were 496 patients with SPADI data available at baseline, 384 at 2 weeks and 330 at 6 months.

All scales fit the Rasch model using the testlet approach (Table 5.2). Total SPADI showed no evidence of multidimensionality indicating it was valid to combine difficulty and pain into one score; sensitivity analysis (not shown) using SPADI pain subscale throughout instead of total SPADI did not alter findings. Figure 5.1 shows transformed total SPADI plotted against original SPADI. This shows that the untransformed score was only approximately linear between values of 20 and 60. For example, the difference between 20 and 25 is the same as the difference between 55 and 60. Differences between scores outside these limits on the same numerical size on the untransformed scale were associated with larger changes in the underlying construct of pain and disability.

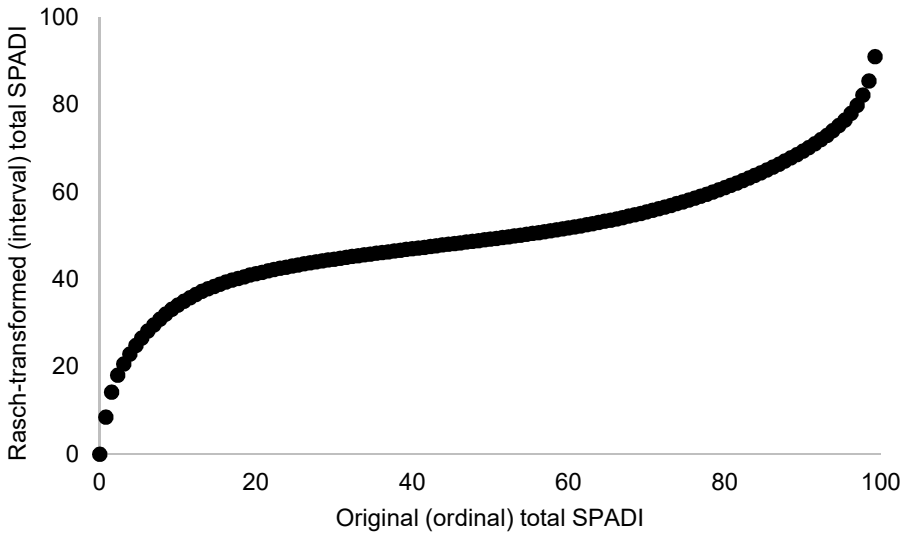


Figure 5.1 Figure plotting transformed total SPADI with original SPADI

Table 5.2 Summary of Rasch model solutions adopting the testlet approach

Scale	Items included in testlet 1	Items included in testlet 2	Item-trait Chisq P value	Mean (SD) person location, logits	CA*	Comments
SPADI	Pain	Disability	p=0.896	0.09 (0.42)	0.77 (n=457)	Testlet 2 fit residual=-2.67
OSS	1-3-5-7-9-11	2-4-6-8-10-12	p=0.925	-0.55 (1.40)	0.91 (n=474)	None
painDetect	1-2-3-4	5-6-7	p=0.148	-0.62 (0.64)	0.70 (n=450)	None
PSEQ	1-3-5-7-9	2-4-6-8-10	p=0.990	1.21 (1.55)	0.95 (n=458)	p<0.05 DIF by age; effect size=0.05
HADS	A1A3A5A7 D2D4D6	A2A4A6 D1D3D5D7	p=0.590	-1.50 (1.28)	0.87 (n=451)	p<0.05 DIF by sex; effect size =0.16
Shoulder activity	1-3-5	2-4	p=0.244	-0.30 (0.95)	0.75 (n=453)	p<0.05 DIF by age; effect size =0.07 p<0.05 DIF by sex; effect size =0.01
Brief IPQ	1-3-5-7	2-4-6-8	p=0.456	0.06 (0.38)	0.77 (n=423)	p<0.05 DIF by age; effect size =0.03

5.5.1 Questionnaire completers and non-completers

Table 5.3 reports baseline characteristics of all patients recruited, patients who returned the questionnaire at 6 months (completers), and those who did not (non-completers). Non-completers were younger and were slightly more anxious and depressed. They were also slightly more likely to have no pathologies visible on their ultrasound scan, although the extent of pain and disability measured by total SPADI at baseline was very similar.

Table 5.3 Baseline characteristics of patients recruited, by questionnaire completion status (baseline and 6 months, baseline only)

	All patients (n=500)	**Completed at baseline and six months (n=330)**	**Completed only at baseline (n=170)**
Age, years: mean (SD)	53.6 (14.5)	57.4 (13.5)	46.2 (13.5)
Female: % (n)	52 (258)	55 (182)	45 (76)
Duration of symptoms, months: median (IQR)	5 (3,10), n=361	6 (3, 10), n=242	5 (3-10), n=119
RC tear (y/n): % (n)	25 (125)	29 (99)	16 (28)
Full thickness RC tear: % (n)	17 (87)	21 (69)	11 (18)
Bursitis: % (n)	71 (354)	71 (234)	71 (120)
Impingement: % (n)	59 (297)	63 (208)	52 (89)
Calcific tendinitis: % (n)	8 (41)	9 (29)	7 (12)
ACJ degeneration: % (n)	47 (235)	52 (173)	36 (62)
Glenohumeral OA: % (n)	3 (17)	4 (13)	2 (4)
Adhesive capsulitis: % (n)	8 (39)	9 (28)	6 (10)
Biceps tenosynovitis: % (n)	4 (22)	4 (14)	5 (8)

Rotator cuff tendinopathy: % (n)	29 (147)	32 (107)	24 (40)
US pathology absent: % (n)	7 (34)	4 (13)	12 (21)
Number of pathologies: median (IQR)	3 (2,3)	3 (2, 4)	2 (1, 3)
BMI, kg/m2, mean (SD)	27.6 (5.1) n=461	27.9 (5.1), n=314	26.9 (5.0) n=147
Number of painful joints, median (IQR)	3 (1-5)	3 (1-5)	2 (1-5)
HADS baseline total, mean (SD)	14.0 (5.9), n=490	13.3 (6.0), n=324	15.4 (5.6), n=166
SPADI baseline total, mean (SD)	51.5 (9.8), n=496	51.2 (9.7), n=328	50.5 (13.3), n=167

5.5.2 Identifying groups using LCA

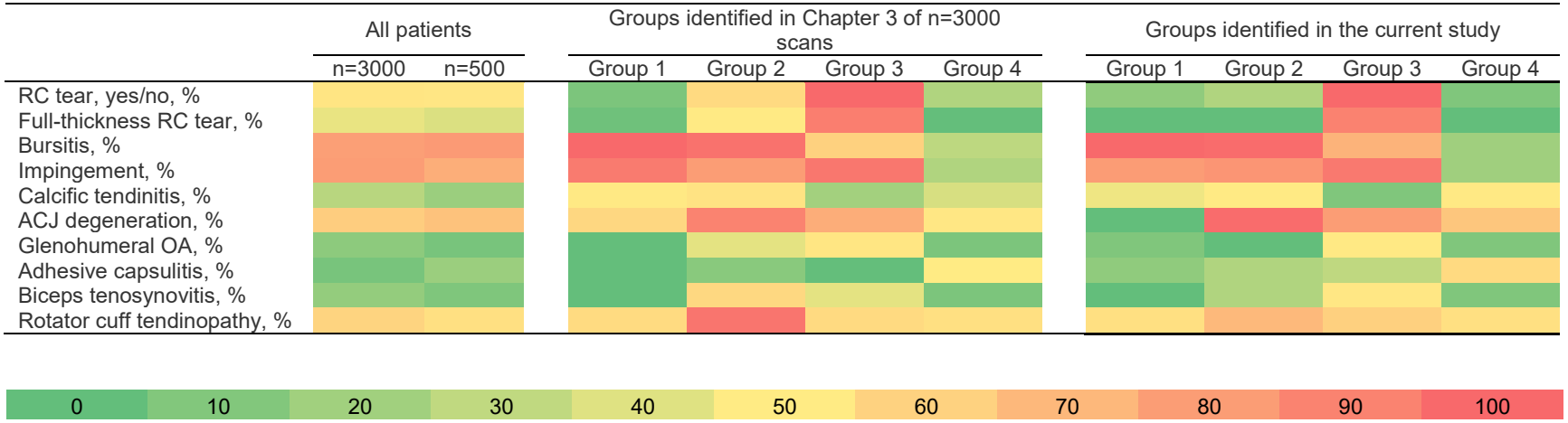
The a priori selected criterion BIC was lowest for a 3 group solution but the BIC value for a 4 group solution was very similar. A bootstrapped likelihood ratio test (demonstrated via simulation to be the best performing of the available criteria (485)) indicated that the 4 class solution was a significantly better fit to the data than the 3 class solution (p=0.010).

AIC, a-BIC & G2 favoured the 4 class solution, while BIC, CAIC & entropy favoured the 3 class solution. The overall proportion of 1000 random seeds associated with the ML model did not favour either solution (both 95%) (see Table 5.4). The groups identified showed a very similar pattern of pathologies compared to those identified in Chapter 3, with the exception that the prevalence of pathologies other than bursitis, impingement and ACJ degeneration in group 2 was lower in the current study. This was particularly true for rotator cuff tendinopathy, despite overall prevalence being similar between the audit and the current study (see Table 5.5).

Table 5.4 Model fit and stability measures for solutions with 2 to 6 classes

Number of classes	df	AIC	BIC	CAIC	a-BIC	Entropy	G^2	Solution %	BLRT p-value
1	502	471.0	508.9	517.9	480.4	1.00	453.0	100%	-
2	492	374.6	454.7	473.7	394.4	0.74	336.6	36%	p=0.010
3	482	259.1	381.3	410.3	289.2	0.89	201.1	95%	p=0.010
4	472	221.3	385.7	424.7	261.9	0.76	143.3	95%	p=0.010
5	462	221.9	428.4	477.4	272.9	0.79	123.9	21%	p=0.800
6	452	219.2	467.8	526.8	280.5	0.80	101.2	39%	p=0.680

Table 5.5 Groups derived via LCA separately in Chapter 3 (n=3000) and current study (n=500)



5.5.3 Developing a simplified rule to assign future patients to pathology groups

The classification rule most commonly identified by CHAID was common to 4/20 imputed datasets; the rules identified in the remaining datasets were similar but not identical. When the selected rule was applied to all imputed datasets, the pathology groups identified via LCA could be approximated with mean 92% accuracy (>91% accuracy in 18/20 datasets; >70% accuracy in 2/20), and mean proportions of positive agreement 93%, 89%, 91%, 95% for pathology groups 1-4 respectively, using only 3 of the pathologies:

Group 1: Bursitis present, ACJ degeneration absent, RC tear absent

Group 2: Bursitis present, ACJ degeneration present, RC tear absent

Group 3: RC tear present

Group 4: Bursitis absent, RC tear absent

5.5.4 Baseline characteristics of pathology groups

The baseline characteristics of the pathology groups are outlined in Table 5.6. Of note, 34/500 patients had no US-detectable pathology, most of whom constituted 36% of the group without bursitis or RC tear. Adjusting for age, sex and symptom duration, baseline total SPADI was highest in the RC tear group and lowest in the group without bursitis or RC tear.

Adjusting for age, sex and HADS there was no difference between groups in 6-month estimated questionnaire return rate (estimated to be 63%, 70%, 69% and 64% in groups 1-4 respectively; p=0.586).In light of the CHAID results, group 1 was deemed ‘bursitis without ACJ degeneration’, group 2 was ‘bursitis with ACJ degeneration’, group 3 was ‘rotator cuff tear’ and group 4 was ‘no bursitis or rotator cuff tear’.

Of the remaining pathologies, impingement was common in groups 1-3 but almost absent in group 4. Calcific tendinitis was observed in approximately

10% of patients in groups 1, 2 & 4, but was almost absent in the RC tear group; this group had the highest prevalence of biceps tenosynovitis and glenohumeral OA, the latter possibly due to their age. Most of the patients with adhesive capsulitis were in group 4, indicating that this often does not overlap with bursitis or RC tear. Rotator cuff tendinopathy was most commonly observed in group 2.

Group 1 was the youngest (mean age 47.0) and group 3 was the oldest (mean age 65.1). The rotator cuff group had the greatest number of pathologies present on their scans; the group without bursitis or RC tear had the fewest. The rotator cuff tear group had the lowest rate of injections at the time of scan – 10%, compared to 50-60% in groups 1 and 2, almost all of whom had bursitis. Adjusting for age, sex and symptom duration, baseline total SPADI was highest in the RC tear group and lowest in the group without bursitis or RC tear. Additionally adjusting for the variables in Table 5.7, total SPADI score at baseline was higher in group 3 (RC tear) than each of the other groups:

- Group 1 (Bursitis without ACJ degeneration)
    - Mean difference (95% CI) 2.84 (0.73, 4.96), p=0.009
- Group 2 (Bursitis with ACJ degeneration)
    - Mean difference (95% CI) 2.73 (0.54, 4.93), p=0.015
- Group 4 (No bursitis or RC tear)
    - Mean difference (95% CI) 2.83 (0.43, 5.24), p=0.021

Although statistically significant, the adjusted differences between group 3 and the remaining groups were well within the reported measurement error for SPADI. A difference of 2.8 on the Rasch-transformed scale is equivalent to 7.7 units on the untransformed scale in the centre of the range, where the mean in group 3 was located; this is within the 18.1 units reported for MCD.

Table 5.6 Summary of baseline characteristics of pathology groups (imputed data; all patients)

	Bursitis (w/o ACJ degeneration)	Bursitis (with ACJ degeneration)	RC tear	No bursitis or RC tear	
% of sample	33	27	21	19	
Age, years: mean (95% CI)	47.0 (44.8, 49.2)	55.5 (53.1, 57.8)	65.1 (62.3, 67.9)	49.5 (46.8, 52.1)	
Female: %	56	52	45	51	
Duration, months: median (95% CI)	5.2 (3.6, 6.7)	5.6 (4.2, 7.0)	4.8 (3.3, 6.2)	5.9 (4.4, 7.3)	
RC tear (y/n): %	3	5	>99	2	
Full thickness RC tear: %	<1	<1	83	<1	
Bursitis: %	>99	98	49	4	
Impingement: %	65	70	89	4	
Calcific tendinitis: %	9	11	2	12	
ACJ degeneration: %	<1	98	64	36	
Glenohumeral OA: %	2	<1	12	2	
Adhesive capsulitis: %	3	5	6	22	
Biceps tenosynovitis: %	<1	5	13	2	
Rotator cuff tendinopathy: %	18	45	29	18	
Probability of membership: mean	0.89	0.94	0.93	0.96	
US pathology absent: %	<1	<1	<1	36	Overall *P* value*
Number of pathologies: median (95% CI)	2.0 (1.9, 2.1)	3.0 (2.9, 3.1)	3.8 (2.7, 4.8)	1.0 (0.8, 1.2)	p<0.001
Injection at time of scan: %	59	49	10	16	p<0.001
BMI: mean (95% CI)	27.4 (26.5, 28.3)	28.5 (27.6, 29.5)	27.1 (26.0, 28.2)	27.3 (26.2, 28.5)	p=0.201
Number of painful joints: median (95% CI)	2.4 (1.2, 3.5)	3.0 (2.5, 3.5)	2.0 (1.4, 2.6)	2.6 (1.4, 3.8)	p=0.159
Uses arms to rise from chair: %	37	53	56	49	p=0.388
Physiotherapy before baseline: %	26	25	28	32	p=0.670
Number of injections 1: % 2: %	16 6	16 6	17 6	14 5	p=0.867

EQ5D-5L index: median (95% CI)	0.80 (0.77, 0.83)	0.77 (0.73, 0.81)	0.72 (0.68, 0.77)	0.80 (0.76, 0.85)	p=0.712
EQ5D-5L VAS: median (95% CI)	72.3 (65.8, 78.7)	71.3 (65.3, 77.2)	78.3 (71.5, 85.0)	75.0 (70.4, 79.5)	p=0.325
Shoulder activity score: mean (95% CI)	10.6 (10.1, 11.2)	9.6 (8.8, 10.4)	9.5 (8.6, 10.4)	9.8 (9.0, 10.5)	p=0.290
Total SPADI: mean (95% CI)	50.3 (48.8, 51.8)	51.3 (49.7, 53.0)	55.1 (53.0, 57.2)	49.7 (47.7, 51.7)	p=0.005
Oxford shoulder: mean (95% CI)	33.9 (33.0, 34.9)	34.1 (33.0, 35.2)	36.6 (35.3, 37.9)	34.0 (32.6, 35.3)	p=0.091
P-SEQ: mean (95% CI)	39.3 (37.7, 40.9)	37.7 (35.9, 39.5)	37.7 (35.7, 39.7)	39.5 (37.4, 41.6)	p=0.085
Brief IPQ: mean (95% CI)	42.4 (41.4, 43.5)	42.1 (40.9, 43.4)	43.1 (41.7, 44.5)	42.3 (40.9, 43.7)	p=0.162
HADS: mean (95% CI)	13.8 (12.9, 14.8)	14.1 (13.1, 15.2)	14.6 (13.4, 15.8)	13.5 (12.3, 14.7)	p=0.160
painDetect: mean (95% CI)	14.3 (13.4, 15.2)	13.9 (12.9, 14.9)	14.7 (13.6, 15.8)	13.4 (12.3, 14.6)	p=0.193
PASS at baseline: %	14	23	18	36	p=0.002

*Adjusted for age, sex and symptom duration

ACJ=acromioclavicular joint; BMI=body mass index; HADS=hospital anxiety and depression scale; IPQ=illness perception questionnaire; PASS=patient acceptable symptom state; P-SEQ=pain self-efficacy questionnaire; RC=rotator cuff; SPADI=shoulder pain and disability index; US=ultrasound

Table 5.7 Multivariable analysis of association between group membership and symptoms (total SPADI) at baseline

	Total SPADI at baseline (n=496) Coefficient* (95% CI), p-value	
	Bivariable	Multivariable
Pathology group:		
Bursitis w/o ACJ degeneration	Reference	Reference
Bursitis with ACJ degeneration	1.00 (-1.22, 3.23), p=0.375	0.11 (-1.71, 1.92), p=0.908
RC tear	4.75 (2.23, 7.27), p<0.001	2.84 (0.73, 4.96), p=0.009
No bursitis, no RC tear	-0.50 (-3.00, 2.00), p=0.694	0.01 (-1.90, 1.91), p=0.995
Age, years	0.10 (0.04, 0.16), p=0.001	0.08 (0.02, 0.13), p=0.005
Female	4.02 (2.33, 5.71), p<0.001	3.01 (1.65, 4.38), p<0.001
Duration of symptoms, months	0.02 (-0.01, 0.04), p=0.245	0.00 (-0.02, 0.02), p=0.900
Uses arms to rise from chair	4.66 (2.97, 6.35), p<0.001	1.13 (-0.31, 2.56), p=0.124
Had physiotherapy before baseline	-1.28 (-3.30, 0.73), p=0.211	-2.10 (-3.72, -0.48), p=0.011
Had 1 injection before baseline	0.82 (-1.62, 3.25), p=0.509	1.01 (-0.90, 2.92), p=0.300
Had 2 injections before baseline	3.63 (-0.28, 7.54), p=0.068	2.45 (-0.59, 5.48), p=0.113
Shoulder activity score at baseline	-0.31 (-0.54, -0.07), p=0.010	0.11 (-0.08, 0.31), p=0.251
P-SEQ at baseline	-0.54 (-0.61, -0.47), p<0.001	-0.33 (-0.41, -0.24), p<0.001
Brief IPQ at baseline	0.69 (0.57, 0.80), p<0.001	0.24 (0.12, 0.37), p<0.001
HADS at baseline	0.61 (0.47, 0.75), p<0.001	-0.03 (-0.17, 0.11), p=0.697
painDetect at baseline	0.87 (0.73, 1.00), p<0.001	0.51 (0.38, 0.63), p<0.001

*Interpreted as unit difference in Rasch-transformed total SPADI score per 1 additional unit of the independent variable

5.5.5 Post-baseline treatment received

Medication records were accessed towards the end of follow-up in 313 of the 330 patients with 6 month SPADI available. Using imputation to address the missing data, we found no substantive differences between groups in the rates of repeat prescriptions for opioids or NSAIDs (see Table 5.8). Adjusting for age, sex and symptom duration, estimated proportions for groups 1-4 were: opioids 12%; 18%; 9%; 9% (overall p=0.289), NSAIDs 6%; 13%; 8%; 6% (overall p=0.347).

Combining results from the 3 month telephone follow-up and 6 month questionnaire, data on post baseline physiotherapy, injections and surgery were available for 296, 285 and 299 patients respectively of the 330 with 6 month SPADI available. Using imputed data for post baseline treatments, there were no adjusted differences between groups in proportions of patients reporting that they had received physiotherapy (55%; 53%; 67%; 58%; overall p=0.476) , but those in groups 1 & 2 (both with bursitis) were more likely to report receiving injections (61%; 56%; 35%; 38%; overall p=0.018).

By inspecting GP records and Leeds NHS hospital records we were able to confirm surgery had occurred between baseline and 6 months in 18 patients. However, three of these patients did not report having had surgery at any point. A further 22 patients reported having surgery which we were unable to confirm from the available records, and may reflect private treatment. A greater number of those with RC tears (group 3) received surgery. Adjusted proportions reporting surgery were 11%; 5%; 26%; 10% (overall p=0.011) in groups 1-4 respectively.

Table 5.8 Estimated probabilities of post baseline treatment by treatment group

Treatment	Model	Bursitis (w/o ACJ degeneration)	Bursitis (with ACJ degeneration)	RC tear	No bursitis or RC tear	Overall P value
Opioids	Unadjusted	0.08 (0.02, 0.14)	0.18 (0.10, 0.26)	0.13 (0.05, 0.21)	0.08 (0.01, 0.16)	p=0.197
	Adjusted*	0.12 (0.04, 0.20)	0.18 (0.10, 0.25)	0.09 (0.03, 0.15)	0.10 (0.02, 0.18)	p=0.306
NSAIDs	Unadjusted	0.04 (0.00, 0.08)	0.14 (0.07, 0.21)	0.12 (0.04, 0.20)	0.05 (-0.01, 0.11)	p=0.127
	Adjusted*	0.05 (-0.01, 0.11)	0.14 (0.07, 0.20)	0.09 (0.02, 0.15)	0.06 (0.00, 0.13)	p=0.320
Physiotherapy (patient-reported)	Unadjusted	0.57 (0.46, 0.68)	0.52 (0.42, 0.63)	0.65 (0.54, 0.76)	0.59 (0.45, 0.72)	p=0.476
	Adjusted*	0.55 (0.43, 0.66)	0.53 (0.42, 0.63)	0.67 (0.56, 0.78)	0.58 (0.45, 0.71)	p=0.337
Injections (patient-reported)	Unadjusted	0.60 (0.49, 0.71)	0.56 (0.44, 0.68)	0.36 (0.22, 0.49)	0.38 (0.24, 0.52)	p=0.013
	Adjusted*	0.61 (0.49, 0.72)	0.56 (0.44, 0.68)	0.35 (0.21, 0.49)	0.38 (0.24, 0.53)	p=0.018
Surgery (patient-reported**)	Unadjusted	0.12 (0.05, 0.19)	0.05 (0.00, 0.10)	0.25 (0.15, 0.35)	0.10 (0.02, 0.18)	p=0.006
	Adjusted*	0.11 (0.04, 0.18)	0.05 (0.00, 0.10)	0.26 (0.15, 0.38)	0.10 (0.02, 0.18)	p=0.011

*Adjusted for age, sex and symptom duration **Imputed surgery=yes for 4 patients confirmed to have had surgery who did not report it

5.5.6 Multivariable analysis of association between group membership and symptoms at 6 months

There were 330 patients with SPADI data available at 6 months. Multivariable analysis of association between group membership and total SPADI at 6 months found that, when adjusted for covariates including baseline SPADI, scores for shoulder pain and disability at 6 months did not differ by treatment group (overall p=0.379). The significant predictors of higher SPADI at 6 months included higher SPADI at baseline and reporting lower shoulder activity level in the 12 months preceding the baseline scan (see Table 5.9).

Table 5.9 Multivariable analysis of association between group membership and symptoms (total SPADI) at 6 months

	Total SPADI (n=330) Coefficient* (95% CI), p-value	
	Bivariable	Multivariable
Pathology group:		
Bursitis w/o ACJ degeneration	Reference	Reference
Bursitis with ACJ degeneration	0.62 (-5.29, 6.54), p=0.835	0.20 (-5.13, 5.54), p=0.940
RC tear	6.83 (1.13, 12.54), p=0.019	5.27 (-1.23, 11.77), p=0.112
No bursitis, no RC tear	0.38 (-5.90, 6.66), p=0.906	2.16 (-3.96, 8.27), p=0.488
Injection at time of scan	4.95 (0.80, 9.10), p=0.020	5.00 (0.53, 9.47), p=0.028
Age, years	0.16 (0.01, 0.31), p=0.037	-0.02 (-0.18, 0.15), p=0.853
Female	1.52 (-2.58, 5.62), p=0.467	-1.53 (-5.43, 2.37), p=0.441
Duration of symptoms, months	0.03 (-0.02, 0.08), p=0.267	0.00 (-0.04, 0.05), p=0.851
Uses arms to rise from chair	8.24 (4.25, 12.23), p<0.001	2.72 (-1.44, 6.88), p=0.199
Had physiotherapy before baseline	0.76 (-3.82, 5.34), p=0.744	-0.21 (-4.84, 4.43), p=0.931
Had 1 injection before baseline	5.15 (-0.21, 10.52), p=0.060	2.18 (-3.07, 7.43), p=0.414
Had 2 injections before baseline	9.84 (0.54, 19.14), p=0.038	6.59 (-2.37, 15.56), p=0.149
Total SPADI score at baseline	0.90 (0.71, 1.08), p<0.001	0.61 (0.34, 0.88), p<0.001
Shoulder activity score at baseline	-0.80 (-1.37, -0.22), p=0.007	-0.60 (-1.16, -0.05), p=0.034

P-SEQ at baseline	-0.68 (-0.87, -0.49), p<0.001	-0.20 (-0.47, 0.07), p=0.141
Brief IPQ at baseline	0.79 (0.50, 1.08), p<0.001	0.20 (-0.15, 0.55), p=0.257
HADS at baseline	0.82 (0.49, 1.15), p<0.001	0.00 (-0.40, 0.40), p=0.993
painDetect at baseline	0.83 (0.46, 1.20), p<0.001	-0.05 (-0.45, 0.36), p=0.814

*Interpreted as unit difference in Rasch-transformed symptom score per 1 additional unit of the independent variable

5.5.7 Analysis of prediction between individual pathologies and symptoms at 6 months

Regression analysis of 6 month total SPADI on individual pathologies in complete and imputed cases found none of the individual pathologies predicted SPADI at 6 months when adjusting for baseline SPADI score (see Table 5.10). Only baseline total SPADI score and baseline shoulder activity were independently predictive of SPADI at 6 months. The more shoulder activity a patient reported performing in the 12 month prior to baseline, the lower their 6 month SPADI was predicted to be, adjusting for the other covariates in the model. Note that this does not imply any causal association, nor that this captures the total extent or direction of any potential causal association between activity level and SPADI.

In a sensitivity analysis, the exclusion of patients with adhesive capsulitis did not affect the number of groups or the predictive ability of pathologies for 6 month SPADI outcome.

Table 5.10 Linear regression of 6 month total SPADI on individual pathologies (imputed data)

	Total SPADI (n=330) Coefficient* (95% CI), p-value	
Baseline characteristic	**Including adhesive capsulitis n=330***	**Excluding adhesive capsulitis n=301****
Age, years	0.00 (-0.17, 0.18), p=0.960	0.04 (-0.14, 0.23), p=0.651
Female	-1.70 (-5.67, 2.27), p=0.401	-1.83 (-6.07, 2.40), p=0.395
RC tear partial	2.54 (-4.37, 9.45), p=0.470	3.01 (-4.37, 10.39), p=0.423
RC tear full	2.71 (-3.67, 9.10), p=0.404	2.70 (-4.11, 9.51), p=0.436
Bursitis	-1.71 (-6.74, 3.32), p=0.505	-1.91 (-7.39, 3.56), p=0.492
Impingement	-0.31 (-5.25, 4.63), p=0.901	-0.33 (-5.55, 4.89), p=0.902
Calcific tendinitis	-2.84 (-9.49, 3.81), p=0.402	-3.49 (-10.64, 3.65), p=0.337
ACJ degeneration	-0.07 (-4.10, 3.96), p=0.972	-1.14 (-5.50, 3.21), p=0.606
Glenohumeral OA	4.99 (-5.05, 15.03), p=0.329	4.47 (-6.23, 15.17), p=0.412
Adhesive capsulitis	-2.29 (-9.35, 4.76), p=0.523	
Biceps tenosynovitis	-3.67 (-13.27, 5.93), p=0.453	-5.20 (-15.69, 5.29), p=0.330
Rotator cuff tendinopathy	0.77 (-3.54, 5.08), p=0.725	0.74 (-3.83, 5.30), p=0.750
Injection at time of scan	4.22 (-0.24, 8.68), p=0.063	4.04 (-0.70, 8.79), p=0.094
Duration of symptoms, months	0.00 (-0.04, 0.05), p=0.889	0.01 (-0.06, 0.09), p=0.716
Uses arms to rise from chair	2.17 (-2.05, 6.40), p=0.312	1.94 (-2.65, 6.54), p=0.406
Had physiotherapy before baseline	0.06 (-4.57, 4.69), p=0.980	0.39 (-4.67, 5.46), p=0.879
Had 1 injection before baseline	2.31 (-3.00, 7.61), p=0.393	2.12 (-3.76, 7.99), p=0.479
Had 2 injections before baseline	5.97 (-3.24, 15.18), p=0.203	6.89 (-2.97, 16.76), p=0.170
Baseline total SPADI	0.62 (0.35, 0.90), p<0.001	0.58 (0.29, 0.87), p=0.000
Shoulder activity score	-0.59 (-1.16, -0.03), p=0.040	-0.61 (-1.24, 0.02), p=0.059
P-SEQ	-0.20 (-0.47, 0.07), p=0.142	-0.20 (-0.49, 0.08), p=0.156
Brief IPQ	0.17 (-0.19, 0.54), p=0.348	0.16 (-0.24, 0.55), p=0.427
HADS	0.03 (-0.37, 0.43), p=0.888	0.02 (-0.42, 0.46), p=0.929
painDetect	-0.01 (-0.42, 0.40), p=0.956	0.08 (-0.36, 0.53), p=0.714
Adjusted R^2	0.23	0.22

* 170 patients did not complete total SPADI at 26 weeks **29 patients had adhesive capsulitis and were excluded

5.5.8 Short-term response to baseline steroid injection

Multiple linear regression was used to identify predictors of total SPADI score at 2 weeks in 384 patients with week 2 data. In a preliminary model, no significant interaction was found between pathology group and injection at scan (p=0.609), indicating that group membership was not predictive of a differential response to injection. Descriptive differences were similar across the groups; average differences in 2 week SPADI by baseline injection status (95% CI) were -11.7 (-16.0, -7.3), -10.1 (-14.7, -5.6), -6.9 (-15.7, 2.0) and -15.1

(-22.5, -7.6) in groups 1-4 respectively. The interaction was removed from the final model, the results from which are presented in **Table 5.11**.

Although groups 1 and 3 differed at week 2 when no other predictors were entered (overall group test p=0.003), this reflected the fact that they already differed at baseline; the pathology grouping was not predictive of total SPADI at 2 weeks in a model including baseline SPADI, injection at the time of scan and additional demographic, patient history and patient-reported outcomes (overall pathology group test p=0.423). When adjusting for the other variables, predicted total SPADI at week 2 was 11 units lower (equivalent to 37.7 units on untransformed scale) in patients who had received an injection at the time of their scan compared to those who had not, and was lower in women, but was higher in those who had received previous injections, in older patients, and in those with higher baseline total HADS scores.

Table 5.11 Predictors of total SPADI at week 2

	Total SPADI (n=384) Coefficient* (95% CI), p-value	
	Bivariable	Multivariable
Pathology group:		
Bursitis w/o ACJ degeneration	Reference	Reference
Bursitis with ACJ degeneration	0.48 (-4.19, 5.15), p=0.839	-1.56 (-6.16, 3.05), p=0.500
RC tear	7.47 (3.50, 11.44), p<0.001	-2.14 (-6.71, 2.43), p=0.356
No bursitis, no RC tear	0.25 (-3.67, 4.17), p=0.899	-3.63 (-7.45, 0.20), p=0.063
Injection at time of scan	-7.78 (-10.41, -5.15), p<0.001	-10.97 (-13.78, -8.16), p<0.001
Age, years	0.12 (0.03, 0.22), p=0.011	0.11 (0.01, 0.21), p=0.035
Female	0.65 (-2.03, 3.32), p=0.635	-2.71 (-5.22, -0.20), p=0.034
Duration of symptoms, months	0.02 (-0.02, 0.06), p=0.345	0.01 (-0.03, 0.04), p=0.668
Uses arms to rise from chair	2.90 (0.23, 5.58), p=0.033	-1.43 (-3.97, 1.12), p=0.270
Had physiotherapy before baseline	-2.22 (-5.28, 0.85), p=0.156	-2.82 (-5.74, 0.11), p=0.059
Had 1 injection before baseline	2.27 (-1.53, 6.08), p=0.241	4.87 (1.35, 8.38), p=0.007
Had 2 injections before baseline	2.77 (-3.53, 9.07), p=0.387	5.00 (-0.72, 10.71), p=0.086
Total SPADI at baseline	0.50 (0.38, 0.63), p<0.001	0.43 (0.26, 0.59), p<0.001
Shoulder activity score at baseline	-0.30 (-0.68, 0.08), p=0.118	-0.06 (-0.42, 0.30), p=0.733
P-SEQ at baseline	-0.34 (-0.46, -0.21), p<0.001	0.01 (-0.15, 0.18), p=0.860
Brief IPQ at baseline	0.57 (0.37, 0.78), p<0.001	0.17 (-0.07, 0.40), p=0.158
HADS at baseline	0.57 (0.35, 0.79), p<0.001	0.27 (0.02, 0.52), p=0.036
painDetect at baseline	0.63 (0.39, 0.86), p<0.001	0.16 (-0.08, 0.40), p=0.191

*Interpreted as unit difference in Rasch-transformed total SPADI score per 1 additional unit of the independent variable

5.5.9 Bursitis, RC tear and steroid injection

In patients with bursitis (n=354), 55% (155/283) of those without RC tears received an injection at their scan compared to 21% (15/71) with a RC tear. Restricting the analysis to patients with bursitis with available 2-week SPADI data (n=282), , there was no differential response, after adjusting for variables in table 4 (estimated difference by injection status (95% CI) -10.7 (-13.9, -7.5) if RC tear absent; -8.8 (-15.8, -1.8) if RC tear present; interaction RC tear x injection p=0.624). So although patients with bursitis were less likely receive an injection with a coexisting RC tear, adjusted 2-week SPADI was 10.4 units lower (95% CI -13.3, -7.5) in those receiving an injection, irrespective of the presence of a tear.

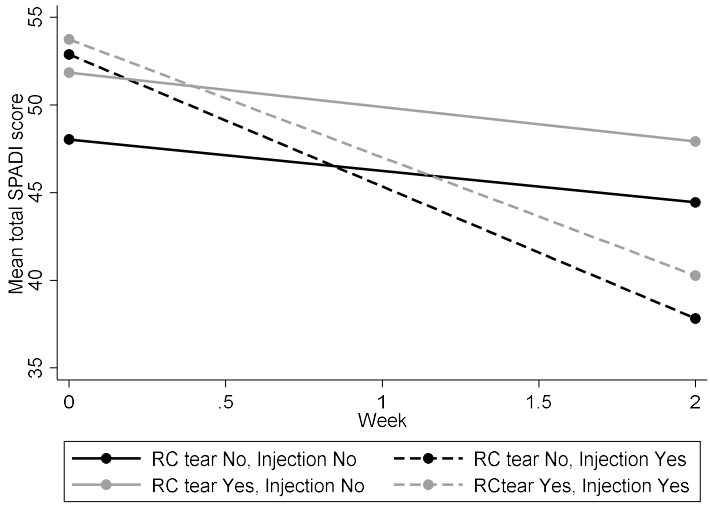
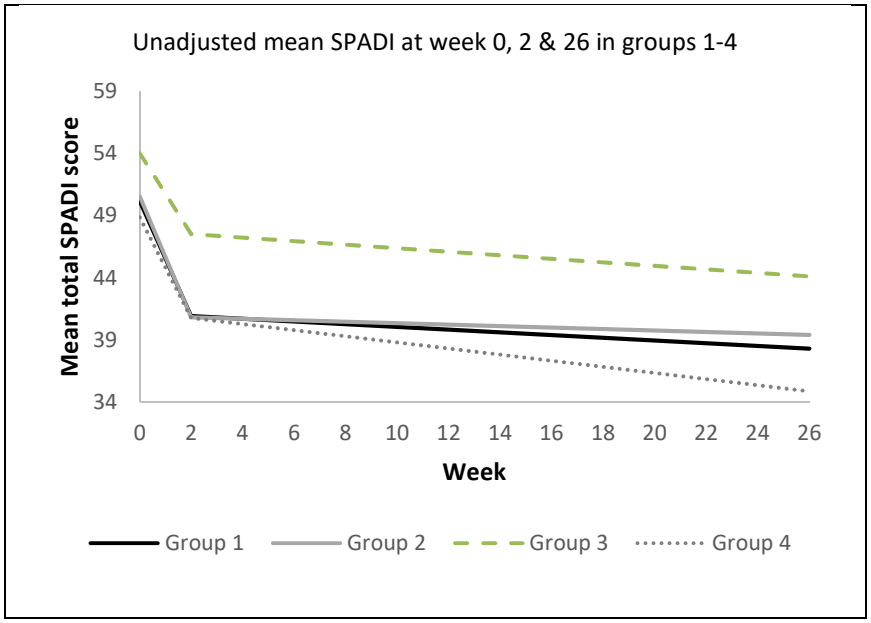


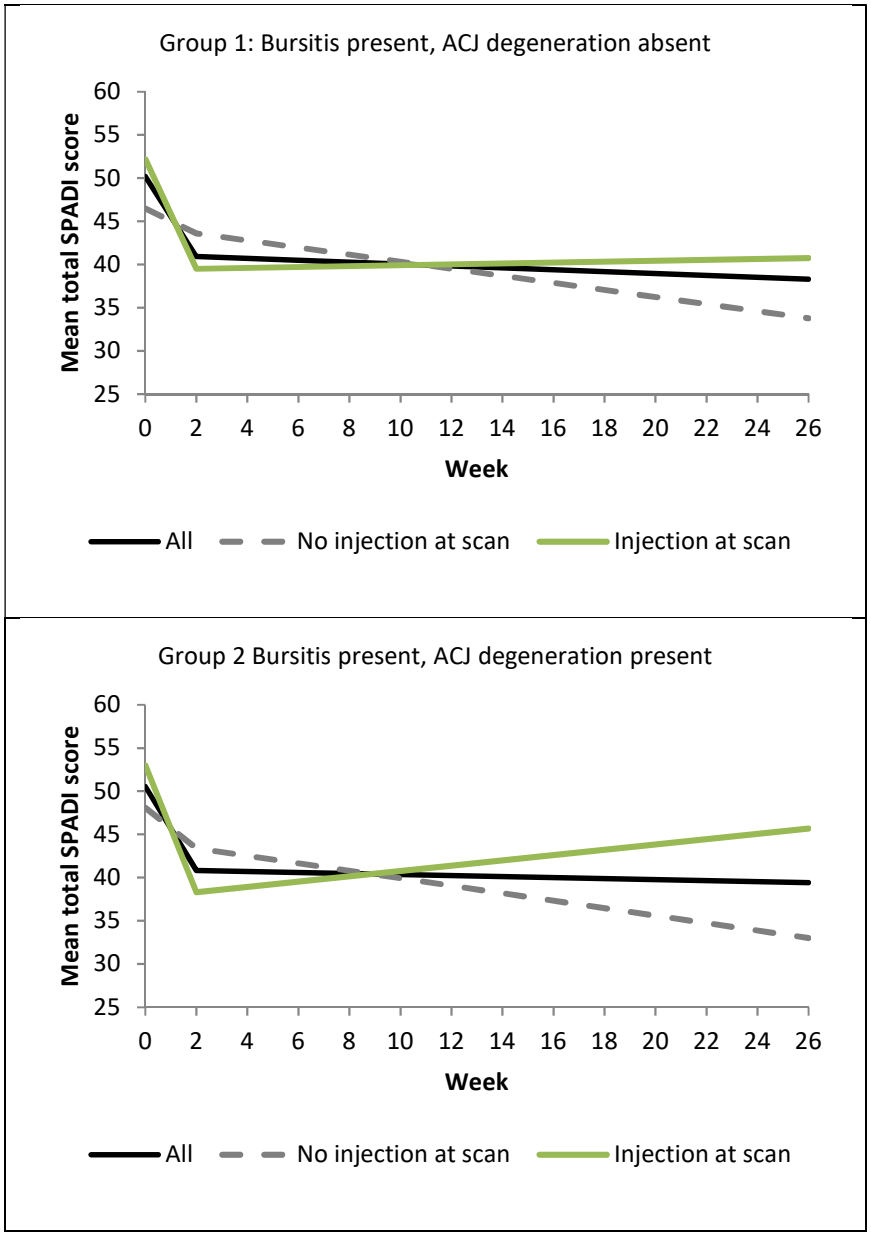
Figure 5.2 Mean total SPADI score at baseline and 2 weeks in patients with bursitis (n=282)

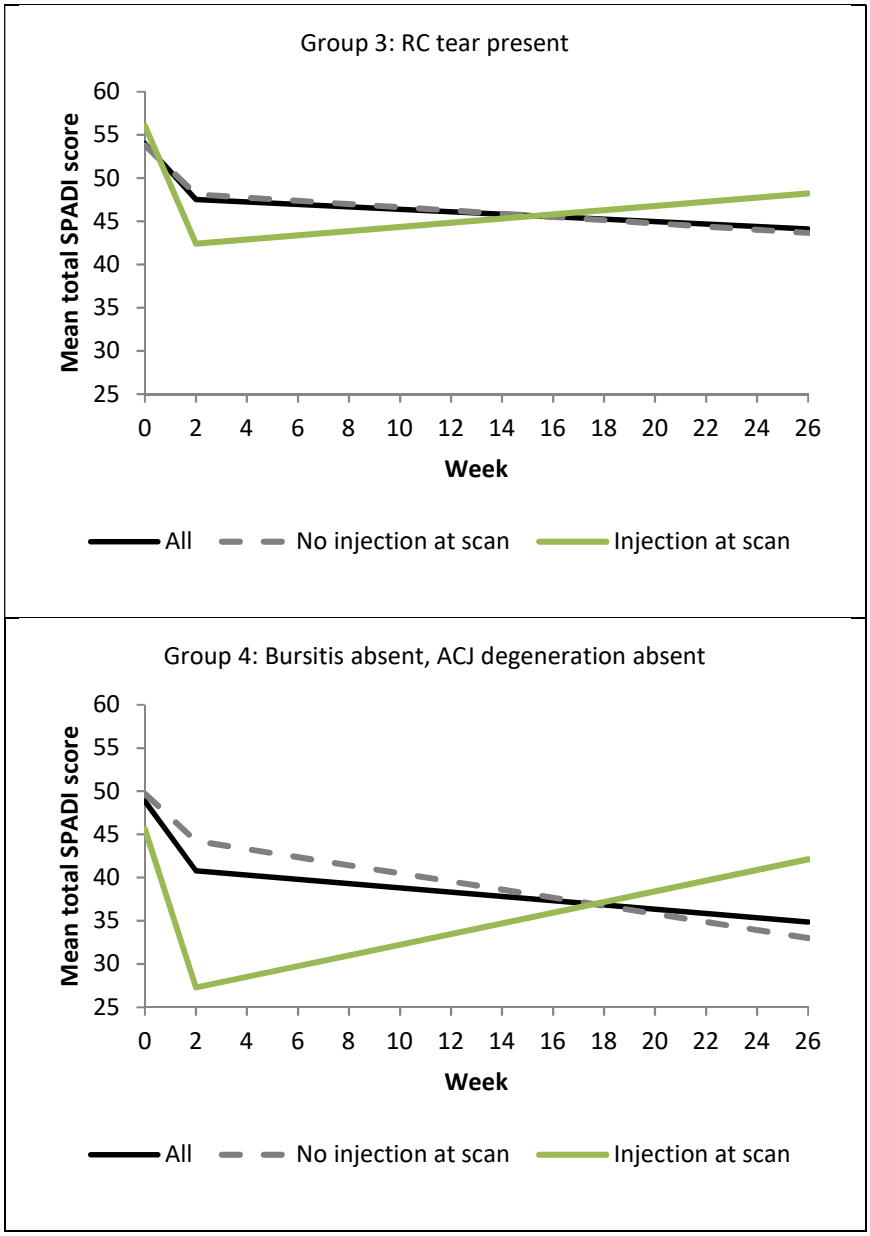
5.5.10 SPADI over time by pathology group and treatment (unadjusted)

Restricting analysis to patients with SPADI score available at all 3 time-points (n=271), overall the 4 pathology groups changed in parallel over time, with most of the change seen in the first 2 weeks. Those receiving an injection

improved their symptoms substantively at 2 weeks compared to those who did not, although they subsequently tended to stay the same or even (apparently) worsen slightly (see Figure 5.3). In patients with full SPADI data, estimated rates of patient-reported post-baseline physiotherapy, injection and surgery were 58%, 49% and 12% respectively using imputed data (52%, 44% and 8% in complete case). We estimated SPADI score at 0, 2 and 26 weeks in patients who reported that they had not received any physiotherapy, injection or surgery either before, at and after baseline, compared to patients who had received any therapy at all, using imputed data on patient-reported treatment. Only 12% of patients were estimated not to have received any therapy in imputed data (15% (36/236) in complete case). Both groups showed improvement at week 2, those who had received therapy had lowest (unadjusted) mean total SPADI. However, at 6 months mean SPADI was similar with or without therapy. The number of patients who did not receive any therapy was too small to meaningfully compare the pathology groups in the absence of therapy.




Group 1: Bursitis present, ACJ degeneration absent
Mean total SPADI score
60
55
50
45
40
35
30
25
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Week
All
No injection at scan
Injection at scan
Group 2 Bursitis present, ACJ degeneration present
Mean total SPADI score
60
55
50
45
40
35
30
25
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Week
All
No injection at scan
Injection at scan


Group 3: RC tear present
Mean total SPADI score
60
55
50
45
40
35
30
25
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Week
All
No injection at scan
Injection at scan
Group 4: Bursitis absent, ACJ degeneration absent
Mean total SPADI score
60
55
50
45
40
35
30
25
0 2 4 6 8 10 12 14 16 18 20 22 24 26
Week
All
No injection at scan
Injection at scan

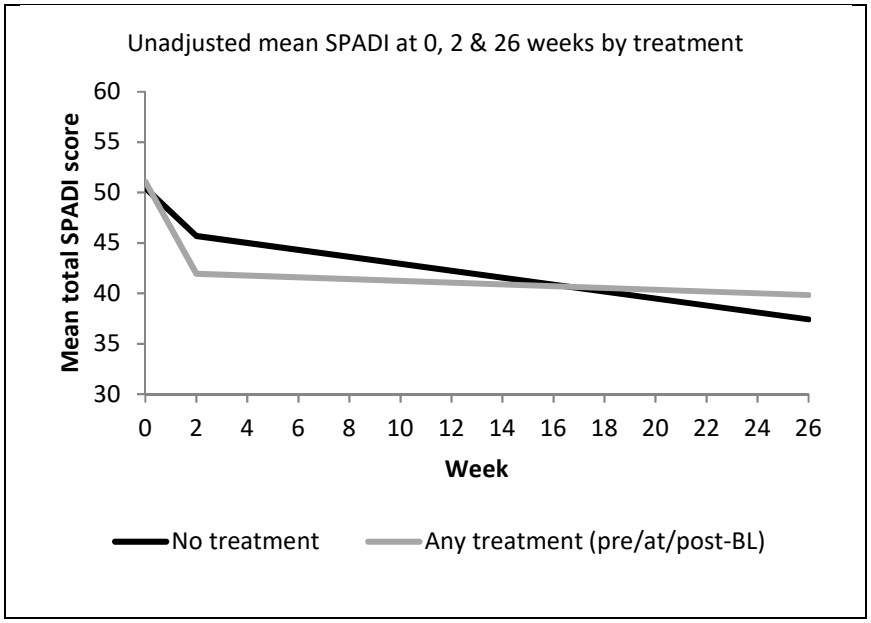


Figure 5.3 Total SPADI over time by pathology group and treatment (unadjusted)

5.5.11 Patients with no US-detectable pathology

Mean SPADI at baseline did not differ in 34 patients without detectable pathology at baseline compared to 462 patients with any pathology (difference (95% CI) unadjusted 2.10 (-1.31, 5.51), p=0.227; adjusted for variables in Table 5.12 0.20 (-2.84, 2.46), p=0.886).

Table 5.12 SPADI at baseline and 6 months comparing patients with no pathologies and any pathology

	Baseline	**6 months**
No pathology, mean (95%CI)	49.3 (45.9, 52.8)	43.7 (34.9, 52.5)
Any pathology, mean (95%CI)	51.6 (50.7, 52.5)	40.0 (37.9, 42.1)
RC tears full, mean (95%CI)	55.6, (53.3, 57.8)	45.1 (41.4, 48.7)
RC tears partial, mean (95%CI)	51.7 (49.1, 54.2)	40.3 (32.7, 47.8)
Bursitis, mean (95%CI)	51.2 (50.2, 52.1)	39.3 (36.9, 41.8)
Impingement, mean (95%CI)	50.7 (49.6, 51.9)	38.5 (35.3, 41.8)
ACJ pathology, mean (95%CI)	51.9 (50.5, 53.3)	40.5 (37.6, 43.4)
Calcific tendinopathy, mean (95%CI)	49.0 (46.1, 51.9)	34.9 (27.1, 42.6)

GHJ OA, mean (95%CI)	56.0 (52.1, 59.9)	50.7 (42.6, 58.7)
Tendinopathy, mean (95%CI)	51.6 (50.2, 53.1)	40.6 (37.2, 44.0)
Biceps tenosynovitis, mean (95%CI)	52.3 (48.4, 57.1)	38.9 (27.0, 50.8)

Eight out of 34 patients attended our clinic for further review by myself and an consultant orthopaedic surgeon. Of these, one reported symptoms were resolving, two had frozen shoulder, two had possible neck pathology with referral to shoulder, one had snapping scapula, one had poor scapula control and one diagnosis was unsure.

Of the 26 patients who did not attend, nine patients were not contactable, eight reported improved or resolved symptoms, five declined the invitation to attend due to time constraints, three were subsequently told of their diagnosis and declined (GHJ OA, neck and labral tear) and one declined further participation in the study.

From the local results server, two out of 34 patients had subsequent ultrasound imaging and steroid injections.

5.5.12 Analysis without adhesive capsulitis

A sensitivity analysis was undertaken to determine if adhesive capsulitis would affect groupings or outcomes.

There were 39 patients with adhesive capsulitis; they were excluded from the LCA. Characteristics of this group are shown in Table 5.13.

Table 5.13 Frequency of ultrasound pathologies excluding adhesive capsulitis

% of sample	**8**
Age, years: mean (SD)	58.2 (10.3)
Female: %	62% (24)
Injection at time of scan: %	23% (9)
RC tear (y/n): %	18% (7)
Full thickness RC tear: %	13% (5)
Bursitis: %	49% (19)
Impingement: %	26% (10)
Calcific tendinitis: %	5% (2)
ACJ degeneration: %	54% (21)
Glenohumeral OA: %	3% (1)
Adhesive capsulitis: %	100% (39)
Biceps tenosynovitis: %	5% (2)
Rotator cuff tendinopathy: %	26% (10)

The CIC, a-BIC, entropy and BLRT favoured the 4 class solution when excluding adhesive capsulitis. There were equivocal BIC values for 3 and 4 class solutions and equivocal AIC values for 4 and 5 class solutions. On the basis of these values, the 4-class solution was retained (see Table 5.14).

Table 5.14 Model fit and stability measures for solutions with 2 to 6 classes with adhesive capsulitis excluded

Number of classes	df	AIC	BIC	CAIC	a-BIC	Entropy	G^2	Solution %	BLRT p-value
1	247	368.7	401.8	409.8	376.4	1.00	352.7	100%	-
2	238	286.1	356.4	373.4	302.5	0.83	252.1	70%	p=0.010
3	229	202.6	310.1	336.1	227.6	0.91	150.6	39%	p=0.010
4	220	168.1	312.8	347.8	201.7	0.78	98.1	98%	p=0.010
5	211	166.4	348.2	392.2	208.6	0.81	78.4	16%	p=0.160
6	202	167.4	386.5	439.5	218.3	0.81	61.4	16%	p=0.380

The ultrasound characteristics of the groups are outlined in Table 5.15. The groups were very similar to those identified in the full cohort, although there were larger proportions with ACJ degeneration in group 1 and RC tears and rotator cuff tendinopathy in group 2. Despite these differences the same group names were used for consistency.

Table 5.15 Characteristics of groups when adhesive capsulitis is excluded

	Bursitis (w/o ACJ degeneration) n=189	**Bursitis (with ACJ degeneration) n=57**	**RC tear n=73**	**No bursitis or RC tear n=142**
% of sample	48	17	16	20
Age, years: mean (95% CI)	48.9 (46.9, 50.9)	62.6 (59.5, 65.7)	65.2 (62.2, 68.1)	46.0 (42.6, 49.4)
Female: %	54	59	43	42
Injection at time of scan: %	60	33	10	16
RC tear (y/n): %	<1	51	99	4
Full thickness RC tear: %	<1	18	93	<1
Bursitis: %	>99	93	36	16
Impingement: %	77	51	99	7
Calcific tendinitis: %	12	2	2	13
ACJ degeneration: %	39	71	63	30
Glenohumeral OA: %	<1	5	13	2
Biceps tenosynovitis: %	<1	19	8	<1
Rotator cuff tendinopathy: %	21	92	7	16

Probability of membership: mean	0.87	0.83	0.94	0.91
US pathology absent: %	<1	<1	<1	38
Number of pathologies: median (IQR)	2 (2, 3)	4 (3, 5)	3 (3, 4)	1 (0, 1)

When analysing the association between class membership and symptoms (total SPADI and OSS) at baseline there were 461 patients (without adhesive capsulitis) with SPADI data available (see Table 5.16).

Table 5.16 Multivariable analysis of association between class membership and symptoms at baseline excluding adhesive capsulitis

	Coefficient* (95% CI), p-value	
	Total SPADI (n=461)	**OSS (n=453)**
Bursitis (limited inflammation)	Reference	Reference
Bursitis (extensive inflammation)	1.17 (-1.07, 3.42), p=0.304	-0.30 (-1.75, 1.14), p=0.680
RC tear	3.83 (1.70, 5.96), p<0.001	1.19 (-0.14, 2.52), p=0.080
Isolated pathology	-1.35 (-3.42, 0.71), p=0.198	-0.98 (-2.17, 0.22), p=0.108
Age, years	0.06 (0.00, 0.12), p=0.045	0.07 (0.04, 0.11), p<0.001
Female	2.78 (1.36, 4.21), p<0.001	2.14 (1.26, 3.02), p<0.001
Duration of symptoms, months	0.02 (-0.02, 0.05), p=0.333	0.00 (-0.02, 0.02), p=0.962
Uses arms to rise from chair	0.97 (-0.56, 2.50), p=0.213	1.34 (0.40, 2.29), p=0.005
Had physiotherapy before baseline	-2.41 (-4.12, -0.70), p=0.006	-0.98 (-2.04, 0.07), p=0.068
Had 1 injection before baseline	1.08 (-1.08, 3.24), p=0.326	0.15 (-1.24, 1.54), p=0.833
Had 2 injections before baseline	2.58 (-0.87, 6.03), p=0.141	1.28 (-0.75, 3.30), p=0.216
Shoulder activity score	0.14 (-0.07, 0.35), p=0.185	0.12 (-0.01, 0.25), p=0.068
P-SEQ	-0.32 (-0.41, -0.23), p<0.001	-0.25 (-0.30, -0.19), p<0.001

Brief IPQ	0.24 (0.11, 0.37), p<0.001	0.20 (0.12, 0.29), p<0.001
HADS	-0.03 (-0.18, 0.12), p=0.716	-0.02 (-0.11, 0.07), p=0.680
painDetect	0.49 (0.35, 0.62), p<0.001	0.19 (0.11, 0.28), p<0.001

*Interpreted as unit difference in Rasch-transformed symptom score per 1 additional unit of the independent variable

The overall p-value for the differences in SPADI between classes was $F_{(3, 364.5)}$=5.02, p=0.002. In this predictive model, adjusting for the other predictors, SPADI was higher in the RC tear group at baseline than the 'bursitis without ACJ degeneration' [difference 3.83 (1.70, 5.96); t=3.53, p<0.001] and 'bursitis with ACJ degeneration' [difference 2.66 (0.12, 5.19); t=2.06, p=0.040] groups and the 'no bursitis or RC tear' group [difference 5.18 (2.51, 7.86); t=3.81, p<0.001]. At the 10% level of significance there was some indication that SPADI was higher in the 'bursitis with ACJ degeneration' group than the 'no bursitis or RC tear' group [difference 2.53 (-0.33, 5.38); t=1.75, p=0.083]. However, most of these differences were within the reported MDC. Predicted SPADI scores were higher in women, older patients, those with higher brief IPQ scores (indicating they found their condition more threatening) and those with higher painDetect scores (indicating a greater level of neuropathic pain). Those who had physiotherapy before baseline tended to have lower predicted SPADI scores, as did those with higher levels of pain self-efficacy. Estimated total SPADI for the isolated pathology group at age=54 (with everything else held at the mean value) was 47.7 for men and 50.5 for women. A difference of 5.18 units from these starting positions on the Rasch-transformed scale is equivalent to a difference of 20 units for men and 15.4 units for women on the original SPADI. For men, at least, the difference in pain and disability at baseline between the patients with RC tears and those without RC tears or bursitis exceeded the MDC for SPADI. Using SPADI pain instead of total SPADI did not affect the overall conclusions.

There were 453 patients (without adhesive capsulitis) with OSS available at baseline. There was limited evidence that OSS differed between the classes [$F_{(3, 368.5)}$=2.38, p=0.069]. For the OSS there were similar trends for the

questionnaires, physiotherapy, age and sex compared to SPADI, but OSS was also higher in those who used their arms to rise from a chair. OSS did not differ according to pre-baseline treatment.

Note that the coefficients reported for this predictive model cannot be considered to indicate the strength or direction of any putative total causal effects; therefore, we cannot conclude that, for example, RC tears cause more pain and disability. We can only conclude that, having adjusted for the specific variables included in this model, in patients selected according to the methods of the study, the predicted baseline total SPADI score is higher in those with RC tears compared to the other groups.

Using simplified models, the conclusions were the same as for the expanded models with the exception that age was not a predictor in either case (see Table 5.17).

Table 5.17 Simplified multivariable analysis of association between class membership and symptoms (total SPADI and OSS) at baseline

	Coefficient* (95% CI), p-value	
	Total SPADI (n=461)	**OSS (n=453)**
Bursitis (limited inflammation)	Reference	Reference
Bursitis (extensive inflammation)	1.91 (-0.74, 4.56), p=0.158	0.60 (-1.14, 2.34), p=0.500
RC tear	5.87 (3.09, 8.64), p<0.001	2.68 (0.89, 4.47), p=0.003
Isolated pathology	-1.90 (-4.32, 0.52), p=0.124	-1.24 (-2.82, 0.34), p=0.125
Age, years	0.00 (-0.07, 0.07), p=0.997	0.03 (-0.01, 0.08), p=0.162
Female	3.96 (2.22, 5.71), p<0.001	2.85 (1.72, 3.99), p<0.001

Adjusting for the other covariates in the model, there was no evidence that pathology group was predictive of total SPADI at 6 months. Only baseline SPADI was a significant predictor of 6 month score. The pathology groups did not predict the OSS at six months either; only baseline OSS, shoulder activity score and pain self-efficacy score were predictive of the score at 6 months,

higher scores on the latter two variables yielding lower predicted 6 month OSS (Table 5.18).

Table 5.18 Multivariable analysis of association between class membership and symptoms (total SPADI and OSS) at 6 months excluding adhesive capsulitis

	Coefficient* (95% CI), p-value	
	Total SPADI (n=461)	**OSS (n=453)**
Bursitis (limited inflammation)	Reference	Reference
Bursitis (extensive inflammation)	0.83 (-5.30, 6.96), p=0.790	0.36 (-2.67, 3.39), p=0.814
RC tear	2.44 (-3.84, 8.72), p=0.445	2.72 (-0.15, 5.58), p=0.063
Isolated pathology	1.49 (-4.54, 7.53), p=0.626	0.14 (-3.03, 3.31), p=0.931
Age, years	0.04 (-0.14, 0.22), p=0.650	0.02 (-0.07, 0.11), p=0.718
Female	-2.03 (-6.23, 2.17), p=0.342	-0.05 (-2.11, 2.02), p=0.966
Duration of symptoms, months	0.01 (-0.06, 0.08), p=0.740	0.02 (-0.03, 0.08), p=0.438
Uses arms to rise from chair	1.98 (-2.54, 6.50), p=0.389	0.43 (-1.80, 2.66), p=0.704
Had physiotherapy before baseline	0.67 (-4.33, 5.67), p=0.793	-0.63 (-3.03, 1.77), p=0.604
Had 1 injection before baseline	3.59 (-2.11, 9.29), p=0.216	1.38 (-1.42, 4.19), p=0.333
Had 2 injections before baseline	8.37 (-1.35, 18.09), p=0.091	4.14 (-0.63, 8.92), p=0.089
Baseline score (SPADI or OSS)	0.64 (0.35, 0.92), p<0.001	0.30 (0.08, 0.53), p=0.009
Shoulder activity score	-0.63 (-1.26, 0.01), p=0.053	-0.42 (-0.73, -0.11), p=0.008
P-SEQ	-0.21 (-0.49, 0.07), p=0.148	-0.16 (-0.30, -0.01), p=0.036
Brief IPQ	0.17 (-0.21, 0.55), p=0.379	0.08 (-0.11, 0.27), p=0.418
HADS	0.00 (-0.43, 0.44), p=0.983	0.07 (-0.14, 0.28), p=0.509

painDetect	0.05 (-0.39, 0.49), p=0.823	0.04 (-0.16, 0.24), p=0.727

*Interpreted as unit difference in Rasch-transformed symptom score per 1 additional unit of the independent variable

Using simplified models, the conclusions were the same as for the expanded models.

Table 5.19 Multivariable analysis of association between class membership and symptoms (total SPADI and OSS) at 6 months excluding adhesive capsulitis

	Coefficient* (95% CI), p-value	
	Total SPADI (n=461)	**OSS (n=453)**
Bursitis (limited inflammation)	Reference	Reference
Bursitis (extensive inflammation)	1.57 (-4.34, 7.48), p=0.602	1.11 (-1.89, 4.11), p=0.466
RC tear	1.01 (-5.23, 7.25), p=0.750	2.37 (-0.56, 5.30), p=0.113
Isolated pathology	1.88 (-4.05, 7.82), p=0.533	0.16 (-2.92, 3.24), p=0.918
Age, years	0.11 (-0.06, 0.27), p=0.209	0.04 (-0.05, 0.12), p=0.406
Female	-1.28 (-5.30, 2.73), p=0.530	0.37 (-1.63, 2.37), p=0.714
Baseline score (SPADI or OSS)	0.89 (0.68, 1.10), p<0.001	0.58 (0.41, 0.75), p<0.001

None of the individual pathologies predicted SPADI at 6 months when adjusting for baseline SPADI score in complete cases (Table 5.20) or imputed cases with additional covariates (Table 5.21).

Table 5.20 Linear regression of 6 month SPADI on individual pathologies (complete case)

	SPADI total		SPADI pain	
	With AC n=328*	**W/O AC n=300**	**With AC n=326****	**W/O AC n=298**
Age, years	0.09 (-0.07, 0.26), p=0.274	0.09 (-0.08, 0.25), p=0.297	-0.01 (-0.18, 0.16), p=0.934	-0.02 (-0.19, 0.16), p=0.860
Female	-0.96 (-4.77, 2.86), p=0.622	-0.89 (-4.70, 2.92), p=0.646	-1.52 (-5.52, 2.47), p=0.453	-1.41 (-5.41, 2.58), p=0.487
RC tear partial	1.23 (-5.71, 8.17), p=0.728	1.40 (-5.52, 8.32), p=0.691	0.57 (-6.68, 7.82), p=0.877	0.89 (-6.35, 8.13), p=0.809
RC tear full	0.12 (-6.00, 6.24), p=0.969	0.24 (-5.86, 6.35), p=0.937	0.71 (-5.68, 7.10), p=0.827	0.90 (-5.48, 7.29), p=0.781
Bursitis	-0.44 (-5.33, 4.45), p=0.858	-0.32 (-5.19, 4.56), p=0.898	-1.37 (-6.48, 3.73), p=0.598	-1.14 (-6.24, 3.95), p=0.659
Impingement	-1.28 (-6.18, 3.61), p=0.606	-0.92 (-5.71, 3.87), p=0.706	-1.37 (-6.51, 3.76), p=0.599	-0.71 (-5.74, 4.32), p=0.782
Calcific tendinitis	-2.89 (-9.59, 3.81), p=0.397	-2.79 (-9.48, 3.90), p=0.412	-3.57 (-10.55, 3.41), p=0.315	-3.37 (-10.35, 3.61), p=0.343
ACJ degeneration	0.17 (-3.85, 4.18), p=0.936	0.04 (-3.96, 4.04), p=0.983	0.92 (-3.27, 5.11), p=0.665	0.71 (-3.47, 4.89), p=0.738

Glenohumeral OA	6.56 (-3.40, 16.51), p=0.196	6.69 (-3.25, 16.64), p=0.186	3.97 (-6.86, 14.80), p=0.471	4.19 (-6.64, 15.03), p=0.447
Adhesive capsulitis	-2.59 (-9.60, 4.42), p=0.468	-	-4.61 (-11.86, 2.65), p=0.213	-
Biceps tenosynovitis	-3.81 (-13.47, 5.84), p=0.438	-4.06 (-13.69, 5.56), p=0.407	-1.82 (-11.90, 8.27), p=0.724	-2.25 (-12.33, 7.82), p=0.660
Rotator cuff tendinopathy	0.62 (-3.68, 4.92), p=0.777	0.77 (-3.50, 5.05), p=0.722	-0.26 (-4.76, 4.24), p=0.910	0.02 (-4.46, 4.50), p=0.993
Baseline SPADI (total or pain)	0.89 (0.69, 1.09), p<0.001	0.87 (0.68, 1.07), p<0.001	0.70 (0.55, 0.85), p<0.001	0.68 (0.53, 0.83), p<0.001
Adjusted R^2	0.20	0.19	0.20	0.20

* 172 patients did not complete total SPADI at both baseline and 26 weeks **174 patients did not complete SPADI pain at both baseline and 26 weeks

Table 5.21 Linear regression of 6 month SPADI on individual pathologies (imputed data; adding covariates)

	SPADI total		SPADI pain	
	With AC n=330*	W/O AC n=301	With AC n=328*	W/O AC n=299
Age, years	0.00 (-0.17, 0.18), p=0.976	0.04 (-0.14, 0.23), p=0.666	-0.09 (-0.27, 0.09), p=0.327	-0.06 (-0.26, 0.13), p=0.524
Female	-1.70 (-5.67, 2.27), p=0.400	-1.82 (-6.06, 2.42), p=0.399	-2.65 (-6.81, 1.51), p=0.211	-2.55 (-7.04, 1.93), p=0.263
RC tear partial	2.54 (-4.37, 9.45), p=0.471	3.05 (-4.32, 10.43), p=0.415	1.77 (-5.48, 9.01), p=0.632	1.71 (-6.07, 9.50), p=0.665
RC tear full	2.74 (-3.66, 9.14), p=0.400	2.77 (-4.09, 9.63), p=0.428	2.68 (-4.00, 9.36), p=0.431	2.83 (-4.39, 10.05), p=0.441
Bursitis	-1.65 (-6.69, 3.39), p=0.520	-1.85 (-7.34, 3.63), p=0.506	-2.34 (-7.61, 2.94), p=0.384	-1.97 (-7.74, 3.80), p=0.501
Impingement	-0.35 (-5.29, 4.59), p=0.890	-0.34 (-5.56, 4.88), p=0.897	-0.71 (-5.90, 4.48), p=0.788	-0.87 (-6.39, 4.64), p=0.755
Calcific tendinitis	-2.82 (-9.47, 3.84), p=0.406	-3.46 (-10.61, 3.69), p=0.341	-3.23 (-10.19, 3.73), p=0.362	-3.55 (-11.05, 3.95), p=0.352
ACJ degeneration	-0.10 (-4.13, 3.93), p=0.961	-1.17 (-5.52, 3.17), p=0.595	0.59 (-3.62, 4.81), p=0.782	-0.29 (-4.88, 4.29), p=0.900
Glenohumeral OA	5.10 (-4.94, 15.14), p=0.319	4.62 (-6.07, 15.31), p=0.396	3.63 (-7.32, 14.57), p=0.515	2.25 (-9.51, 14.01), p=0.706

Adhesive capsulitis	-2.23 (-9.28, 4.82), p=0.534	-	-4.88 (-12.24, 2.48), p=0.193	-
Biceps tenosynovitis	-3.79 (-13.43, 5.85), p=0.440	-5.42 (-15.99, 5.15), p=0.313	-1.99 (-12.09, 8.10), p=0.698	-3.93 (-15.05, 7.18), p=0.487
Rotator cuff tendinopathy	0.83 (-3.48, 5.13), p=0.706	0.81 (-3.75, 5.37), p=0.726	-0.08 (-4.60, 4.44), p=0.974	-0.13 (-4.94, 4.69), p=0.959
Injection at time of scan	4.24 (-0.22, 8.70), p=0.063	4.07 (-0.67, 8.82), p=0.092	3.60 (-1.09, 8.29), p=0.132	3.16 (-1.87, 8.18), p=0.217
Duration of symptoms, months	0.00 (-0.05, 0.05), p=0.895	0.01 (-0.06, 0.09), p=0.731	-0.01 (-0.06, 0.04), p=0.700	-0.02 (-0.10, 0.07), p=0.685
Uses arms to rise from chair	2.29 (-1.93, 6.50), p=0.286	2.06 (-2.54, 6.65), p=0.379	0.89 (-3.56, 5.35), p=0.693	0.59 (-4.29, 5.48), p=0.811
Had physiotherapy before baseline	0.14 (-4.54, 4.82), p=0.952	0.60 (-4.54, 5.73), p=0.819	-0.63 (-5.47, 4.22), p=0.799	-0.21 (-5.54, 5.12), p=0.938
Had 1 injection before baseline	2.22 (-3.08, 7.52), p=0.411	1.98 (-3.90, 7.86), p=0.507	3.07 (-2.48, 8.62), p=0.277	3.26 (-2.92, 9.45), p=0.299
Had 2 injections before baseline	5.96 (-3.34, 15.26), p=0.208	6.88 (-3.10, 16.85), p=0.176	6.30 (-3.42, 16.03), p=0.203	7.15 (-3.35, 17.65), p=0.181
Baseline SPADI (total or pain)	0.62 (0.35, 0.89), p<0.001	0.58 (0.29, 0.87), p=0.000	0.56 (0.37, 0.75), p<0.001	0.55 (0.34, 0.76), p<0.001
Shoulder activity score	-0.59 (-1.17, -0.02), p=0.041	-0.61 (-1.25, 0.03), p=0.060	-0.64 (-1.25, -0.04), p=0.037	-0.69 (-1.37, -0.01), p=0.048
P-SEQ	-0.20 (-0.47, 0.07), p=0.148	-0.20 (-0.49, 0.08), p=0.164	-0.25 (-0.52, 0.03), p=0.075	-0.26 (-0.55, 0.04), p=0.087

Brief IPQ	0.18 (-0.18, 0.54), p=0.333	0.16 (-0.23, 0.56), p=0.409	0.09 (-0.29, 0.47), p=0.639	0.06 (-0.35, 0.48), p=0.760
HADS	0.02 (-0.38, 0.43), p=0.911	0.01 (-0.42, 0.45), p=0.950	-0.05 (-0.47, 0.38), p=0.834	-0.04 (-0.50, 0.42), p=0.863
painDetect	-0.01 (-0.42, 0.40), p=0.961	0.09 (-0.36, 0.53), p=0.705	0.00 (-0.43, 0.42), p=0.983	0.07 (-0.38, 0.53), p=0.748
Adjusted R^2	0.23	0.22	0.23	0.21

* 170 patients did not complete total SPADI at 26 weeks **172 patients did not complete SPADI pain at 26 weeks

In conclusion, the inclusion of adhesive capsulitis did not affect the number of groups or the predictive ability of pathologies for 6 month SPADI outcome

5.6 **Discussion**

This is the largest prospective, longitudinal study on community-based patients undergoing an ultrasound scan of their painful shoulder, and the first to look at the use of both multiple and individual ultrasound pathologies in predicting outcome.

This prospective longitudinal study demonstrated that ultrasound-detected pathologies, whether grouped or individually, do not predict medium-term outcomes when used in a current usual care pathway, if differences at baseline are accounted for. The strongest predictor of medium-term outcomes is baseline symptoms.

This study found four groups of patients with different patterns of ultrasound-detected shoulder pathologies: bursitis with no ACJ degeneration; bursitis with ACJ degeneration; RC tears; group with no RC tear or bursitis. These groups differed only slightly from our earlier retrospective study(265). In the current study, more covariates were included in the LCA model, improving classification accuracy. The groups were re-named to reflect the main pathologies that determined group membership.

These groups may represent a chronological progression of shoulder problems, as the “bursitis without ACJ degeneration” group and group with “no tears or bursitis” were youngest. Patients with “bursitis with ACJ degeneration” were the next oldest group, followed by “RC tear” group. ACJ degeneration increases with age, and if ACJ degeneration may be an incidental finding (given that radiographic OA can be asymptomatic), three groups exist: bursitis, tears or neither of these pathologies. Knowledge of these pathologies and the use of the simplified rule may be helpful in the clinical setting if effective treatments are developed.

Although the change in symptoms between time-points did not differ between groups, injections improved short-term symptoms for all groups. No differences in short-term response to steroids between groups with inflammation (bursitis groups 1 and 2) and no inflammation (groups 3 and 4) were found. Adjusting for the other variables in the model, predicted 6-month

SPADI was higher in patients who received an injection at baseline. However, because this was an observational study it cannot conclude that corticosteroids lead to poorer long-term outcome.

Although those in the bursitis groups were more likely to receive injection and RC tear group were more likely to receive surgery after scan, no differences in outcomes between groups were found. This suggests that although ultrasound diagnosis may influence treatment received, it does not affect medium-term outcome.

Patients with bursitis were less likely to receive steroid injections if they had concomitant RC tears compared to those without. However, patients receiving injections improved their symptoms irrespective of a tear. A previous study also found that patients with tears receiving corticosteroid injection had pain relief at 3 months(486). Patients are less likely to receive corticosteroids due to the putative deleterious effects on tendons. However, no evidence for such effects has been found in clinical practice(487).

Adhesive capsulitis may be considered a separate disease entity and a sensitivity analysis showed little difference when this was excluded. Similar groups were identified and neither individual pathologies nor identified groups predicted medium-term outcomes when used in a current usual care pathway. The strongest predictor of medium-term outcomes was baseline symptoms.

Pathologies exist in symptomatic and asymptomatic shoulders(82) and there is a lack of understanding in the causal relationship between imaging-detected pathology and symptoms. This thesis did not fully assess the structure-pain relationship as the population only included patients with shoulder pain and did not capture the full range of covariates necessary for this analysis. However, the study has captured detailed data on the association between pathologies and symptoms in patients seeking treatment for shoulder pain.

UK guidelines advise the use of imaging of the RC, ideally following secondary care referral, once conservative treatment has failed(378). These guidelines were developed from expert opinion and available evidence, but did not include any study evaluating the predictive value of ultrasound pathologies.

Recent studies comparing surgery for patients with subacromial pain(488), impingement syndrome(489) or RC tears(490) with no treatment or conservative treatment found all patients improved and no clinically significant differences between groups in the medium to long-term. A recent randomised control trial found no difference in patients receiving individual ultrasound-pathology tailored treatment compared to usual care at 12 months, although combination of multiple pathologies was not assessed and the study was under-enrolled by 50%(375).

Given our finding that the use of ultrasound does not predict medium-term outcomes in a usual care situation, and if patients tend to improve to the same extent irrespective of the pathology present, knowing which specific pathologies are present will only be useful if effective treatments targeted to these pathologies are available. The precise role of ultrasound in the shoulder pain pathway currently remains uncertain.

5.7 Limitations

There were limitations to this study. Although 500 patients were recruited, only 330 (66%) completed follow-up. Although these numbers were sufficient for evaluating our primary outcome, this may result in bias. However, this can be considered an acceptable response rate for a survey study, as the overall response rates for surveys across 1607 studies was found to be 48.3%(481). Additionally, although those who completed follow-up were older and less anxious and depressed than non-completers, other characteristics including SPADI were similar. This was an observational study and there may be recall bias amongst some of the patient-reported outcome measures, especially with treatment.

This study evaluated outcomes according to current treatment pathways, therefore treatment was not standardised. Treatment including physiotherapy and steroids such as dose, frequency, duration and type may have varied. Compliance in patients undertaking physiotherapy could not be ensured. It is possible that there was channelling bias to treatment by pathologies found, although SPADI outcomes were adjusted for reported treatment. Although

analgesia could be determined from electronic records of prescriptions, the use of over-the-counter NSAIDS could not be excluded.

Other than other than full thickness and partial tears, the severity of ultrasound pathologies was not assessed and it is possible that severity, rather than presence, of pathology would be a more important predictor of outcome. For example, the severity of RC tendinopathy was not captured. The inter reader and intra-reader reliability of ultrasound scans was not assessed. There were 8 ultrasound technicians, and this may lead to a wide variability in results. Standardised definitions are essential to understand outcomes. Although I tried to standardise the definition of ultrasound pathologies, there is still the potential for variations in interpreting pathologies. For example, pressure applied when using the probe and the room temperature may affect the results. The point at which measurements should be taken from (e.g the inner or outer surface of the bursa) could also affect interpretation.

There was only one ultrasound time-point, at baseline. It would be interesting to see how pathologies change over time, if the described groupings change, and if patients move between groups. Chapter 3 found enlarging RC tears was associated with an increased incidence of symptoms, although analysis of pathology combinations was not assessed in the studies included in the review. Serial ultrasound scans may provide insight into this.

When assessing the patients with no detectable ultrasound pathology, the clinician was aware of the ultrasound results.

5.8 **Conclusions**

There were no differences in medium-term outcomes of patients undergoing their first shoulder ultrasound by pathology group membership or individual pathologies. Accurately diagnosed pathologies do not predict medium-term outcomes in the current care pathway. The role of ultrasound in shoulder care pathways needs re-evaluation. Ultrasonography may be useful for guiding injections or if evidence-based therapies for individual pathologies are developed.

6 Chapter 6 - Defining a cut-off for the Patient Acceptable Symptom State: longitudinal data from a community cohort using the Shoulder Pain and Disability Index

6.1 Introduction

As discussed in Chapter 2, one example of a commonly used PROM for shoulder pain is the SPADI, which is responsive, reliable and has construct validity. SPADI measures pain and physical function, and is measured on an ordinal scale. Results are often presented as changes in mean or median values between treatment groups. When discriminating between treatments at a population level, analysing ordinal scores provides the greatest power. The clinical relevance of these results, however, are not always easily interpretable at the level of an individual response: clinicians need to understand the number of patients who have a response to treatment and how well they are doing. A statistically significant change in the score may not necessarily reflect therapeutic success.

Improving clinical interpretation can be achieved by dichotomising therapeutic success. One method of understanding the relevance of PROMS at the individual level is the patient acceptable symptom state (PASS) which, as discussed in Chapter 2, is defined as the value on a scale beyond which the patient feels good enough to continue in that state. Understanding the level for PASS would provide information on therapeutic success or failure at the individual level in addition to the summary effects calculated from the SPADI score at the group level. Establishing the SPADI cut-off for PASS would therefore provide a tool for standardising responder rates in clinical trials.

6.2 Aims

There has been no previous study evaluating the PASS for SPADI in a longitudinal, prospective cohort of community-based patients. The aim of this Chapter is to determine, for a primary care population, the PASS thresholds for SPADI and its pain and function subsets over time, and to evaluate if any

variables may influence the PASS threshold. The relationship between PASS at baseline and subsequent treatments received was also evaluated.

6.3 Materials and methods

The (Leeds Observational Cohort Ultrasound Study) LOCUS study was carried out with ethical approval from North East - Newcastle & North Tyneside 2 Research Ethics Committee (16/NE/0108) and given Research and Development permission from Leeds Teaching Hospitals Trust (R&I number RR16/128 (201260))

6.3.1 Study population

The study population was the same as those recruited in Chapter 5.

6.3.2 Data collection

Patients were asked to complete a questionnaire at both baseline and at 6 months. Data collection included age (years), gender, body mass index (BMI), duration of disease prior to scan, currently in pain (yes/no), co-morbidities and other joints affected. Treatment received (physio, number of injections and/or surgery) prior to initial scan was asked at baseline and treatments received during the study was collected at 6 months. Injections at baseline was also recorded as treatment might alter a patient's perception of their care and their expectations, which may in turn affect the likelihood of reporting PASS (248). To avoid recruitment bias, patients were recruited until the following quotas were met: males aged <54 (25%), males aged ≥54 (22%), females aged <54 (25%), females aged ≥54 (28%). These estimates were derived from the retrospective study described in Chapter 4.

Patients completed a set of questionnaires, including SPADI and PASS on the day of the scan. At 6 months, patients were asked to complete a postal questionnaire which included SPADI and PASS. In order to maximise the response rate at 6 months, strategies such as minimising the length of the questionnaire whilst maintaining readability, as well as including a stamped addressed return envelope alongside the questionnaire were employed.

Patients were asked “in the next few months, if you were to remain as you were during the last 48 hours, would this be acceptable or unacceptable to you?”; this is the PASS wording recommended by an OMERACT special interest group (248).

6.3.3 Statistical analysis

Descriptive statistics were used to describe the study sample. The SPADI scores were Rasch transformed as described in Chapter 5.

PASS was calculated using 2 approaches which have previously been described. Tubach *et al.* (491) estimated PASS by constructing cumulative percentages curve of patients who considered their state acceptable as a function of the PROM score. The 75th percentile was chosen as this most easily represented point where the curve plateaued. PASS can also be calculated using the receiver operating characteristic (ROC) curve by identifying cut-offs that yielded the lowest number of false positives and false negatives (492). This was achieved using the Youden index, as has been recommended (493).

The association between PASS and SPADI, with other co-variates, was assessed using logistic regression. Interaction terms were added between baseline SPADI and 6 month SPADI to evaluate if the 6 month PASS cut-off depended on baseline value. To illustrate the influence of baseline score on PASS at 6 months, cut-offs were calculated separately within tertiles of baseline SPADI. Reliability of SPADI was evaluated using standard error of measurement (SEM) and smallest detectable change (SDC) using Cronbach’s alpha. Descriptive statistics was used to evaluate the relationship between PASS at baseline and treatment received in the subsequent 6 months.

6.4 Results

500 patients were recruited into this study. 164 patients were lost to follow-up (2 of whom did not complete PASS at baseline): 26 no longer wished to take part; 138 did not return their postal questionnaire. Of those who responded, 11 patients did not complete their PASS question at 6 months, 1 of which did

not have a baseline score. 5 patients did not complete PASS at baseline but completed PASS at 6 months. A total of 320 participants (64%) had PASS data at both time-points.

Using a testlet approach the total SPADI showed acceptable fit to the partial credit Rasch model (total item-trait interaction Chi-square=10.95, p=0.896; person separation index=0.87; Cronbach's alpha=0.88; individual testlet fit Chi-squares pain p=0.96, disability p=0.56; acceptable fit residual for pain -2.35, slightly low fit residual for disability -2.67; person location mean=0.09, SD=0.42; person fit residual mean=-0.54, SD=0.84; only four patients of 492 in the calibration sample had extreme scores). In particular there was no evidence of multidimensionality (2.83% of t-tests significant at 5% level), indicating that a total score combining the pain and disability subscales was valid. There was no evidence of substantive DIF (criterion: effect size >0.2 for paired comparison of person estimates before and after splitting for DIF) by age, sex, shoulder side or visit, the latter indicating that the SPADI scale remains invariant over time.

Questionnaire responders and non-responders were compared at 6 months (Table 6.1). The non-responders were significantly younger (mean age 46.7 $p<0.05$) and had significantly higher levels of anxiety (HADS score 6) and depression (HADS 5). Age, BMI, baseline SPADI and PASS did not differ between the groups.

Patients who did not report PASS at baseline were significantly more anxious (HADS = 5, $p<0.05$) and depressed (HADS = 4, $p<0.05$) (Table 6.2). Those that did not report PASS at baseline had higher SPADI baseline scores compared to those who did report PASS. Significant differences were seen for injection at scan and all SPADI scores including subscales at baseline. There was no difference in age, gender or duration of pain at baseline between patients who reported PASS and who did not report PASS at 6 months.

In patients who reported PASS at baseline (n=69), 59 remained in PASS at 6 months; in patients who did not report PASS at baseline (n=251), 144 reported PASS at 6 months.

Table 6.1 Characteristics of responders and non-responders

	PASS data both time points *n* = 320	Only PASS data at baseline *n* = 164	p-value
Female, N (%)	175 (55)	89 (54)	0.06
Age, years, mean (SD)	57.7 (13.7)	46.7 (13.2)	<0.001
BMI, kg/m^2, mean (SD)	27.8 (5.35)	27.0 (5.12)	0.09
Pain duration, months, median (IQR)	6.2 (3.7-10.3)	5.7 (3.3-10.5)	0.31
Painful joints, median (IQR)	3 (1-5)	2 (1-5)	0.28
Injection received, N (%)	127 (40)	55 (34)	0.19
HADS anxiety, median (IQR)	4 (2-8)	6 (3-10)	0.001
HADS depression, median (IQR)	3 (1-6)	5 (2-8)	<0.001
Bilateral shoulder pain, yes, N (%)	53 (17)	20 (12)	0.21
PASS, +ve, N (%)	69 (22)	34 (21)	0.88
SPADI total, mean (SD)	51.1 (9.6)	52.0 (9.9)	0.32
SPADI pain, mean (SD)	49.2 (13.3)	50.4 (13.4)	0.38
SPADI disability, mean (SD)	45.2 (14.0)	45.9 (15.9)	0.65

Table 6.2 Baseline characteristics based on baseline PASS classification

	All patients (N=492)	PASS+ (n=105)	PASS – (n=387)	p-Value
Female, N (%)	259 (52)	53 (51)	203 (53)	0.72
Age, years, mean (SD)	54.2 (14.5)	53.8 (16.4)	54.2 (14.0)	0.83
BMI, kg/m^2, mean (SD)	27.6 (5.26)	27.4 (5.38)	27.6 (5.25)	0.51
Pain duration, months, median (IQR)	6.0 (3.6-10.4)	6.3 (3.6-12.6)	5.7 (3.6-10.1)	0.26
Painful joints, median (IQR)	3 (1-5)	2 (1-4)	3 (1-5)	0.001
Injection received, N (%)	189 (37.8)	24 (23)	162 (42)	<0.001
HADS anxiety, median (IQR)	5 (2-5)	3 (1-6)	5 (2-9)	<0.001
HADS depression, median (IQR)	4 (2-7)	3 (1-5)	4 (2-8)	<0.001
Bilateral shoulder pain, N (%)	78 (16)	16 (15)	60 (16)	0.94
SPADI total, mean (SD)	51.5 (9.8)	45.3 (10.5)	53.5 (8.5)	<0.001
SPADI pain mean (SD)	49.6 (13.4)	40.5 (11.0)	52.2 (13.0)	<0.001
SPADI disability mean (SD)	45.6 (14.7)	36.7 (15.0)	48.2 (13.6)	<0.001

Tests are t-tests, Mann-Whitney, or chi-squared as appropriate

Those that reported PASS at 6 months did not differ in age, gender or duration of pain at baseline from those who did not report PASS (Table 6.3), but patients reporting PASS at 6 months reported less severe anxiety and depression at the 6 month time-point, and were less likely to report pain in both shoulders.

Table 6.3 Baseline characteristics based on 6 months PASS classification in patients with PASS at both time-points

	PASS (+ve) *n* = 203	PASS (-ve) *n* = 117	p-value
Female, N (%)	106 (52)	69 (59)	0.24
Age, years, mean (SD)	57.9 (13.9)	57.4 (13.6)	0.76
BMI, kg/m^2, mean (SD)	27.5 (5.35)	28.6 (5.30)	0.10
Pain duration, months, median (IQR)	6.3 (3.8-10.4)	5.5 (3.6-10.3)	0.42
Painful joints, median (IQR)	3 (1-4)	3 (2-5)	0.19
Injection received, N (%)	68 (33)	62 (52)	0.001
HADS anxiety, median (IQR)	4 (2-7)	6 (2-10)	0.01
HADS depression, median (IQR)	3 (1-6)	4 (2-8)	0.01
Bilateral shoulder pain, N (%)	25 (12)	28 (24)	0.007
SPADI total, mean (SD)	49.2 (8.8)	54.2 (9.9)	<0.001
SPADI pain, mean (SD)	46.4 (11.3)	54.2 (15.1)	<0.001
SPADI disability, mean (SD)	43.1 (12.8)	48.8 (15.4)	<0.001

Unadjusted PASS cut-offs for SPADI total and its subscales are shown in Table 6.4. The PASS for SPADI at baseline was 49.8 and 46.9 using the 75th percentile method and ROC method (AUC 0.77; 95% CI=0.71, 0.83) respectively. At 6 months, the PASS cut-off values were 46.2 and 45.1 respectively, a small decrease from baseline. The SEM for SPADI total, pain and disability was 3.5, 5.3 and 5.2 respectively, and SDC was 12.9, 14.4 and 12.2 respectively. This shows that those small changes over time were within measurement error. These values were smaller than the reported MDC for SPADI but were derived using different methods, and using Rasch model-transformed, interval scaled values. The majority of people reporting

improvement greater than SDC were PASS (+ve) at 6 months: total SPADI 97/108 (90%), SPADI pain 105/124 (85%) and SPADI disability 113/130 (87%).

Adjusting for baseline SPADI score, PASS at 6 months was significantly associated with 6 month total SPADI score, but not age or gender (Table 6.5). At the 10% level of significance, those who had received injections at baseline were less likely to report PASS at 6 months (OR (95% CI)=0.59 (0.32, 1.07); p=0.080). Patients who had injections had more severe pain, worse illness perception and more painful joints at baseline (Table 6.6).

Table 6.4 Unadjusted PASS cut-offs for SPADI (n=320)

	75th percentile method					ROC method					
SPADI score	Cut-off	Sensitivity	Specificity	PPV	NPV	Cut-off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV
Total baseline	49.8	0.75	0.63	0.36	0.90	46.9	0.77 (0.71,0.83)	0.59	0.80	0.45	0.88
Total 6 months	46.2	0.75	0.80	0.87	0.66	45.1	0.87 (0.83,0.91)	0.72	0.86	0.90	0.64
Pain baseline	45.6	0.77	0.65	0.38	0.91	41.7	0.79 (0.73,0.85)	0.65	0.82	0.51	0.89
Pain 6 months	39.5	0.73	0.84	0.89	0.64	42.3	0.88 (0.85,0.92)	0.84	0.78	0.87	0.74
Disability baseline	45.7	0.70	0.64	0.35	0.88	44.6	0.79 (0.73,0.85)	0.70	0.68	0.38	0.89
Disability 6 months	40.8	0.74	0.79	0.86	0.64	41.2	0.88 (0.85,0.92)	0.76	0.78	0.86	0.65

Table 6.5 The association of PASS at 6 months with other covariates

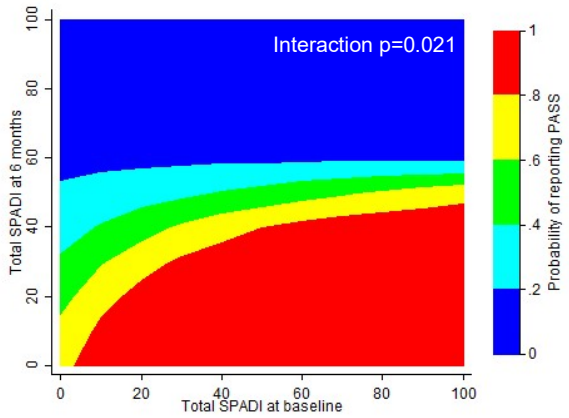
	Without interaction			With interaction		
	OR	95% CI	p-value	OR	95% CI	p-value
Total SPADI 6 months	0.858	0.821, 0.896	<0.001	0.856	0.820, 0.893	<0.001
Total SPADI baseline	1.027	0.983, 1.073	0.224	1.045	1.003, 1.090	0.037
Age, per year	1.016	0.993, 1.038	0.175	1.016	0.993, 1.039	0.170
Sex (male)	1.166	0.636, 2.137	0.619	1.128	0.612, 2.079	0.699
Injection received at baseline	0.585	0.321, 1.065	0.080	0.556	0.303, 1.022	0.059
Number of joints	0.981	0.898, 1.073	0.679	0.985	0.899, 1.079	0.749
SPADI interaction (6 months X baseline)	-	-	-	0.998	0.996, 1.000	0.021

Table 6.6 Characteristics of patients by baseline shoulder steroid injection status

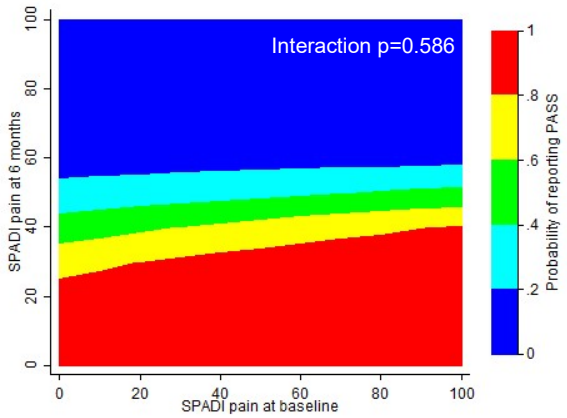
	Injection (*n*=127)	No injection (*n*=192)	p-value
Female, N (%)	107 (56)	67 (53)	0.60
Age, years, mean (SD)	57.6 (12.2)	57.9 (14.8)	0.89
BMI, kg/m^2, mean (SD)	28.1 (5.0)	27.8 (5.5)	0.65
Baseline HADS anxiety, median (IQR)	4 (2-9)	4 (2-8)	0.45
Baseline HADS depression, median (IQR)	4 (2-6)	3 (1-6)	0.14
Baseline bilateral shoulder pain, N (%)	29 (23)	23 (12)	0.01
Baseline painful joints, median (IQR)	3 (2-5)	2 (1-4)	0.03
Pain duration, months, median (IQR)	6.6 (3.9-12.4)	5.6 (3.6-9.5)	0.24
SPADI pain, mean (SD)			
Baseline	50.9 (13.0)	48.2 (13.5)	0.08
6 months	39.7 (18.4)	34.7 (20.6)	0.03
SPADI disability, mean (SD)			
Baseline	46.8 (12.2)	44.2 (15.1)	0.10
6 months	37.7 ± 19.2	30.8 ± 20.7	0.004
Illness perception, median (IQR)			
Baseline	47 (39-54)	41 (35-49)	<0.001
6 months	44 (32-53)	37 (29-47)	<0.001

There was no evidence that achieving PASS at 6 month might vary by age, gender, baseline injection or the number of painful joints (all interactions $p>0.1$, data not shown). However, there was a significant interaction indicating that the association between the 6 month total SPADI score and 6 month PASS differed according to baseline total SPADI score (Table 6.5; Figure 6.1a). The point on the 6 month score associated with a high probability of reporting PASS increased with baseline score. This was driven by disability (Figure 6.1b) rather than pain (Figure 6.1c). Patients with more severe disability at baseline were willing to accept a comparatively greater degree of disability at 6 months. In contrast, there was a more stable upper limit of pain that was acceptable at 6 months, irrespective of pain at baseline.

a)



b)



c)

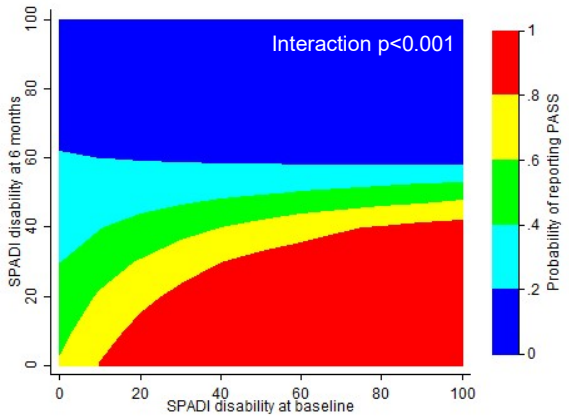


Figure 6.1 Association between the 6 month total SPADI score and 6 month PASS differed according to baseline total SPADI score

In these plots, completely horizontal shaded bands would indicate no influence of baseline SPADI on the association between 6 month SPADI and PASS. Figure 1b shows very little effect of baseline SPADI pain; most of the effect seen for total SPADI is driven by the disability subscale.

When baseline SPADI total score and SPADI subscales were divided into tertiles, the more symptomatic a patient was at baseline (higher SPADI score), the higher their SPADI cut-off was for PASS at 6 months (Table 6.7; Figure 6.2). Despite the lack of significant interaction, the pain cut-off varied to a degree by baseline score; however, the effect was much more pronounced for disability.

Table 6.7 Variability in PASS cut-offs at 6 months

		75th percentile method					ROC method				
SPADI total	**Range**	**Cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Tertile 1	0-45	39.4	76 (64, 85)	83 (65, 94)	92 (82, 97)	58 (42, 73)	40.6	80 (69, 88)	80 (61, 92)	91 (81, 97)	62 (45, 77)
Tertile 2	46-66	47.2	75 (64, 84)	78 (58, 91)	91 (81, 97)	53 (36, 69)	44.9	65 (53, 76)	93 (76, 99)	96 (87, 100)	48 (34, 62)
Tertile 3	67-96	49.4	76 (61, 87)	88 (77, 95)	83 (67, 93)	83 (71, 91)	50.3	78 (64, 89)	88 (77, 95)	84 (69, 93)	84 (72, 92)
SPADI pain	**Range**	**Cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Tertile 1	0-58	37.3	76 (65, 85)	79 (58, 93)	92 (83, 98)	50 (33, 67)	33.5	68 (57, 78)	92 (73, 99)	96 (88, 100)	47 (32, 62)
Tertile 2	60-74	40.6	77 (65, 86)	73 (55, 87)	86 (75, 94)	59 (42, 74)	36.7	62 (50, 73)	94 (80, 99)	96 (86, 100)	53 (39, 66)
Tertile 3	76-100	44.8	76 (61, 87)	88 (77, 95)	84 (70, 93)	81 (70, 90)	40.1	71 (57, 83)	97 (88, 100)	95 (82, 99)	80 (69, 89)
SPADI disability	**Range**	**Cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Cut-off**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Tertile 1	0-35	25.1	75 (64, 84)	73 (52, 88)	89 (79, 96)	50 (33, 67)	33.0	87 (77, 94)	69 (48, 86)	89 (80, 95)	64 (44, 81)
Tertile 2	36-61	43.4	77 (65, 86)	61 (42, 78)	82 (70, 90)	54 (37, 71)	44.2	84 (73, 92)	61 (42, 78)	83 (72, 91)	63 (44, 80)
Tertile 3	62-95	46.8	76 (62, 87)	86 (74, 94)	83 (69, 92)	80 (68, 89)	47.2	82 (69, 91)	86 (74, 94)	84 (70, 93)	84 (72, 93)

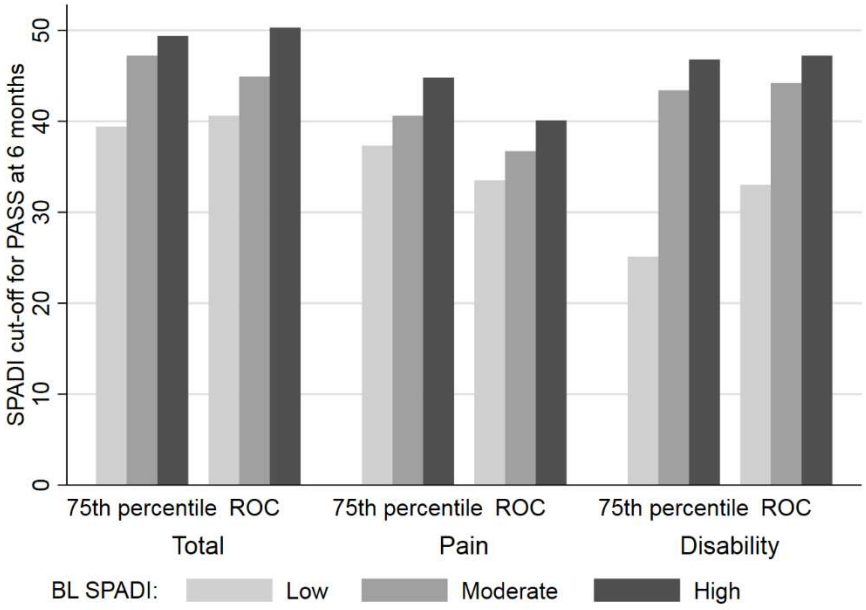


Figure 6.2 Variation in 6 month SPADI PASS cut-offs according to baseline (BL) SPADI, by each of two methods

Patients who reported PASS at baseline went on to receive fewer treatments (corticosteroids injections, physiotherapy, or surgery) in the 6 month follow-up compared to those who did not report PASS (Table 6.8).

Table 6.8 Patients reporting PASS at baseline and subsequent treatment received

	Treatments received over 6 months		Total
	Yes	No	
Baseline PASS -ve (%)	203 (83.2)	43 (63.2)	246 (78.9)
Baseline PASS +ve (%)	41 (16.8)	25 (36.8)	66 (21.1)
Total	244	68	312

6.5 **Discussion**

This is the first study to evaluate the PASS threshold for SPADI over time in a community-based cohort. The PASS cut-off varied between the different methods employed and baseline severity affected PASS cut-off at follow-up. The likelihood of achieving PASS for a given 6 month score depended on the baseline score. The factors associated with achieving PASS were steroid injections at baseline and SPADI at 6 months. Small changes in group-level PASS threshold over time were within measurement error.

PASS provides information on therapeutic success at the individual level and is a useful tool for standardising responder rates in clinical trials. However, the construct of PASS does not reflect the desire to improve from the current state: patients may define their state as acceptable, but still want to feel better.

The 75th percentile method may not be appropriate for determining change in PASS over time, because the scores within those reporting PASS may decrease, affecting the location of the 75th percentile. Although the SPADI cut-offs for PASS identified using the 75th percentile and ROC methods demonstrated similar trends over time, cut-off values differed between methods. The optimum method for calculating PASS has not been demonstrated (493). In our study, the ROC method was more sensitive and the 75th percentile method more specific. The optimum method may therefore be more suitable depending on the intended purpose of the PASS cut-off.

The PASS cut-offs for SPADI differ compared to a previous study. In a prospective cohort study of 100 consecutive patients with inflammatory or degenerative shoulder disease undergoing shoulder surgery (arthroplasty or non-arthroplasty), the PASS and SPADI were evaluated at 1 year follow-up (494). The score for SPADI needed for PASS was 33.7 using the 75th percentile threshold and 41 for the ROC curve method (AUC 0.90). There may be several reasons for this difference. Christie *et al.* used a different definition of PASS with no time anchor. The demographics and inclusion criteria also differed. In the study by Christie *et al.* 75% were female, had an average age of 63.2 and included patients with both degenerative and inflammatory

conditions. In contrast, our study involved 52% females with an average age 9 years younger at 54.2 years. Inflammatory conditions were also excluded. Treatment expectation may also influence PASS (495) and those who have undergone surgery may expect a better improvement and therefore have a lower cut-off for PASS.

The 75th percentile method and ROC curve method showed overall that although patients reported slightly lower levels of symptoms as acceptable at 6 months compared to baseline, this was within measurement error. Substantive longitudinal changes in PASS threshold at the group level, where they are found, may be a result of expectations of improvement in symptoms at 6 months. In a study evaluating patients treated with adalimumab for ankylosing spondylitis, PASS thresholds declined over 24 weeks, which may reflect the change of expectations from a highly effective treatment (495). In another study, PASS appeared stable over time only after 6 months after joint replacement (496). The PASS threshold at 3 months was lower, suggesting that PASS may change with treatment expectation. In agreement with our findings, previous longitudinal studies evaluating PASS in rheumatoid arthritis (497) and ankylosing spondylitis in patients treated with anti-inflammatories (498), the PASS was found to be stable over time over a 52 week and 10 week period respectively. Although these conflicting findings may be a result of varying treatment expectation, PASS may also be disease specific.

Disease adaptation may alter interpretation of a questionnaire, changing a patient's individual PASS threshold over time. This response shift can only be assessed if the measurement properties of the questionnaire itself are time invariant, which was confirmed to be the case. The level of symptoms that patients found acceptable at 6 months has been shown to be associated with severity of symptoms at baseline: patients in higher baseline tertiles of symptoms reported acceptable states with higher levels of symptoms at 6 months. In addition, the likelihood of PASS at 6 months for a given 6 month score was dependent on baseline score.

Tubach et al. (499) evaluated PASS for VAS and Neer rating function subscale after 7 days follow-up in patients with *acute* rotator cuff syndrome. They

reported that initial level of pain or function did not seem to affect PASS, although their reported PASS threshold for function on the Neer scale varied by 8.6 points out of 100 between the lowest and middle tertiles of baseline score. This study had a shorter follow up period in those with shoulder pain, which may explain why their results for the shoulder were not as striking as ours. In the same paper, in patients with chronic knee osteoarthritis, PASS for functional impairment at follow-up appeared to vary according to baseline: those with initial higher levels of functional impairment had higher levels of acceptable states. The authors reported that in both diseases, the PASS was more consistent across the baseline scores for pain than for function, and suggested that patients were able to adapt to functional impairment over time, but not to higher levels of pain. This is in keeping with our findings. In contrast, a study of patients who underwent total hip and knee replacement found those who were in a lower tertile of pain/function at baseline required a higher pain/function status for PASS cut-off at 1 year compared to those in a higher tertile (496).

In this Chapter, age and gender did not affect PASS cut-offs at 6 months when accounting for baseline score. The test for interaction may have lacked power. Previous studies for different PROMs found age and gender affected PASS cut-off, although they did not formally test these effects and did not simultaneously adjust for other covariates such as baseline score, which may explain these differences (495, 497).

Surprisingly, patients receiving treatment during follow-up period were less likely to achieve PASS. This may be a result of treatment expectation, or because those receiving treatment had more severe disease. However, only limited conclusions could be drawn from this finding as the type, frequency and duration of treatment was not captured.

The likelihood of achieving PASS was dependent on both the baseline and 6 month SPADI. A study of post-arthroplasty patients found baseline Simple Shoulder Test (OR 2.04, CI 1.01-4.14 p=0.047), but not VAS or American Shoulder and Elbow Surgeons score was associated with achieving PASS at follow-up (500). In our study, age and gender did not affect the likelihood of

achieving PASS. Conversely, male and age <40 years were independently associated with attaining PASS (495).

There are several strengths to this paper. Previous studies have used different wording and time anchors to determine the PASS (494, 500). Standardisation of the wording for PASS is important for comparison across studies, disease and languages, and variations in wording have been shown to influence results (493). This study used the timeframe of “next few months” as recommended by the OMERACT group (248).

SPADI underwent Rasch model transformation prior to analysis. Although this did not influence the calculation of PASS, this allowed for inferential testing by converting an ordinal score into a linear, interval scale. Other studies did not Rasch analyse their data, and therefore assumptions of linearity may be violated in their statistical analysis. This may account for the conflicting findings between this study and others. Furthermore, the advantage of Rasch transformation in eliminating factors such as response bias, provides additional strengths to this study.

A recently published Delphi process identified assessment of treatment success as one of the 4 inner core domains to include in a COS for shoulder disorders, which could be used in future clinical studies (181). The use and evaluation of PASS has the potential to be one such instrument to measure this domain.

As well as a valuable tool for future clinical trials, PASS may also have an important role in the clinical care pathway. Patients who reported PASS at baseline went on to receive significantly fewer treatments compared to those who did not report PASS. Patients who find their symptoms acceptable at presentation may therefore require fewer investigations or interventions.

6.6 Limitations

There are some limitations to this study. 164 patients did not respond to the 6 month follow-up questionnaire. Those who did not respond were significantly younger and this may bias the results. However, the baseline SPADI and

PASS were similar between these groups, suggesting that this may not be the case. Other potential factors that may influence PASS, such as occupation, were not included in this study. This study involved self-completion of questionnaires and therefore the accuracy of the answers could not be validated and there is the possibility of recall bias. Our local care pathway recommends referral for ultrasound in patients >65 with a normal radiograph of their shoulder, patients with a severe painful arc and pain refractory to physiotherapy. This may result in channelling bias although our experience suggests that patients with a broad range of shoulder symptoms are referred.

6.7 **Conclusion**

This study has shown for the first time the PASS cut-off for SPADI in a longitudinal community-based cohort. The likelihood of achieving PASS is dependent on symptom severity at baseline, driven mainly by disability rather than pain: patients with more severe disability at baseline were willing to accept a greater degree of disability at 6 months. Currently, the relationship between SPADI and objective disease parameters is not clearly defined. It is therefore important to understand the PASS threshold as this can be utilised in clinical research on therapeutic outcomes. Understanding the acceptable symptom state at presentation would also have implications for patient utilisation of healthcare resources.

While this is the first community based study evaluating PASS for SPADI, further work in different centres is required to substantiate these findings.

7 Chapter 7 - Discussion, future directions and conclusions

7.1 Thesis synopsis

This thesis was concerned with understanding the role of ultrasound and PASS in shoulder pain management. It aimed to identify if groups of ultrasound-detected pathologies existed and evaluate the longitudinal relationship between ultrasound based-pathology findings with outcomes. It also evaluated the factors that influence PASS and the relationship between PASS and treatments received.

The main findings from Chapters 3, 4, 5 and 6 in this thesis are as follows:

7.1.1 Chapter 3

The aim of this Chapter was to systematically review the available literature regarding the relationship between imaging detected pathologies, symptoms (function and pain) and the persistence of these symptoms. This review incorporated quality scoring and adjustment using the GRADE criteria, and assessment of confounders. The Chapter included 52 studies describing imaging modalities of radiographs, ultrasound, CT, PET and MRI.

The review concluded that there were conflicting results on the association of imaging features with symptoms and their persistence. It found that, in low quality studies, enhancement of the joint capsule on MRI and increased uptake on PET were associated with symptoms in adhesive capsulitis. Enlarging RC tears were associated with an increased incidence of symptoms in high quality studies.

Pathologies in the shoulder often occur in combination rather than in isolation. Only one out of the 56 studies included, however, analysed the relationship between a combination of pathologies and symptoms. This low quality and unadjusted study found that SAB effusions were associated with shoulder pain independent of the underlying pathology.

The paucity of high quality studies evaluating the association between multiple pathologies and symptoms may account for the inability to understand the

relationship between imaging features and symptoms. This systematic review highlighted the need for further studies to determine if a combination of imaging-detected pathologies is associated with symptoms and outcomes. This unmet need was addressed in subsequent studies presented in the following Chapters.

7.1.2 Chapter 4

The aim of this Chapter was to determine, in a retrospective observational study, if groups with different patterns of ultrasound-detected pathologies existed and explore the outcomes of these groups. Data from 3000 shoulder ultrasound reports of patients from primary care with shoulder pain were retrospectively analysed for ultrasound pathologies. LCA was used to identify if patients would group into clusters of ultrasound-detected pathology and the optimum number of groups was determined using best model fits alongside clinical judgement. Patients were subsequently asked to complete a questionnaire at a single time-point after their scan. Regression analysis allowed comparison of questionnaire responses between the pathology groups.

The findings demonstrated that patients with shoulder pain could be grouped according to ultrasound-detected pathologies. Furthermore, the initial work suggested that these groups may receive different treatments and have different outcomes. Though it involved a large number of patients, this study was limited by its retrospective design and a prospective study in subsequent Chapters was undertaken to confirm the identity of different groups and determine if their long-term outcomes would differ.

7.1.3 Chapter 5

The aim of this Chapter was to confirm the existence of ultrasound-detected pathology groups and explore if these groups or individually detected pathologies had different outcomes and different responses to treatment at 6-months. In this prospective, observational study, 500 patients with shoulder pain were recruited from primary care and asked to complete questionnaires at baseline and 6 months. SPADI was also collected at 2 weeks. LCA was

used to identify groups. Regression analysis was used to compare questionnaire responses between the pathology groups and individual pathologies. Response to treatment between groups and between individual pathologies was also evaluated.

This study again found that four groups existed. These groups differed in symptoms to a small extent at baseline, but did not differ in their change of symptoms at 6 months. Additionally, no individual pathologies were associated with change of symptoms at 6 months. Patients in all groups had a short-term improvement when given steroid injections. These findings suggest that neither ultrasound-detected pathology groups determined by LCA nor individual pathologies are predictors of outcome when used in the employed usual-care treatment pathway, although ultrasound may be useful to identify subgroups if targeted therapies can be demonstrated to be effective.

7.1.4 Chapter 6

The aim of this Chapter was to determine the PASS thresholds for SPADI and its pain and function subdomains over time, and to evaluate if any variables may influence the PASS threshold, in a primary care population. The relationship between PASS and treatments received was also evaluated. Data was collected from the prospective observational study undertaken in Chapter 5. Data was available from 336 patients. PASS was calculated as the 75th percentile on a cumulative percentages curve of patients who considered their state acceptable as a function of SPADI and by identifying cut-offs that yielded the lowest number of false positives and false negatives on a ROC curve. Logistic regression analysed the association of PASS with other co-variates.

The PASS threshold for SPADI was found to be stable over time and was dependent on severity of baseline score. Those who reported PASS at baseline reported receiving fewer treatments at 6 months, supporting the PASS construct. This was the first study to evaluate the relationship between SPADI and PASS in a longitudinal, prospective cohort of patients. These findings could provide a useful tool for future clinical trials by providing the clinical relevance of commonly used PROMS such as SPADI. These findings

would also enable comparison with previous trials, where PASS has not been reported. PASS may have an important role in the clinical care pathway as patients who find their symptoms acceptable at presentation may require fewer investigations or interventions.

7.1.5 Overall summary

The over-arching hypothesis underlying this thesis was that aspects of the shoulder pain pathway can be improved through better utilisation of ultrasound and applying the concept of a PASS. This thesis demonstrated that patients with shoulder pain could be classified according to groups of ultrasound pathologies. However, neither individual nor groups of ultrasound-detected pathologies differed in their outcomes in the medium-term when ultrasound was utilised in the context of a usual care treatment pathway. All groups responded to shoulder injections in the short-term, suggesting that although ultrasound scans may not improve medium-term outcomes in the usual care pathway, there may be a potential role for ultrasound in delivering short-term improvements by ultrasound guided injections. The SPADI cut-off for PASS was also reported, which will improve interpretation of therapeutic success or failure for clinical trials and allow clinically meaningful comparison across studies using this PROM. People reporting PASS had fewer subsequent treatments, which could have implications for managing patients with shoulder pain. Insights from this work suggest that there is no role for ultrasound in predicting outcomes in a 'usual care' pathway and there is potential in using the concept of PASS to improve the care of people with shoulder pain.

7.2 Thesis findings and the recent literature

The findings of this thesis should be interpreted within the context of an update of the literature published since the literature in Chapters 2 and 3 was reviewed. This is discussed below in the context of salient themes that have arisen from the findings of this thesis: new insights into shoulder pain (clinical and imaging); new treatments, including outcome measures for future clinical

trials of interventions; and new guidelines and considerations for shoulder care pathways.

7.2.1 New insights into shoulder pain

7.2.1.1 Risk factors

Chapter 2 described how physical activity and psychosocial aspects may be risk factors for the incidence and persistence of shoulder pain. These findings were supported in a recent prospective longitudinal study, where 3,710 workers in central France without shoulder pain were followed up 2-5 years after completing their baseline questionnaire (501). The authors found a relationship with shoulder pain and perceived stress in males, as well as with physical risk factors (defined as working with arms abducted, working with arms at or above shoulder level and perceived physical exertion) in both genders. This study was limited by the use of self-reported questionnaires, which may result in recall bias. A systematic review into work-related risk factors for "shoulder disorders" found arm-hand elevation, shoulder load, hand force exertion and hand-arm vibration may contribute to shoulder disorders (502). However, this review was limited by the heterogeneity of classification criteria and the low number of studies per risk factor, with some risk factors including only 1 risk factor. In contrast, this thesis found that high levels of shoulder activity (including handling objects overhead and performing swinging motions frequently) were found to be a predictor of high SPADI at 6 months. In addition, although baseline anxiety and depression were not predictive of SPADI at 6 months, patients were less likely to report being in an acceptable state at 6 months if they were more anxious or depressed at baseline. Future work involving physical activity and psychosocial risk factors are discussed below.

The development of shoulder symptoms may be in part due to genetic factors. A recent systematic review has attempted to identify the genetic susceptibility for RC disease (503). The authors found a familial predisposition to RC tears and reported several significant associations with specific haplotypes and single nucleotide polymorphisms (SNPs). These haplotypes include

oestrogen-related receptor beta (*ESRRB*), fibroblast growth factor 3 (*FGF3*), fibroblast growth factor 10 (*FGF10*), fibroblast growth factor receptor 1 (*FGFR1*) and defensin, beta 1 (*DEFB1*). *ESRRB* encodes an oestrogen receptor-like protein, and oestrogen has been associated with poor tendon healing. *FGF3* and *FGF10* encode fibroblast growth factor proteins and are involved in cell growth and tissue repair. *FGFR1* is associated with fibroblast growth factor and limb development. *DEFB1* is an antimicrobial peptide. Genome-wide association study (GWAS) found the SNPs *SAP30BP* and *SASH1* have been found to be associated with RC tears also. Their biological function have been implicated in apoptosis and cancer respectively.

However, there were limitations to this review: most studies involved small sample sizes (ranging from n=62 to n=311). The largest study (n=3091) (504) found that there was an increased relative risk in patients with RC disease and first and second degree relatives, although no predisposing genes were identified; all studies used controls from the general population, which could result in inaccurate findings as this assumed that RC disorders have a low prevalence; there was no adjustment for other characteristics related to RC disease risk; there remains an overall difficulty in understanding and interpreting the role of gene–gene interactions, gene-environment interaction and epigenetic modification. This thesis and the current care pathway do not involve the use of genetic markers as the role of genes is still unknown. More work on their relevance, perhaps to particular pathologies or therapies, is required before they could be considered for incorporation into a shoulder pain pathway.

7.2.1.2 Imaging

One new study assessed the relationship between structure and pain. In a recent prospective observational MRI study of 115 patients using an un-validated semi-quantitative score of ACJ, SAB and RC pathologies scanned using non-contrast MRI, change in the SPADI score between baseline and one year follow-up were significantly associated with baseline MRI score (505). There are several reasons that the authors may have differing results to the work in this thesis. Unlike the work in this thesis, patients the authors

did not adjust for baseline. Patients were excluded if they had an initial SPADI score of <20, which may bias the results, as those with low pain/function scores were not captured. In the prospective study described in Chapter 5, 10% of patients had a score of <20. The authors also randomised patients to supervised physiotherapy +/- shock wave therapy. This was in contrast to the observational study in this thesis, which assessed the use of ultrasound in patients receiving treatment (physiotherapy, corticosteroid injections or surgery) in the usual care pathway. As previously discussed in Chapter 2, the sensitivity and specificity for detecting RC lesions is similar for MRI and ultrasound (273). However, there is no study comparing ACJ or SAB detection between MRI and ultrasound. Furthermore, the scoring criteria used by Kvalvaag *et al.* for ACJ pathology involved detection of bone marrow oedema, subchondral cyst formation and capsular distention, which ultrasound cannot detect.

7.2.2 Treatment

Since Chapter 2 was written, further reviews and studies have evaluated the effects of different therapies on shoulder pain outcome. This may have implications for future studies involving potential treatments of the groups identified in this thesis. Similar to Chapter 2, the studies included in these reviews used differing classifications of shoulder symptoms and there was a lack of high quality studies resulting from flaws in the methodological design.

7.2.2.1 Physiotherapy

A recently published systematic review and meta-analysis on randomised control trials found exercise was better than non-exercise intervention, and specific exercise were better than non-specific exercises for improving pain and function in “impingement” (506). The authors also reported that manual therapy combined with exercise was superior to exercises alone, at the shortest follow-up period. However, quality of evidence was low in all studies as most trials had a high risk of bias; there was a large variation in duration of follow-up; and studies used different classification criteria for impingement.

A review of specific scapula-focused resistance exercises (scapular stabilization, positioning, proprioception, neuromuscular control, strengthening and stretching involving resistance such as body weight or elastic resistance) in patients with clinically diagnosed subacromial impingement syndrome found limited evidence to support specific resistance exercises for <8 weeks duration on conferring short-term (4-8 weeks) improvement in shoulder pain or function, when compared to general exercises (507). These findings were similar to the previous review discussed in Chapter 2, although the earlier review did not evaluate resistive exercises (299).

One recent review found low to moderate quality evidence supporting manual therapy for RC disease, subacromial impingement syndrome and adhesive capsulitis when used alone or in addition to other therapies (508). Physiotherapy alone may be beneficial for RC disease, although surgery in combination with physiotherapy may be superior in the long-term (508). However, the studies included varied in type, frequency and duration of treatment. Conversely when pain was categorised as present or absent, surgery was better than exercise in two low quality studies with a high risk of bias (506).

Overall, the findings from these reviews on physiotherapy were similar to those described in Chapter 2: exercise and manual therapy may offer benefit to patients with shoulder pain in the short term and may be as effective as surgery. Work in this thesis found that treatment (including physiotherapy) did not affect 6 months outcome, although as an observational study of patients being treated according to the usual care pathway and it was not designed to assess the effect of physiotherapy on shoulder pain outcomes. Future work involving physiotherapy is discussed below.

7.2.2.2 Corticosteroid Injections

In a systematic review and meta-analysis of randomised control trials of patients with subacromial impingement, those receiving steroids did better than the control group, ultrasound-guided injections were superior to blind

injections and corticosteroid injections (location not defined) were superior to physical therapy in the short-term only (506). The quality of the included studies was very low as a result of high risk of bias and classification criteria for impingement varied. Another review found in studies with low risk of bias that steroid injections for “RC related shoulder pain” may have a short-term benefit (up to 8 weeks) over local anaesthetic injections alone (509). However, the studies included again used different medications, doses and outcome measures making comparisons and synthesis of data difficult.

In line with other reviews discussed earlier in this thesis, a recent meta-analysis of 4 randomised controlled trials and 1 prospective trial found intra-articular steroid injections for adhesive capsulitis were more effective in reducing the pain score at 0 to 8 weeks and ROM at 24 weeks, but not after, compared to placebo (510). These findings are limited by the low sample size (n≤40), attrition rate of studies up to 20% and heterogeneity of outcome measures and drugs used.

Overall, recent findings suggested that corticosteroids may help with subacromial pain and adhesive capsulitis in the short-term. This confirms the work in this thesis which also found a short-term, but not medium-term, benefit of steroid injection, irrespective of pathologies. The future role of corticosteroid injections is discussed in section 1.3.2 below.

7.2.2.3 Surgery

Three recent randomised controlled trials have been published evaluating the role of subacromial decompression on subacromial impingement (488, 489, 511).

In a multicentre, randomised control trial across 32 UK hospitals, arthroscopic subacromial decompression (n=106) was compared with investigational arthroscopy only (patient blinded) (n=103) and no treatment (n=104). Patients were included if they had subacromial pain for > 3 months, were eligible for arthroscopic surgery, and had previously completed a non-operative management programme (including exercise therapy and >1 steroid injection patients). Patients were excluded if they had full thickness RC tears. There

was no difference in OSS between surgical groups and a small but not clinically important difference between surgical groups and no treatment group at 12 months. Patients in the surgical arm continued to receive post-operative physiotherapy, which may have affected results. Additionally, patients were unable to be blinded in the 'no treatment' arm, which may have adversely affected their outcome as their treatment may have been perceived to be inferior to surgery. Investigational arthroscopy may not be a placebo surgical intervention as suggested by the authors, as there is a possible therapeutic effect of joint lavage (488) .

In a comparable randomised control, subacromial decompression (n=59), diagnostic arthroscopy (placebo-control) (n=63), and exercise therapy (n=71) was compared in Scandinavia. Inclusion criteria were similar to Beard *et al.*: subacromial pain for > 3 months; previously completed a non-operative management programme; had physical examination signs of pain provoked by abduction and positive painful arc, positive impingement test (relieved by subacromial injection of lidocaine) and ≥2 out of 3 isometric tests: pain on abduction 0° and 30° or external rotation. Patients with full thickness RC tear, OA or substantial (the definition of which was undefined) calcific deposits were excluded. No clinical differences in VAS score seen between the groups at 24 months (489).

In the third study, patients with subacromial impingement syndrome were randomised to open acromioplasty (n=23), arthroscopic acromioplasty (n=23) and physiotherapy for 3-6 months (n=31). Unlike the previous two RCTs, there was no placebo intervention. Inclusion criteria were: subacromial pain >6 months; failed conservative therapy (non-structured physiotherapy, NSAIDs, local corticosteroid injection); positive for impingement (Neer sign or Hawkin test). Exclusion criteria included OA, full thickness RC tears, "stage III" subacromial impingement syndrome (defined as chronic changes such as partial or complete tears of the RC appearing in >40 year olds). Surgical treatment was found to have better clinical outcomes than physiotherapy at 10 years (511). However, this study was limited by the very small sample size, 24.2% attrition rate (38% in the surgical arm), and differences between groups

at baseline. Ensuring physiotherapy compliance was also difficult. Furthermore, the PROM used, the Constant score, is a poorly validated tool as discussed in Chapter 3. In a previous review discussed in Chapter 2, surgery was found to improve function in calcific tendinopathy up to 7 years post-operatively (338). In a recent systematic review evaluating the different types of surgery for calcific tendinopathy, there was no significant difference between acromioplasty with the removal of the calcific deposits, acromioplasty or solely the removal of the calcific deposits in pain or function, with similar complication rates (512). However, the included studies were heterogeneous in length of follow-up (6 weeks to 5 years) and outcome measures used. The authors of this systematic review evaluated function outcome using Constant and UCLA scores. However, these scores are composite measures of pain, function and range of motion. Furthermore, only studies with calcification confirmed on radiographs were included, which may exclude other relevant studies.

For adhesive capsulitis, a meta-analysis of 11 randomised control trials found there was no or limited benefit of arthrographic distension compared to steroids alone, physiotherapy or manipulation (363), which is in line with previous reviews discussed (324, 362, 363). However, arthrographic distension volume and drug dose varied across the different studies and studies also used different outcome measures. There is an ongoing randomised controlled trial of 500 patients with clinical diagnosis of frozen shoulder. Physiotherapy with intra-articular steroid injection will be compared with manipulation under anaesthesia and steroid injection or arthroscopic capsular release and manipulation (513).

As a result of these recent studies, the precise role of surgery in the shoulder care pathway remains uncertain. In the UK Database of Evidence Uncertainties, the type of surgery, optimum timing and selection of patients who would benefit from surgery remains unknown (514). Similarly, the role of surgery for RC tears (partial or full) is also unknown (515). These RCTs show that there appears to be no overall benefit for surgical decompression in subacromial impingement. Ultrasound scans are commonly used prior to

surgery for diagnosing subacromial pathologies and RC tears. Work in this thesis demonstrated that, in the usual care pathway, 6 month outcomes were similar in between all ultrasound-based pathology groups (including the bursitis group and RC tears), those with individual pathologies (including impingement, bursitis, RC tears) and those undergoing surgery. This appears to supports the findings that surgery may not improve shoulder pain, although in my study the numbers undergoing surgery were small and the follow-up period of 6 months was short. Future consideration should include understanding how surgery can be incorporated into the care pathway and identifying risk factors in patients who would benefit from surgical intervention.

7.2.2.4 Assessing shoulder symptoms in clinical trials

As discussed in Chapter 2, OMERACT recently published a Delphi process outlining 4 mandatory domains as a COS for all trials of shoulder disorders, in order to reduce heterogeneity in outcome measures in shoulder trials: pain, physical functioning, health related quality of life, and assessment of treatment success (181). A multidisciplinary steering committee including patients recently convened to discuss these findings (516). Global assessment of treatment success was changed to global perceived effect as some trials used a “no treatment” arm or “usual care” arm, and treatment success may not be a relevant concept. Health related quality of life was not included in the mandatory core domain as some of its sub-domains, for example physical function, were already identified in other domains. An adverse events domain was included.

A third round of Delphi to finalise definitions and wordings of domains, as well as which instruments can be endorsed to measure these domains, is awaited. This will help inform future studies deriving from this thesis.

7.2.3 Guidelines and considerations for shoulder care pathways

In a recent update of clinical consensus guidelines, the European Society of Musculoskeletal Radiology made no changes to previous recommendations for referral of ultrasound of the shoulder, as no new relevant evidence was found to change the recommended clinical indications for ultrasound scan

(517). These guidelines were focussed on indications for ultrasound in diagnosing structural pathologies. The work in this thesis could have implications for such guidelines as it has found that individual or groups of ultrasound pathologies does not predict 6 months outcome in the current care pathway. Guidelines, therefore, should incorporate the value of ultrasound in affecting management and outcomes, rather than its diagnostic value alone.

7.3 Directions for future research

This thesis has explored some important elements of current shoulder care: a novel approach in interpreting ultrasound findings and their predictive validity and the levels of acceptable symptom states in patients with shoulder pain. Further areas of study arising from this thesis have been identified as a result of this work and are discussed below.

7.3.1 Improving understanding of structure-pain relationships

Neither the novel structural classification system in this thesis, nor individual pathologies, related to any differences in medium-term outcomes when used in a usual-care pathway. This may in part be due to our lack of understanding of the relationship between structural pathologies and pain, and an understanding of this relationship could provide opportunities for therapeutic targets. Although part of this thesis investigated the predictive ability of an imaging modality rather than the relationship between structure and pain, the importance of understanding this relationship might be considered in light of what we have learnt from the study of other painful musculoskeletal conditions.

Looking at common musculoskeletal conditions with pain as their presenting problem, there has been much work in the area of structural pathology in OA and relationship to symptoms. As with shoulders, understanding such relationships is difficult in part due to the complexity of measuring pain, and the variability in measuring structure. Pain is a multifaceted and subjective experience, and measuring pain experience is difficult due to the various modifiers of pain (such as intensity, location, mood and beliefs). Structure measurements can be difficult due to the varying reliability of both imaging

techniques and interpretation of images. Ultrasound scans are operator dependent and any study evaluating this modality requires the assessment of inter-reader reliability. One limitation of the work in this thesis is that this was not assessed.

Whilst there is evidence supporting the contributory effect of structural pathology with pain, the particular structural pathology/pathologies responsible have yet to be identified. Areas such as subchondral bone, periosteum, synovium, ligaments and peri-articular muscle contain nociceptive receptors, and represent potential targets (518). Further work in the shoulder, therefore, needs to involve deeper understanding of the relationship between structural pathologies and pain to enable appropriately targeted therapies. MRI would enable the evaluation of more pathologies than would otherwise be detectable.

In order to understand the structure-pain relationship, however, certain methodological challenges need to be overcome. The ‘natural history’ of structural lesions and symptom development needs to be understood. Including all structural lesions in a statistical model, such as regression analysis, to obtain “independent” associations of various structural pathologies and risk of outcome without knowing the chronology of disease occurrence and casual pathway may result in “collider stratification bias”, where the analysis may impart an association on two otherwise independent variables. This could result in biasing the effect estimates of independent variables. A diagrammatic illustration of this can be seen in Figure 7.1 below.

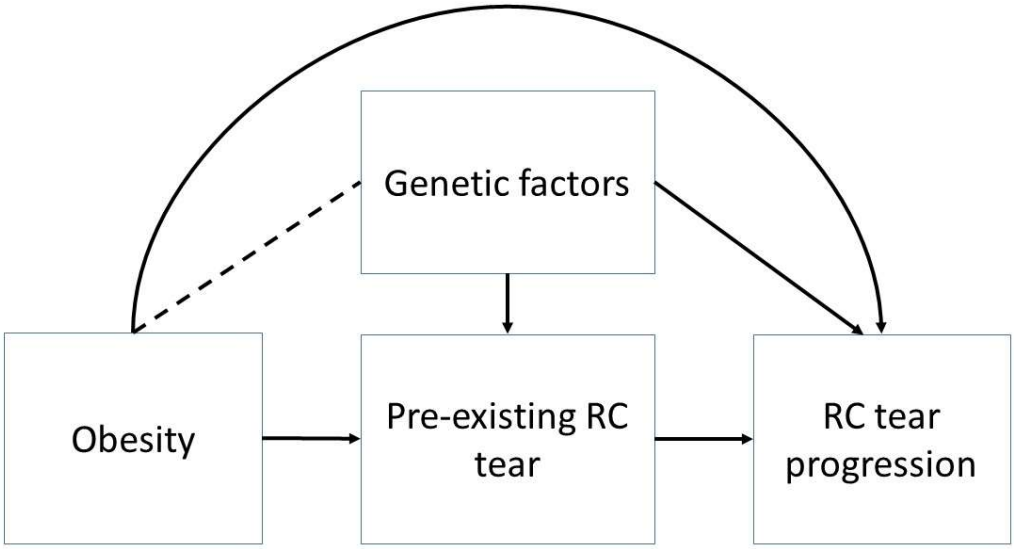


Figure 7.1 A causal diagram of an observational study showing the assessment of the effect of obesity on RC tear progression among shoulders with pre-existing RC tear at baseline.

Adapted from (519)

Analysis on baseline RC tear results in its causes (i.e. obesity and the genetic factor) becoming directly associated, as indicated by a dotted line between obesity and genetic factors, even though these two factors are not associated before the shoulders developed RC tears. Such analysis opens an alternative path from obesity to RC tear progression (i.e. obesity --- genetic factor → RC tear progression), thus biasing the effect of obesity on RC tear progression.. Furthermore, the effect estimates may be incomparable between structures as there may be different causal and interrelated pathways (519-521).

Additionally, in order to understand the full causal effect of a particular pathology on pain, the chronology of when that shoulder pathology occurs in shoulder pain needs to be known. This may otherwise lead to a risk of including mediating variables (including other pathologies) that occur after the development of the pathology in question but before pain has occurred, which could dilute or attenuate the effect of the pathology of interest. Including

mediators in the analysis risk underestimating or even overlooking the association between the pathology of interest and pain.

The difficulty in understanding the degree to which structural pathology accounts for pain and the casual contributions of different structural pathologies may in part be due to studying shoulder pain in the late stages. A large, longitudinal prospective study of patients with limited initial pathologies, perhaps in people at risk of shoulder pain, would therefore be required to understand the natural history of shoulder pain and subsequent structure-pain relationship. The Osteoarthritis Initiative (OAI) (522) is a multi-centre, longitudinal, prospective observational study where 5,000 age-eligible patients with knee OA were recruited and clinical data, joint imaging biomarkers (magnetic resonance imaging and radiography), biochemical and genetic markers (blood and urine) were collected to help understand disease onset and progression. Something similar could be replicated for shoulder pain, the "Shoulder Pain Initiative", where ultrasound scans are used in addition to MRI and radiographs.

In order to detect structural changes over time, a responsive, reliable and sensitive measure is needed to avoid the need to recruit very large cohorts. Furthermore, severity of structural pathologies need to be accurately detected. One of the limitations of this thesis is that pathology severity was not documented (other than full thickness and partial tears), and it may be the severity rather than merely presence of lesions that may be important. Quantitative methods such as active appearance modelling have shown potential in understanding osteoarthritis pathogenesis and for use in clinical trials (523). Quantitative tools have allowed a greater understanding of the relationship between temporal and spatial changes in structural pathologies in OA, and can help define earlier OA phenotypes. Quantitative tools for shoulder tendons using ultrasound have been previously described (524), and this may provide an imaging biomarker for progression and targets for therapy. Quantitative measures using MRI, previously used in other joints, may also be replicated for the shoulder.

The diagnostic interpretation of imaging-detected structural abnormalities can also be challenging as abnormalities exist in asymptomatic individuals. This suggests that there are other contributory factors which cause symptoms. Pain is a subjective experience modified by biopsychosocial factors including self-efficacy, cultural and genetic influences and understanding how these factors contribute to shoulder pain is important.

Although these concerns prevented this thesis from studying the structure pain relationship, this has does not affect the validity of the statistical analyses presented, because good *predictors* of an outcome need not be on the causal pathway provided causal inferences are not drawn. Ultrasound pathology (individual or groups) could still have a role in predicting 6 month outcome without having to be causally related.

However, this means the development of therapeutic approaches within each group could only confidently proceed if these were directed at treating the symptoms. For example, if ultrasound helped to identify a patient group that has worse outcomes at 6 months (irrespective of causality), this group could be treated with more pain relief interventions. Targeted therapies aimed at preventing/modifying the pathologies themselves would only improve pain outcomes if they were definitely on the causal pathway, and therefore an inception cohort study such as the Shoulder Pain Initiative described above would be needed to show this was the case before proceeding to test whether such interventions worked.

7.3.2 Improving treatments

Currently, treatment of shoulder pain involves corticosteroid injections, pharmacological therapies, physiotherapy or surgery. These main treatment modalities have not been shown to demonstrate any long-term benefits. One reason for this may be because they have been used inappropriately, for example at the wrong time or for the wrong duration. Future work would involve understanding how to best utilise treatment modalities and learning lessons from other musculoskeletal conditions.

7.3.2.1 Corticosteroid injections

In this thesis, ultrasound-guided injection provided short-term relief in all patients. Ultrasound guided corticosteroid injections have been shown to have increased accuracy compared to non-guided injections, although there is conflicting evidence on increased efficacy (326, 525). No study has evaluated the role of ultrasound in delivering therapy when unguided injections fail. A trial of guided injections following previously 'failed' (inadequate response to) unguided injections compared with usual care may help us understand if there are benefits to ultrasound guided injections in this way.

7.3.2.2 Pharmacological

Assessing different pain sensitisation mechanisms may offer opportunities for targeted pharmacological therapies in the future (526). For example, tumour necrosis factor α may contribute to sensitisation (527) and one argument for the success of targeting this cytokine in rheumatoid arthritis is due to an effect on pain sensitisation. Similarly, Nerve Growth Factor (NGF) has been implicated in pain signalling via peripheral and central nociceptive receptors as well as inducing inflammatory mediators. Early phase trials against NGF in OA have shown efficacy in symptom relief (528). Developing treatments targeting shoulder symptom modification rather than solely structural modification in the form of shoulder surgery, therefore, may be appropriate.

7.3.2.3 Physiotherapy

The average number of physiotherapy sessions in clinical trials has been reported to be 10, with the duration of most shoulder physiotherapy interventions less than 3 months (292, 529). This number of physiotherapy sessions is higher than in clinical practice in the UK, where resources are often limited. For example, in the prospective study in Chapter 5, the average number of physiotherapy sessions was reported to be 2 at 3 months.

Physiotherapy dose may therefore have implications on successful outcomes. As discussed in Chapter 2, physiotherapy trials have shown improvements of symptoms ≤6 months. In this thesis, where physiotherapy is given according

to usual care, symptoms were no different at 6 months. In other musculoskeletal disease areas such as osteoarthritis, rehabilitation programmes involving education, self-management, coping strategies and an individualised exercise regimen have been delivered in the community (530). Each programme consists of 12 sessions and participation has been shown to improve pain, function, HADS and wellbeing. A community programme in Denmark (GLA:D) involving 12 sessions delivered over 6 weeks has shown improvements in pain, function and quality of life for people with hip and knee OA (531). A similar programme could be developed and delivered for shoulder pain and its effect on pain, function, quality of life and well-being could be evaluated.

Patients with shoulder pain have been shown to have joint pains in other sites. For example, in patients with persistent knee pain, there was an increased risk of bilateral shoulder pain, which was partially mediated by leg weakness (532). The work in this thesis showed that using arms to rise from a chair (a surrogate marker of quadriceps weakness) at baseline was not predictive of 6 month SPADI. However, the mean age of this group was 53.6 years and these finding may not be reflective of all age groups. A longitudinal study evaluating shoulder pain and improvements in forearm and quadriceps strength in those at an increased risk of persistent shoulder pain, such as the elderly >70 years, could demonstrate how simple exercises in this particular demographic could be used effectively.

7.3.2.4 PASS in trials involving treatments for shoulder pain

The use of PASS as an outcome measure in clinical trials would help understand treatment success. Current trials often report outcome measures using continuous variables. Whilst this is useful for understanding group changes (e.g. effect size), these tools may not be meaningful to the patient. Using PASS in future clinical trials will help understand the impact of treatments. Furthermore, PASS would allow comparisons of interventions across different studies.

7.3.3 Improving care pathways

7.3.3.1 Imaging

This thesis has found that, in the usual care pathway, individual or groups of pathologies did not have different outcomes at 6 months. One limitation to these findings is that the study was undertaken in a pathway involving a single (albeit large) centre. However, it is likely given the very limited treatment options that this pathway is very similar to that used in other centres.

Ultrasound, therefore, is not useful in the current care pathway as conducted in a large single UK centre. As the work in this thesis involved an observational study only, a multi-centre randomised control trial comparing the use of ultrasound with no ultrasound would provide further insight into any benefits that this imaging modality would provide. Patients with shoulder pain presenting to primary care could be randomised to receive ultrasound and treatment tailored to ultrasound findings, or usual care. In the absence of any definitive evidence-based treatment for shoulder pain, a Delphi consensus meeting should take place initially to determine the most appropriate treatments. Stakeholders should include physiotherapists, surgeons, rheumatologists, radiologists and patients. Outcomes including pain, physical functioning, health related quality of life, and global perceived effect, outlined by the OMERACT group (516) and discussed earlier, could then be compared.

An economic evaluation to compare the costs and health outcomes with and without the use of ultrasound in the care pathway would provide an insight into healthcare costs and potential savings. These economic evaluations may involve assessing the cost-effectiveness, cost-utility and cost-benefit of using ultrasound as described in Chapter 2.

One limitation of using ultrasound is that it is not able to visualise all pathologies. Other imaging modalities, such as MRI, are able to detect certain pathologies ultrasound scans cannot. Although ultrasound and MRI are comparable in sensitivity and specificity for detecting RC lesions, as discussed in Chapter 2 (273), MRI is better at detecting other pathologies such as deeper

ligamentous structures, labral lesions or bone marrow lesions and, as discussed earlier on in this Chapter, may predict outcome (505). Currently, MRI is recommended to evaluate prolonged, refractory, or unexplained shoulder pain; impingement; instability; and limited range of movement (253), although when it should be used over other imaging modalities is uncertain. Repeating this work using MRI would be important to see if any identifiable groups can predict outcomes. In addition, a trial comparing MRI with ultrasound and seeing how this affects management and outcomes would inform how MRI can be effectively incorporated into the current care pathway.

7.3.3.2 PASS

Further work would be required to look beyond the imaging component of the care pathway. This thesis found that those who reported PASS were less likely to receive treatment but also remain in PASS at 6 months. This is important as although patients complain of pain, this may be acceptable to the patient. The biggest determinant of PASS at 6 months, other than the concurrent level of symptoms, was baseline function. Therefore, a study investigating how functional activities affect long-term outcomes on the first presentation, through history and examination rather than imaging, may be necessary.

Interestingly, some patients who reported acceptable symptoms continued to receive treatment and utilise the healthcare system. Qualitative work understanding why patients reporting PASS continue to seek medical attention would be valuable in understanding the role of PASS and its use in care pathways.

Improvements in the triaging aspect of shoulder care pathways could mirror recent work towards improving back pain, where imaging is not required, but where the concept of PASS may be incorporated. Similar to shoulder pain, imaging is often used for lower back pain but, in the absence of serious underlying conditions (such as infection or malignancy), it has not been shown to improve outcomes (533). Despite this, the rate of spinal MRI imaging is increasing (534). Features identified through imaging of the spine also have poor predictive correlation with symptoms (535) and therefore its utility

remains uncertain. In order to improve the care of back pain, a validated prognostic tool, STarTback, was developed by identifying clinical prognostic constructs, and not imaging findings, that could be modified by primary care treatment (536). This was matched with stratified treatments and tested in a randomised control trial (447). Subsequent qualitative research and health-economics studies were undertaken to demonstrate the positive effects of this stratified model (537). A similar model involving the concept of PASS could be developed. This potential model could be used in patients who present to their primary care practitioner with shoulder pain, prior to referral to ultrasound. Patients could be asked if they have symptoms which are acceptable. If they do report PASS, then the qualitative work discussed above may help identify drivers to improving their shoulder pain. If they do not report PASS, then relevant prognostic constructs (such as certain physical activities and psychosocial factors discussed above) can be used to stratify patients into different risk groups requiring different treatments such as observation, usual treatment or intensive treatment. This could then be tested in subsequent trials.

7.4 Conclusions

The substantial individual and socio-economic burden of shoulder pain highlights the need for effective treatment. A better classification of shoulder pain phenotype may allow stratification of patient outcomes and targeted therapies. In studies to date, the failure to link the association of structural pathologies to outcomes may be a result of the inability to incorporate multiple pathologies into a model. A systematic literature review identified a lack of high quality studies evaluating the relationship between combined imaging-detected pathologies and outcomes, and this thesis provides an important contribution to this unmet need. This thesis has demonstrated from retrospective data that patients can be grouped into ultrasound-detected pathologies. A subsequent prospective study confirmed that groups exist although it found that pathologies (groups or individuals) do not differ in outcomes when used in a usual-care treatment pathway. This thesis also

reported for the first time the longitudinal relationship between PASS, symptoms and treatments received. The use of ultrasound in managing patients requires careful consideration, and understanding clinical criteria such as PASS will help improve shoulder care pathways.

List of References

1. Badley EM, Tennant A. Changing profile of joint disorders with age: findings from a postal survey of the population of Calderdale, West Yorkshire, United Kingdom. Ann Rheum Dis. 1992;51(3):366-71.
2. Linsell L, Dawson J, Zondervan K, Rose P, Randall T, Fitzpatrick R, et al. Prevalence and incidence of adults consulting for shoulder conditions in UK primary care; patterns of diagnosis and referral. Rheumatology (Oxford). 2006;45(2):215-21.
3. Virta L, Joranger P, Brox JI, Eriksson R. Costs of shoulder pain and resource use in primary health care: a cost-of-illness study in Sweden. BMC Musculoskelet Disord. 2012;13:17.
4. Littlewood C, Malliaras P, Mawson S, May S, Walters SJ. Self-managed loaded exercise versus usual physiotherapy treatment for rotator cuff tendinopathy: a pilot randomised controlled trial. Physiotherapy. 2014;100(1):54-60.
5. van den Heuvel SG, Ijmker S, Blatter BM, de Korte EM. Loss of Productivity Due to Neck/Shoulder Symptoms and Hand/Arm Symptoms: Results from the PROMO-Study. Journal of Occupational Rehabilitation. 2007;17(3):370-82.
6. van der Windt DA, Koes BW, de Jong BA, Bouter LM. Shoulder disorders in general practice: incidence, patient characteristics, and management. Ann Rheum Dis. 1995;54(12):959-64.
7. Pope DP, Croft PR, Pritchard CM, Silman AJ. Prevalence of shoulder pain in the community: the influence of case definition. Ann Rheum Dis. 1997;56(5):308-12.
8. Turk DC. The potential of treatment matching for subgroups of patients with chronic pain: lumping versus splitting. Clin J Pain. 2005;21(1):44-55; discussion 69-72.
9. Lenza M, Buchbinder R, Takwoingi Y, Johnston RV, Hanchard NC, Faloppa F. Magnetic resonance imaging, magnetic resonance arthrography and ultrasonography for assessing rotator cuff tears in people with shoulder pain for whom surgery is being considered. Cochrane Database Syst Rev. 2013(9):CD009020.
10. Dinnes J, Loveman E, McIntyre L, Waugh N. The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review. Health technology assessment (Winchester, England). 2003;7(29).
11. Arthritis Research UK. Early diagnostic ultrasound for shoulder pain: effect on clinical decision-making and patient outcomes. 2012.
12. Croft P, Pope D, Silman A. The clinical course of shoulder pain: prospective cohort study in primary care. Primary Care Rheumatology Society Shoulder Study Group. BMJ. 1996;313(7057):601-2.
13. Chard MD, Hazleman R, Hazleman BL, King RH, Reiss BB. Shoulder disorders in the elderly: a community survey. Arthritis Rheum. 1991;34(6):766-9.

14. Wang HL, Keck JF, Weaver MT, Mikesky A, Bunnell K, Buelow JM, et al. Shoulder pain, functional status, and health-related quality of life after head and neck cancer surgery. Rehabil Res Pract. 2013;2013:601768.
15. Kemp BJ, Bateham AL, Mulroy SJ, Thompson L, Adkins RH, Kahan JS. Effects of reduction in shoulder pain on quality of life and community activities among people living long-term with SCI paraplegia: a randomized control trial. J Spinal Cord Med. 2011;34(3):278-84.
16. Smith KL, Harryman DT, 2nd, Antoniou J, Campbell B, Sidles JA, Matsen FA, 3rd. A prospective, multipractice study of shoulder function and health status in patients with documented rotator cuff tears. J Shoulder Elbow Surg. 2000;9(5):395-402.
17. Kasper DL, Harrison TR. Harrison's principles of internal medicine. 16th ed. New York ; London: McGraw-Hill, Medical Pub. Division; 2005. xxvii, 2607, A-15, I-128 p. p.
18. Hegedus EJ, Goode AP, Cook CE, Michener L, Myer CA, Myer DM, et al. Which physical examination tests provide clinicians with the most value when examining the shoulder? Update of a systematic review with meta-analysis of individual tests. Br J Sports Med. 2012;46(14):964-78.
19. Moen MH, de Vos RJ, Ellenbecker TS, Weir A. Clinical tests in shoulder examination: how to perform them. Br J Sports Med. 2010;44(5):370-5.
20. Huisstede BM, Miedema HS, Verhagen AP, Koes BW, Verhaar JA. Multidisciplinary consensus on the terminology and classification of complaints of the arm, neck and/or shoulder. Occup Environ Med. 2007;64(5):313-9.
21. McClure PW, Michener LA. Staged Approach for Rehabilitation Classification: Shoulder Disorders (STAR-Shoulder). Phys Ther. 2015;95(5):791-800.
22. Papadonikolakis A, McKenna M, Warme W, Martin BI, Matsen FA, 3rd. Published evidence relevant to the diagnosis of impingement syndrome of the shoulder. J Bone Joint Surg Am. 2011;93(19):1827-32.
23. Braman JP, Zhao KD, Lawrence RL, Harrison AK, Ludewig PM. Shoulder impingement revisited: evolution of diagnostic understanding in orthopedic surgery and physical therapy. Med Biol Eng Comput. 2014;52(3):211-9.
24. de Witte PB, de Groot JH, van Zwet EW, Ludewig PM, Nagels J, Nelissen RG, et al. Communication breakdown: clinicians disagree on subacromial impingement. Med Biol Eng Comput. 2014;52(3):221-31.
25. Mitchell C, Adebajo A, Hay E, Carr A. Shoulder pain: diagnosis and management in primary care. BMJ. 2005;331(7525):1124-8.
26. ICD-10 Version:2016. 2018 [cited 2018 26/10/2018]. Available from: http://apps.who.int/classifications/icd10/browse/2016/en#/M75.
27. Juel NG, Natvig B. Shoulder diagnoses in secondary care, a one year cohort. BMC Musculoskelet Disord. 2014;15:89.
28. de Winter AF, Jans MP, Scholten RJ, Deville W, van Schaardenburg D, Bouter LM. Diagnostic classification of shoulder disorders: interobserver agreement and determinants of disagreement. Ann Rheum Dis. 1999;58(5):272-7.
29. Hegedus EJ, Goode A, Campbell S, Morin A, Tamaddoni M, Moorman CT, 3rd, et al. Physical examination tests of the shoulder: a systematic review

with meta-analysis of individual tests. Br J Sports Med. 2008;42(2):80-92; discussion
30. Hanchard NC, Lenza M, Handoll HH, Takwoingi Y. Physical tests for shoulder impingements and local lesions of bursa, tendon or labrum that may accompany impingement. Cochrane Database Syst Rev. 2013(4):CD007427.
31. Uhthoff HK, Sarkar K. An algorithm for shoulder pain caused by soft-tissue disorders. Clin Orthop Relat Res. 1990(254):121-7.
32. Schellingerhout JM, Verhagen AP, Thomas S, Koes BW. Lack of uniformity in diagnostic labeling of shoulder pain: time for a different approach. Man Ther. 2008;13(6):478-83.
33. Gomoll AH, Katz JN, Warner JJ, Millett PJ. Rotator cuff disorders: recognition and management among patients with shoulder pain. Arthritis Rheum. 2004;50(12):3751-61.
34. Gray M, Wallace A, Aldridge S. Assessment of shoulder pain for non-specialists. BMJ. 2016;355:i5783.
35. Song KD, Kwon JW, Yoon YC, Choi SH. Indirect MR arthrographic findings of adhesive capsulitis. American Journal of Roentgenology. 2011;197(6):W1105-W9.
36. Hodgson RJ, O'Connor PJ, Hensor EMA, Barron D, Robinson P. Contrast-enhanced MRI of the subdeltoid, subacromial bursa in painful and painless rotator cuff tears. The British journal of radiology. 2012;85(1019):1482.
37. Anderson JA. Industrial rheumatology and the shoulder. Br J Rheumatol. 1987;26(5):326-8.
38. Bamji AN, Erhardt CC, Price TR, Williams PL. The painful shoulder: can consultants agree? Br J Rheumatol. 1996;35(11):1172-4.
39. Norregaard J, Krogsgaard MR, Lorenzen T, Jensen EM. Diagnosing patients with longstanding shoulder joint pain. Ann Rheum Dis. 2002;61(7):646-9.
40. Ostor AJ, Richards CA, Prevost AT, Hazleman BL, Speed CA. Interrater reproducibility of clinical tests for rotator cuff lesions. Ann Rheum Dis. 2004;63(10):1288-92.
41. Liesdek C, van der Windt DAWM, Koes BW, Bouter LM. Soft-tissue Disorders of the Shoulder. Physiotherapy.83(1):12-7.
42. Palmer K, Walker-Bone K, Linaker C, Reading I, Kellingray S, Coggon D, et al. The Southampton examination schedule for the diagnosis of musculoskeletal disorders of the upper limb. Ann Rheum Dis. 2000;59(1):5-11.
43. Palmer KT. The Southampton Examination Schedule for the diagnosis of musculoskeletal disorders of the upper limb. Med Lav. 2007;98(2):111-7.
44. Pellecchia GL, Paolino J, Connell J. Intertester reliability of the cyriax evaluation in assessing patients with shoulder pain. J Orthop Sports Phys Ther. 1996;23(1):34-8.
45. Croft P, Pope D, Boswell R, Rigby A, Silman A. Observer variability in measuring elevation and external rotation of the shoulder. Primary Care Rheumatology Society Shoulder Study Group. Br J Rheumatol. 1994;33(10):942-6.
46. Buchbinder R, Goel V, Bombardier C. Lack of concordance between the ICD-9 classification of soft tissue disorders of the neck and upper limb and

chart review diagnosis: one steel mill's experience. Am J Ind Med. 1996;29(2):171-82.
47. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA. The demographic and morphological features of rotator cuff disease: A comparison of asymptomatic and symptomatic shoulders. Journal of Bone and Joint Surgery - Series A. 2006;88(8):1699-704.
48. Brasseur J-L, Lucidarme O, Tardieu M, Tordeur M, Montalvan B, Parier J, et al. Ultrasonographic rotator-cuff changes in veteran tennis players: the effect of hand dominance and comparison with clinical findings. Eur Radiol. 2004;14(5):857.
49. Iagnocco A, Coari G, Leone A, Valesini G. Sonographic study of painful shoulder. Clin Exp Rheumatol. 2003;21(3):355.
50. Mohamed RE, Amin MA, Aboelsafa AA. Ultrasonographic and clinical study of post-stroke painful hemiplegic shoulder. Egyptian Journal of Radiology and Nuclear Medicine. 2014;45(4):1163-70.
51. Schmidt WA, Schmidt H, Schicke B, Gromnica-Ihle E. Standard reference values for musculoskeletal ultrasonography. Ann Rheum Dis. 2004;63(8):988-94.
52. Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. Ann Rheum Dis. 1998;57(11):649-55.
53. Nakamura M, Nishiwaki Y, Ushida T, Toyama Y. Prevalence and characteristics of chronic musculoskeletal pain in Japan. J Orthop Sci. 2011;16(4):424-32.
54. Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. Pain. 2003;102(1-2):167-78.
55. Oksanen AM, Laimi K, Loyttyniemi E, Kunttu K. Trends of weekly musculoskeletal pain from 2000 to 2012: National study of Finnish university students. Eur J Pain. 2014;18(9):1316-22.
56. Manahan L, Caragay R, Muirden KD, Allander E, Valkenburg HA, Wigley RD. Rheumatic pain in a Philippine village. A WHO-ILAR COPCORD Study. Rheumatol Int. 1985;5(4):149-53.
57. Cunningham LS, Kelsey JL. Epidemiology of musculoskeletal impairments and associated disability. Am J Public Health. 1984;74(6):574-9.
58. Andersson HI, Ejlertsson G, Leden I, Rosenberg C. Chronic pain in a geographically defined general population: studies of differences in age, gender, social class, and pain localization. Clin J Pain. 1993;9(3):174-82.
59. Makela M, Heliovaara M, Sainio P, Knekt P, Impivaara O, Aromaa A. Shoulder joint impairment among Finns aged 30 years or over: prevalence, risk factors and co-morbidity. Rheumatology (Oxford). 1999;38(7):656-62.
60. Adebajo AO, Hazleman BL. Soft tissue shoulder lesions in the African. Br J Rheumatol. 1992;31(4):275-6.
61. Vogt MT, Simonsick EM, Harris TB, Nevitt MC, Kang JD, Rubin SM, et al. Neck and shoulder pain in 70- to 79-year-old men and women: findings from the Health, Aging and Body Composition Study. Spine J. 2003;3(6):435-41.

62. Parsons S, Breen A, Foster NE, Letley L, Pincus T, Vogel S, et al. Prevalence and comparative troublesomeness by age of musculoskeletal pain in different body locations. Fam Pract. 2007;24(4):308-16.
63. Kuijpers T, van der Windt DA, van der Heijden GJ, Bouter LM. Systematic review of prognostic cohort studies on shoulder disorders. Pain. 2004;109(3):420-31.
64. van der Heijden GJ. Shoulder disorders: a state-of-the-art review. Baillieres Clin Rheumatol. 1999;13(2):287-309.
65. Greving K, Dorrestijn O, Winters JC, Groenhof F, van der Meer K, Stevens M, et al. Incidence, prevalence, and consultation rates of shoulder complaints in general practice. Scand J Rheumatol. 2012;41(2):150-5.
66. Engebretsen KB, Grotle M, Natvig B. Patterns of shoulder pain during a 14-year follow-up: results from a longitudinal population study in Norway. Shoulder Elbow. 2015;7(1):49-59.
67. Harkness EF, Macfarlane GJ, Silman AJ, McBeth J. Is musculoskeletal pain more common now than 40 years ago?: Two population-based cross-sectional studies. Rheumatology (Oxford). 2005;44(7):890-5.
68. Nygren A, Berglund A, von Koch M. Neck-and-shoulder pain, an increasing problem. Strategies for using insurance material to follow trends. Scand J Rehabil Med Suppl. 1995;32:107-12.
69. Murphy RJ, Carr AJ. Shoulder pain. BMJ Clin Evid. 2010;2010.
70. Hsu JE, Anakwenze OA, Warrender WJ, Abboud JA. Current review of adhesive capsulitis. J Shoulder Elbow Surg. 2011;20(3):502-14.
71. Gill TK, Shanahan EM, Allison D, Alcorn D, Hill CL. Prevalence of abnormalities on shoulder MRI in symptomatic and asymptomatic older adults. Int J Rheum Dis. 2014;17(8):863-71.
72. Cadogan A, Laslett M, Hing WA, McNair PJ, Coates MH. A prospective study of shoulder pain in primary care: prevalence of imaged pathology and response to guided diagnostic blocks. BMC Musculoskelet Disord. 2011;12:119.
73. Louwerens JK, Sierevelt IN, van Hove RP, van den Bekerom MP, van Noort A. Prevalence of calcific deposits within the rotator cuff tendons in adults with and without subacromial pain syndrome: clinical and radiologic analysis of 1219 patients. J Shoulder Elbow Surg. 2015;24(10):1588-93.
74. Bosworth BM. Examination of the shoulder for calcium deposits: Technique of Fluoroscopy and Spot-Film Roentgenography. JBJS. 1941;23(3):567-77.
75. Iagnocco A, Filippucci E, Sakellariou G, Ceccarelli F, Di Geso L, Carli L, et al. Ultrasound imaging for the rheumatologist XLIV. Ultrasound of the shoulder in healthy individuals. Clin Exp Rheumatol. 2013;31(2):165-71.
76. Girish G, Lobo LG, Jacobson JA, Morag Y, Miller B, Jamadar DA. Ultrasound of the shoulder: asymptomatic findings in men. AJR Am J Roentgenol. 2011;197(4):W713-9.
77. Needell SD, Zlatkin MB, Sher JS, Murphy BJ, Uribe JW. MR imaging of the rotator cuff: peritendinous and bone abnormalities in an asymptomatic population. AJR Am J Roentgenol. 1996;166(4):863-7.
78. Chandnani V, Ho C, Gerharter J, Neumann C, Kursunoglu-Brahme S, Sartoris DJ, et al. MR findings in asymptomatic shoulders: a blind analysis using symptomatic shoulders as controls. Clin Imaging. 1992;16(1):25-30.

79. Meroni R, Piscitelli D, Valerio S, Boria P, Perin C, De Vito G, et al. Ultrasonography of the shoulder: asymptomatic findings from working-age women in the general population. J Phys Ther Sci. 2017;29(7):1219-23.
80. Schibany N, Zehetgruber H, Kainberger F, Wurnig C, Ba-Ssalamah A, Herneth AM, et al. Rotator cuff tears in asymptomatic individuals: a clinical and ultrasonographic screening study. Eur J Radiol. 2004;51(3):263-8.
81. Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. J Shoulder Elbow Surg. 1999;8(4):296-9.
82. Minagawa H, Yamamoto N, Abe H, Fukuda M, Seki N, Kikuchi K, et al. Prevalence of symptomatic and asymptomatic rotator cuff tears in the general population: From mass-screening in one village. J Orthop. 2013;10(1):8-12.
83. Stein BE, Wiater JM, Pfaff HC, Bigliani LU, Levine WN. Detection of acromioclavicular joint pathology in asymptomatic shoulders with magnetic resonance imaging. J Shoulder Elbow Surg. 2001;10(3):204-8.
84. Department of Health and Social Security. Third national morbidity survey in general practice. Royal College of General Practitioners; Office of Populations, Censuses and Surveys. 1980-1981.
85. Allander E. Prevalence, incidence, and remission rates of some common rheumatic diseases or syndromes. Scand J Rheumatol. 1974;3(3):145-53.
86. Ostor AJ, Richards CA, Prevost AT, Speed CA, Hazleman BL. Diagnosis and relation to general health of shoulder disorders presenting to primary care. Rheumatology (Oxford). 2005;44(6):800-5.
87. White D, Choi H, Peloquin C, Zhu Y, Zhang Y. Secular trend of adhesive capsulitis. Arthritis Care Res (Hoboken). 2011;63(11):1571-5.
88. Galvin JW, Ernat JJ, Waterman BR, Stadecker MJ, Parada SA. The Epidemiology and Natural History of Anterior Shoulder Instability. Curr Rev Musculoskelet Med. 2017;10(4):411-24.
89. Nakamura M, Nishiwaki Y, Ushida T, Toyama Y. Prevalence and characteristics of chronic musculoskeletal pain in Japan: a second survey of people with or without chronic pain. J Orthop Sci. 2014;19(2):339-50.
90. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain. 2006;10(4):287-333.
91. Reilingh ML, Kuijpers T, Tanja-Harfterkamp AM, van der Windt DA. Course and prognosis of shoulder symptoms in general practice. Rheumatology (Oxford). 2008;47(5):724-30.
92. van der Windt DA, Koes BW, Boeke AJ, Deville W, De Jong BA, Bouter LM. Shoulder disorders in general practice: prognostic indicators of outcome. Br J Gen Pract. 1996;46(410):519-23.
93. Macfarlane GJ, Hunt IM, Silman AJ. Predictors of chronic shoulder pain: a population based prospective study. J Rheumatol. 1998;25(8):1612-5.
94. Struyf F, Geraets J, Noten S, Meeus M, Nijs J. A Multivariable Prediction Model for the Chronification of Non-traumatic Shoulder Pain: A Systematic Review. Pain Physician. 2016;19(2):1-10.
95. Bot SD, van der Waal JM, Terwee CB, van der Windt DA, Scholten RJ, Bouter LM, et al. Predictors of outcome in neck and shoulder symptoms: a cohort study in general practice. Spine (Phila Pa 1976). 2005;30(16):E459-70.

96. Lombardi I, Jr., Magri AG, Fleury AM, Da Silva AC, Natour J. Progressive resistance training in patients with shoulder impingement syndrome: a randomized controlled trial. Arthritis Rheum. 2008;59(5):615-22.
97. Ludewig PM, Borstad JD. Effects of a home exercise programme on shoulder pain and functional status in construction workers. Occup Environ Med. 2003;60(11):841-9.
98. Desmeules F, Boudreault J, Dionne CE, Fremont P, Lowry V, MacDermid JC, et al. Efficacy of exercise therapy in workers with rotator cuff tendinopathy: a systematic review. J Occup Health. 2016;58(5):389-403.
99. Vastamaki H, Kettunen J, Vastamaki M. The natural history of idiopathic frozen shoulder: a 2- to 27-year followup study. Clin Orthop Relat Res. 2012;470(4):1133-43.
100. Wong CK, Levine WN, Deo K, Kesting RS, Mercer EA, Schram GA, et al. Natural history of frozen shoulder: fact or fiction? A systematic review. Physiotherapy. 2017;103(1):40-7.
101. Eljabu W, Klinger HM, von Knoch M. The natural course of shoulder instability and treatment trends: a systematic review. J Orthop Traumatol. 2017;18(1):1-8.
102. Saccomanno MF, Fodale M, Capasso L, Cazzato G, Milano G. Generalized joint laxity and multidirectional instability of the shoulder. Joints. 2013;1(4):171-9.
103. Hsu J, Keener JD. Natural History of Rotator Cuff Disease and Implications on Management. Oper Tech Orthop. 2015;25(1):2-9.
104. Maman E, Harris C, White L, Tomlinson G, Shashank M, Boynton E. Outcome of nonoperative treatment of symptomatic rotator cuff tears monitored by magnetic resonance imaging. J Bone Joint Surg Am. 2009;91(8):1898-906.
105. Fucentese SF, von Roll AL, Pfirrmann CW, Gerber C, Jost B. Evolution of nonoperatively treated symptomatic isolated full-thickness supraspinatus tears. J Bone Joint Surg Am. 2012;94(9):801-8.
106. Ogon P, Suedkamp NP, Jaeger M, Izadpanah K, Koestler W, Maier D. Prognostic factors in nonoperative therapy for chronic symptomatic calcific tendinitis of the shoulder. Arthritis Rheum. 2009;60(10):2978-84.
107. Cho NS, Lee BG, Rhee YG. Radiologic course of the calcific deposits in calcific tendinitis of the shoulder: does the initial radiologic aspect affect the final results? J Shoulder Elbow Surg. 2010;19(2):267-72.
108. de Witte PB, van Adrichem RA, Selten JW, Nagels J, Reijnierse M, Nelissen RG. Radiological and clinical predictors of long-term outcome in rotator cuff calcific tendinitis. Eur Radiol. 2016;26(10):3401-11.
109. Oudelaar BW, Ooms EM, Huis In 't Veld R, Schepers-Bok R, Vochteloo AJ. Smoking and morphology of calcific deposits affect the outcome of needle aspiration of calcific deposits (NACD) for calcific tendinitis of the rotator cuff. Eur J Radiol. 2015;84(11):2255-60.
110. Wijnhoven HAH, de Vet HCW, Picavet HSJ. Prevalence of musculoskeletal disorders is systematically higher in women than in men. Clin J Pain. 2006;22(8):717-24.
111. Larsson B, Sogaard K, Rosendal L. Work related neck-shoulder pain: a review on magnitude, risk factors, biochemical characteristics, clinical

picture and preventive interventions. Best Pract Res Clin Rheumatol. 2007;21(3):447-63.
112. Unruh AM, Ritchie J, Merskey H. Does gender affect appraisal of pain and pain coping strategies? Clin J Pain. 1999;15(1):31-40.
113. Kroner-Herwig B, Gassmann J, Tromsdorf M, Zahrend E. The effects of sex and gender role on responses to pressure pain. Psychosoc Med. 2012;9:Doc01.
114. Longo UG, Rizzello G, Loppini M, Locher J, Buchmann S, Maffulli N, et al. Multidirectional Instability of the Shoulder: A Systematic Review. Arthroscopy. 2015;31(12):2431-43.
115. Peacock S, Patel S. Cultural Influences on Pain. Rev Pain. 2008;1(2):6-9.
116. Nicholl BI, Smith DJ, Cullen B, Mackay D, Evans J, Anderson J, et al. Ethnic differences in the association between depression and chronic pain: cross sectional results from UK Biobank. BMC Fam Pract. 2015;16:128.
117. Owens BD, Dawson L, Burks R, Cameron KL. Incidence of shoulder dislocation in the United States military: demographic considerations from a high-risk population. J Bone Joint Surg Am. 2009;91(4):791-6.
118. Juel NG, Brox JI, Brunborg C, Holte KB, Berg TJ. Very High Prevalence of Frozen Shoulder in Patients With Type 1 Diabetes of >/=45 Years' Duration: The Dialong Shoulder Study. Arch Phys Med Rehabil. 2017.
119. Moulton SG, Greenspoon JA, Millett PJ, Petri M. Risk Factors, Pathobiomechanics and Physical Examination of Rotator Cuff Tears. Open Orthop J. 2016;10:277-85.
120. Sayampanathan AA, Andrew TH. Systematic review on risk factors of rotator cuff tears. J Orthop Surg (Hong Kong). 2017;25(1):2309499016684318.
121. Chillemi C, Franceschini V. Shoulder osteoarthritis. Arthritis. 2013;2013:370231.
122. Sansone V, Consonni O, Maiorano E, Meroni R, Goddi A. Calcific tendinopathy of the rotator cuff: the correlation between pain and imaging features in symptomatic and asymptomatic female shoulders. Skeletal Radiol. 2016;45(1):49-55.
123. Hakim AJ, Cherkas LF, Spector TD, MacGregor AJ. Genetic associations between frozen shoulder and tennis elbow: a female twin study. Rheumatology (Oxford). 2003;42(6):739-42.
124. Harvie P, Ostlere SJ, Teh J, McNally EG, Clipsham K, Burston BJ, et al. Genetic influences in the aetiology of tears of the rotator cuff. Sibling risk of a full-thickness tear. J Bone Joint Surg Br. 2004;86(5):696-700.
125. Palmer KT, Syddall H, Cooper C, Coggon D. Smoking and musculoskeletal disorders: findings from a British national survey. Ann Rheum Dis. 2003;62(1):33-6.
126. Evanoff A, Sabbath EL, Carton M, Czernichow S, Zins M, Leclerc A, et al. Does obesity modify the relationship between exposure to occupational factors and musculoskeletal pain in men? Results from the GAZEL cohort study. PLoS One. 2014;9(10):e109633.
127. Viester L, Verhagen EA, Oude Hengel KM, Koppes LL, van der Beek AJ, Bongers PM. The relation between body mass index and musculoskeletal

symptoms in the working population. BMC Musculoskelet Disord. 2013;14:238.
128. Rechardt M, Shiri R, Karppinen J, Jula A, Heliovaara M, Viikari-Juntura E. Lifestyle and metabolic factors in relation to shoulder pain and rotator cuff tendinitis: a population-based study. BMC Musculoskelet Disord. 2010;11:165.
129. Franceschi F, Papalia R, Paciotti M, Franceschetti E, Di Martino A, Maffulli N, et al. Obesity as a risk factor for tendinopathy: a systematic review. Int J Endocrinol. 2014;2014:670262.
130. L'Assurance Maladie. Rapport de Gestion. 2015.
131. Miranda H, Viikari-Juntura E, Martikainen R, Takala EP, Riihimaki H. A prospective study of work related factors and physical exercise as predictors of shoulder pain. Occup Environ Med. 2001;58(8):528-34.
132. Punnett L, Fine LJ, Keyserling WM, Herrin GD, Chaffin DB. Shoulder disorders and postural stress in automobile assembly work. Scand J Work Environ Health. 2000;26(4):283-91.
133. van der Windt DA, Thomas E, Pope DP, de Winter AF, Macfarlane GJ, Bouter LM, et al. Occupational risk factors for shoulder pain: a systematic review. Occup Environ Med. 2000;57(7):433-42.
134. English CJ, Maclaren WM, Court-Brown C, Hughes SP, Porter RW, Wallace WA, et al. Relations between upper limb soft tissue disorders and repetitive movements at work. Am J Ind Med. 1995;27(1):75-90.
135. Pope DP, Croft PR, Pritchard CM, Silman AJ, Macfarlane GJ. Occupational factors related to shoulder pain and disability. Occup Environ Med. 1997;54(5):316-21.
136. Bjelle A, Hagberg M, Michaelsson G. Clinical and ergonomic factors in prolonged shoulder pain among industrial workers. Scand J Work Environ Health. 1979;5(3):205-10.
137. Malchaire J, Cock N, Vergracht S. Review of the factors associated with musculoskeletal problems in epidemiological studies. Int Arch Occup Environ Health. 2001;74(2):79-90.
138. Eatough EM, Way JD, Chang CH. Understanding the link between psychosocial work stressors and work-related musculoskeletal complaints. Appl Ergon. 2012;43(3):554-63.
139. van Rijn RM, Huisstede BM, Koes BW, Burdorf A. Associations between work-related factors and specific disorders of the shoulder--a systematic review of the literature. Scand J Work Environ Health. 2010;36(3):189-201.
140. Laslett LL, Otahal P, Hensor EM, Kingsbury SR, Conaghan PG. Knee Pain Predicts Subsequent Shoulder Pain and the Association Is Mediated by Leg Weakness: Longitudinal Observational Data from the Osteoarthritis Initiative. J Rheumatol. 2016;43(11):2049-55.
141. Titchener AG, White JJ, Hinchliffe SR, Tambe AA, Hubbard RB, Clark DI. Comorbidities in rotator cuff disease: a case-control study. J Shoulder Elbow Surg. 2014;23(9):1282-8.
142. van der Windt DA, Kuijpers T, Jellema P, van der Heijden GJ, Bouter LM. Do psychological factors predict outcome in both low-back pain and shoulder pain? Ann Rheum Dis. 2007;66(3):313-9.

143. Schiefer M, Teixeira PF, Fontenelle C, Carminatti T, Santos DA, Righi LD, et al. Prevalence of hypothyroidism in patients with frozen shoulder. J Shoulder Elbow Surg. 2017;26(1):49-55.
144. Bunker TD, Esler CN. Frozen shoulder and lipids. J Bone Joint Surg Br. 1995;77(5):684-6.
145. Wolf JM, Green A. Influence of comorbidity on self-assessment instrument scores of patients with idiopathic adhesive capsulitis. J Bone Joint Surg Am. 2002;84-A(7):1167-73.
146. Oliva F, Osti L, Padulo J, Maffulli N. Epidemiology of the rotator cuff tears: a new incidence related to thyroid disease. Muscles Ligaments Tendons J. 2014;4(3):309-14.
147. Largacha M, Parsons IMt, Campbell B, Titelman RM, Smith KL, Matsen F, 3rd. Deficits in shoulder function and general health associated with sixteen common shoulder diagnoses: a study of 2674 patients. J Shoulder Elbow Surg. 2006;15(1):30-9.
148. Parsons S, Carnes D, Pincus T, Foster N, Breen A, Vogel S, et al. Measuring troublesomeness of chronic pain by location. BMC Musculoskelet Disord. 2006;7:34.
149. Gartsman GM, Brinker MR, Khan M, Karahan M. Self-assessment of general health status in patients with five common shoulder conditions. J Shoulder Elbow Surg. 1998;7(3):228-37.
150. Harris AH, Youd J, Buchbinder R. A comparison of directly elicited and pre-scored preference-based measures of quality of life: the case of adhesive capsulitis. Qual Life Res. 2013;22(10):2963-71.
151. Rozencwaig R, van Noort A, Moskal MJ, Smith KL, Sidles JA, Matsen FA, 3rd. The correlation of comorbidity with function of the shoulder and health status of patients who have glenohumeral degenerative joint disease. J Bone Joint Surg Am. 1998;80(8):1146-53.
152. Bagheri F, Ebrahimzadeh MH, Moradi A, Bidgoli HF. Factors Associated with Pain, Disability and Quality of Life in Patients Suffering from Frozen Shoulder. Arch Bone Jt Surg. 2016;4(3):243-7.
153. Harryman DT, 2nd, Hettrich CM, Smith KL, Campbell B, Sidles JA, Matsen FA, 3rd. A prospective multipractice investigation of patients with full-thickness rotator cuff tears: the importance of comorbidities, practice, and other covariables on self-assessed shoulder function and health status. J Bone Joint Surg Am. 2003;85-A(4):690-6.
154. Kuijpers T, van Tulder MW, van der Heijden GJ, Bouter LM, van der Windt DA. Costs of shoulder pain in primary care consulters: a prospective cohort study in The Netherlands. BMC Musculoskelet Disord. 2006;7:83.
155. Mroz TM, Carlini AR, Archer KR, Wegener ST, Hoolachan JI, Stiers W, et al. Frequency and cost of claims by injury type from a state workers' compensation fund from 1998 through 2008. Arch Phys Med Rehabil. 2014;95(6):1048-54 e6.
156. Pribicevic M, Pollard H, Bonello R. An epidemiologic survey of shoulder pain in chiropractic practice in australia. J Manipulative Physiol Ther. 2009;32(2):107-17.
157. van den Hout WB, Vermeulen HM, Rozing PM, Vliet Vlieland TP. Impact of adhesive capsulitis and economic evaluation of high-grade and low-grade mobilisation techniques. Aust J Physiother. 2005;51(3):141-9.

158. Ravenscroft M, Calvert P. Utilisation of shoulder arthroplasty in the UK. Ann R Coll Surg Engl. 2004;86(1):25-8.
159. Vitale MA, Arons RR, Hurwitz S, Ahmad CS, Levine WN. The rising incidence of acromioplasty. J Bone Joint Surg Am. 2010;92(9):1842-50.
160. Yu E, Cil A, Harmsen WS, Schleck C, Sperling JW, Cofield RH. Arthroscopy and the dramatic increase in frequency of anterior acromioplasty from 1980 to 2005: an epidemiologic study. Arthroscopy. 2010;26(9 Suppl):S142-7.
161. Blaine TA, Kim YS, Voloshin I, Chen D, Murakami K, Chang SS, et al. The molecular pathophysiology of subacromial bursitis in rotator cuff disease. J Shoulder Elbow Surg. 2005;14(1 Suppl S):84S-9S.
162. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152(3 Suppl):S2-15.
163. Sanchis MN, Lluch E, Nijs J, Struyf F, Kangasperko M. The role of central sensitization in shoulder pain: A systematic literature review. Semin Arthritis Rheum. 2015;44(6):710-6.
164. Noten S, Struyf F, Lluch E, D'Hoore M, Van Looveren E, Meeus M. Central Pain Processing in Patients with Shoulder Pain: A Review of the Literature. Pain Pract. 2017;17(2):267-80.
165. Neer CS, 2nd. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. J Bone Joint Surg Am. 1972;54(1):41-50.
166. de Witte PB, Nagels J, van Arkel ER, Visser CP, Nelissen RG, de Groot JH. Study protocol subacromial impingement syndrome: the identification of pathophysiologic mechanisms (SISTIM). BMC Musculoskelet Disord. 2011;12:282.
167. Khan Y, Nagy MT, Malal J, Waseem M. The painful shoulder: shoulder impingement syndrome. Open Orthop J. 2013;7:347-51.
168. Factor D, Dale B. Current concepts of rotator cuff tendinopathy. Int J Sports Phys Ther. 2014;9(2):274-88.
169. Sejersen MH, Frost P, Hansen TB, Deutch SR, Svendsen SW. Proteomics perspectives in rotator cuff research: a systematic review of gene expression and protein composition in human tendinopathy. PLoS One. 2015;10(4):e0119974.
170. Seitz AL, McClure PW, Finucane S, Boardman ND, 3rd, Michener LA. Mechanisms of rotator cuff tendinopathy: intrinsic, extrinsic, or both? Clin Biomech (Bristol, Avon). 2011;26(1):1-12.
171. Nho SJ, Yadav H, Shindle MK, Macgillivray JD. Rotator cuff degeneration: etiology and pathogenesis. Am J Sports Med. 2008;36(5):987-93.
172. Raney EB, Thankam FG, Dilisio MF, Agrawal DK. Pain and the pathogenesis of biceps tendinopathy. Am J Transl Res. 2017;9(6):2668-83.
173. Ahrens PM, Boileau P. The long head of biceps and associated tendinopathy. J Bone Joint Surg Br. 2007;89(8):1001-9.
174. Verstraelen FU, In den Kleef NJ, Jansen L, Morrenhof JW. High-energy versus low-energy extracorporeal shock wave therapy for calcifying tendinitis of the shoulder: which is superior? A meta-analysis. Clin Orthop Relat Res. 2014;472(9):2816-25.

175. Oliva F, Via AG, Maffulli N. Physiopathology of intratendinous calcific deposition. BMC Med. 2012;10:95.
176. Tamai K, Akutsu M, Yano Y. Primary frozen shoulder: brief review of pathology and imaging abnormalities. J Orthop Sci. 2014;19(1):1-5.
177. Le HV, Lee SJ, Nazarian A, Rodriguez EK. Adhesive capsulitis of the shoulder: review of pathophysiology and current clinical treatments. Shoulder Elbow. 2017;9(2):75-84.
178. Tamai K, Akutsu M, Yano Y. Primary frozen shoulder: brief review of pathology and imaging abnormalities. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association. 2014;19(1):1.
179. Page MJ, McKenzie JE, Green SE, Beaton DE, Jain NB, Lenza M, et al. Core domain and outcome measurement sets for shoulder pain trials are needed: systematic review of physical therapy trials. J Clin Epidemiol. 2015;68(11):1270-81.
180. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol. 2014;67(7):745-53.
181. Page MJ, Huang H, Verhagen AP, Buchbinder R, Gagnier JJ. Identifying a core set of outcome domains to measure in clinical trials for shoulder disorders: a modified Delphi study. RMD Open. 2016;2(2):e000380.
182. Oh JH, Jo KH, Kim WS, Gong HS, Han SG, Kim YH. Comparative evaluation of the measurement properties of various shoulder outcome instruments. Am J Sports Med. 2009;37(6):1161-8.
183. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
184. Husted JA, Cook RJ, Farewell VT, Gladman DD. Methods for assessing responsiveness: a critical review and recommendations. J Clin Epidemiol. 2000;53(5):459-68.
185. Wells G, Beaton D, Shea B, Boers M, Simon L, Strand V, et al. Minimal clinically important differences: review of methods. J Rheumatol. 2001;28(2):406-12.
186. Angst F, Schwyzer HK, Aeschlimann A, Simmen BR, Goldhahn J. Measures of adult shoulder function: Disabilities of the Arm, Shoulder, and Hand Questionnaire (DASH) and its short version (QuickDASH), Shoulder Pain and Disability Index (SPADI), American Shoulder and Elbow Surgeons (ASES) Society standardized shoulder assessment form, Constant (Murley) Score (CS), Simple Shoulder Test (SST), Oxford Shoulder Score (OSS), Shoulder Disability Questionnaire (SDQ), and Western Ontario Shoulder Instability Index (WOSI). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S174-88.
187. Booker S, Alfahad N, Scott M, Gooding B, Wallace WA. Use of scoring systems for assessing and reporting the outcome results from shoulder surgery and arthroplasty. World J Orthop. 2015;6(2):244-51.
188. Williams JW, Jr., Holleman DR, Jr., Simel DL. Measuring shoulder function with the Shoulder Pain and Disability Index. J Rheumatol. 1995;22(4):727-32.
189. MacDermid JC, Solomon P, Prkachin K. The Shoulder Pain and Disability Index demonstrates factor, construct and longitudinal validity. BMC Musculoskelet Disord. 2006;7:12.

190. Heald SL, Riddle DL, Lamb RL. The shoulder pain and disability index: the construct validity and responsiveness of a region-specific disability measure. Phys Ther. 1997;77(10):1079-89.
191. Ekeberg OM, Bautz-Holter E, Tveita EK, Keller A, Juel NG, Brox JI. Agreement, reliability and validity in 3 shoulder questionnaires in patients with rotator cuff disease. BMC Musculoskelet Disord. 2008;9:68.
192. Tveita EK, Ekeberg OM, Juel NG, Bautz-Holter E. Responsiveness of the shoulder pain and disability index in patients with adhesive capsulitis. BMC Musculoskelet Disord. 2008;9:161.
193. Angst F, Goldhahn J, Pap G, Mannion AF, Roach KE, Siebertz D, et al. Cross-cultural adaptation, reliability and validity of the German Shoulder Pain and Disability Index (SPADI). Rheumatology (Oxford). 2007;46(1):87-92.
194. Roach KE, Budiman-Mak E, Songsiridej N, Lertratanakul Y. Development of a shoulder pain and disability index. Arthritis Care Res. 1991;4(4):143-9.
195. Angst F, Pap G, Mannion AF, Herren DB, Aeschlimann A, Schwyzer HK, et al. Comprehensive assessment of clinical outcome and quality of life after total shoulder arthroplasty: usefulness and validity of subjective outcome measures. Arthritis Rheum. 2004;51(5):819-28.
196. Roy JS, MacDermid JC, Woodhouse LJ. Measuring shoulder function: a systematic review of four questionnaires. Arthritis Rheum. 2009;61(5):623-32.
197. Schmitt JS, Di Fabio RP. Reliable change and minimum important difference (MID) proportions facilitated group responsiveness comparisons using individual threshold criteria. J Clin Epidemiol. 2004;57(10):1008-18.
198. Paul A, Lewis M, Shadforth MF, Croft PR, Van Der Windt DA, Hay EM. A comparison of four shoulder-specific questionnaires in primary care. Ann Rheum Dis. 2004;63(10):1293-9.
199. Dawson J, Fitzpatrick R, Carr A. Questionnaire on the perceptions of patients about shoulder surgery. J Bone Joint Surg Br. 1996;78(4):593-600.
200. Dawson J, Rogers K, Fitzpatrick R, Carr A. The Oxford shoulder score revisited. Arch Orthop Trauma Surg. 2009;129(1):119-23.
201. Clement ND, Court-Brown CM. Oxford shoulder score in a normal population. Int J Shoulder Surg. 2014;8(1):10-4.
202. Wilson J, Baker P, Rangan A. Is retrospective application of the Oxford Shoulder Score valid? J Shoulder Elbow Surg. 2009;18(4):577-80.
203. Baker P, Nanda R, Goodchild L, Finn P, Rangan A. A comparison of the Constant and Oxford shoulder scores in patients with conservatively treated proximal humeral fractures. J Shoulder Elbow Surg. 2008;17(1):37-41.
204. Hapuarachchi KS, Poon PC. A correlation study of the American Shoulder and Elbow Society Score and the Oxford Shoulder Score with the use of regression analysis to predict one score from the other in patients undergoing reverse shoulder joint arthroplasty for cuff tear arthropathy. Shoulder Elbow. 2014;6(2):81-9.
205. van Kampen DA, Willems WJ, van Beers LW, Castelein RM, Scholtes VA, Terwee CB. Determination and comparison of the smallest detectable change (SDC) and the minimal important change (MIC) of four-shoulder patient-reported outcome measures (PROMs). J Orthop Surg Res. 2013;8:40.

206. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med. 1996;29(6):602-8.
207. Kennedy CA BD, Solway S, McConnell S, Bombardier C. Disabilities of the Arm, Shoulder and Hand (DASH). The DASH and QuickDASH Outcome Measure User's Manual. Third ed: Toronto, Ontario: Institute for Work & Health; 2011.
208. Gummesson C, Ward MM, Atroshi I. The shortened disabilities of the arm, shoulder and hand questionnaire (QuickDASH): validity and reliability based on responses within the full-length DASH. BMC Musculoskelet Disord. 2006;7:44.
209. Mintken PE, Glynn P, Cleland JA. Psychometric properties of the shortened disabilities of the Arm, Shoulder, and Hand Questionnaire (QuickDASH) and Numeric Pain Rating Scale in patients with shoulder pain. J Shoulder Elbow Surg. 2009;18(6):920-6.
210. Beaton DE, Wright JG, Katz JN, Upper Extremity Collaborative G. Development of the QuickDASH: comparison of three item-reduction approaches. J Bone Joint Surg Am. 2005;87(5):1038-46.
211. Constant CR, Murley AH. A clinical method of functional assessment of the shoulder. Clin Orthop Relat Res. 1987(214):160-4.
212. Constant CR, Gerber C, Emery RJ, Sojbjerg JO, Gohlke F, Boileau P. A review of the Constant score: modifications and guidelines for its use. J Shoulder Elbow Surg. 2008;17(2):355-61.
213. Razmjou H, Bean A, Macdermid JC, van Osnabrugge V, Travers N, Holtby R. Convergent validity of the constant-murley outcome measure in patients with rotator cuff disease. Physiother Can. 2008;60(1):72-9.
214. Matsen. 2018 [cited 2017 23/8/2017]. Available from: http://www.orthop.washington.edu/?q=patient-care/articles/shoulder/simple-shoulder-test.html.
215. Schmidt S, Ferrer M, Gonzalez M, Gonzalez N, Valderas JM, Alonso J, et al. Evaluation of shoulder-specific patient-reported outcome measures: a systematic and standardized comparison of available evidence. J Shoulder Elbow Surg. 2014;23(3):434-44.
216. Godfrey J, Hamman R, Lowenstein S, Briggs K, Kocher M. Reliability, validity, and responsiveness of the simple shoulder test: psychometric properties by age and injury type. J Shoulder Elbow Surg. 2007;16(3):260-7.
217. Amstutz HC, Sew Hoy AL, Clarke IC. UCLA anatomic total shoulder arthroplasty. Clin Orthop Relat Res. 1981(155):7-20.
218. Ellman H, Kay SP. Arthroscopic subacromial decompression for chronic impingement. Two- to five-year results. J Bone Joint Surg Br. 1991;73(3):395-8.
219. Zandi H, Coghlan JA, Bell SN. Mini-incision rotator cuff repair: a longitudinal assessment with no deterioration of result up to nine years. J Shoulder Elbow Surg. 2006;15(2):135-9.
220. Coghlan JA, Bell SN, Forbes A, Buchbinder R. Comparison of self-administered University of California, Los Angeles, shoulder score with traditional University of California, Los Angeles, shoulder score completed by

clinicians in assessing the outcome of rotator cuff surgery. J Shoulder Elbow Surg. 2008;17(4):564-9.
221. Nutton RW, McBirnie JM, Phillips C. Treatment of chronic rotator-cuff impingement by arthroscopic subacromial decompression. J Bone Joint Surg Br. 1997;79(1):73-6.
222. Richards RR, An KN, Bigliani LU, Friedman RJ, Gartsman GM, Gristina AG, et al. A standardized method for the assessment of shoulder function. J Shoulder Elbow Surg. 1994;3(6):347-52.
223. Agel J, Swiontkowski MF. Guide to outcomes instruments for musculoskeletal trauma research. J Orthop Trauma. 2006;20(8 Suppl):S1-146.
224. Beaton D, Richards RR. Assessing the reliability and responsiveness of 5 shoulder questionnaires. J Shoulder Elbow Surg. 1998;7(6):565-72.
225. Carr AJ, Higginson IJ. Are quality of life measures patient centred? BMJ. 2001;322(7298):1357-60.
226. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
227. van Reenen M, Janssen B. EQ-5D-5L User Guide Basic information on how to use the EQ-5D-5L instrument. 2015.
228. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: Past, Present and Future. Appl Health Econ Health Policy. 2017;15(2):127-37.
229. NICE. Guide to the methods of technology appraisal: London, UK: National Institute of Health and Care Excellence; 2013.
230. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Health Econ. 2017.
231. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013;22(7):1717-27.
232. Sakthong P, Sonsa-Ardjit N, Sukarnjanaset P, Munpan W. Psychometric properties of the EQ-5D-5L in Thai patients with chronic diseases. Qual Life Res. 2015;24(12):3015-22.
233. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
234. Driskell LD, Starosta AJ, Brenner LA. Clinical utility and measurement characteristics of the Hospital Anxiety and Depression Scale for individuals with traumatic brain injury. Rehabil Psychol. 2016;61(1):112-3.
235. Whelan-Goodinson R, Ponsford J, Schonberger M. Validity of the Hospital Anxiety and Depression Scale to assess depression and anxiety following traumatic brain injury as compared with the Structured Clinical Interview for DSM-IV. J Affect Disord. 2009;114(1-3):94-102.
236. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes. 2003;1:29.
237. NICE. Depression in adults. 2011.
238. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52(2):69-77.

239. Bell ML, Fairclough DL, Fiero MH, Butow PN. Handling missing items in the Hospital Anxiety and Depression Scale (HADS): a simulation study. BMC Res Notes. 2016;9(1):479.
240. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res. 2006;60(6):631-7.
241. Storheim K GAM. Evaluation Of The Brief Illness Perception Questionnaire In Sub-Acute And Chronic Low Back Pain Patients: Data Quality, Reliability And Validity. Journal of Pain & Relief. 2013;02(03).
242. Broadbent E, Wilkes C, Koschwanez H, Weinman J, Norton S, Petrie KJ. A systematic review and meta-analysis of the Brief Illness Perception Questionnaire. Psychol Health. 2015;30(11):1361-85.
243. Nicholas MK. The pain self-efficacy questionnaire: Taking pain into account. Eur J Pain. 2007;11(2):153-63.
244. Freynhagen R, Baron R, Gockel U, Tolle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22(10):1911-20.
245. Cappelleri JC, Koduru V, Bienen EJ, Sadosky A. A cross-sectional study examining the psychometric properties of the painDETECT measure in neuropathic pain. J Pain Res. 2015;8:159-67.
246. Brophy RH, Beauvais RL, Jones EC, Cordasco FA, Marx RG. Measurement of shoulder activity level. Clin Orthop Relat Res. 2005;439:101-8.
247. Hepper CT, Smith MV, Steger-May K, Brophy RH. Normative data of shoulder activity level by age and sex. Am J Sports Med. 2013;41(5):1146-51.
248. Tubach F, Ravaud P, Beaton D, Boers M, Bombardier C, Felson DT, et al. Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. J Rheumatol. 2007;34(5):1188-93.
249. Yeranosian MG, Terrell RD, Wang JC, McAllister DR, Petrigliano FA. The costs associated with the evaluation of rotator cuff tears before surgical repair. J Shoulder Elbow Surg. 2013;22(12):1662-6.
250. Parker L, Nazarian LN, Carrino JA, Morrison WB, Grimaldi G, Frangos AJ, et al. Musculoskeletal imaging: medicare use, costs, and potential for cost substitution. J Am Coll Radiol. 2008;5(3):182-8.
251. Department of Health. 2012–13 tariff information spreadsheet website documents: Department of Health 2013 [cited 2017 5/10/17]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/151953/dh_133578.xls.xls.
252. Oh CH, Schweitzer ME, Spettell CM. Internal derangements of the shoulder: decision tree and cost-effectiveness analysis of conventional arthrography, conventional MRI, and MR arthrography. Skeletal Radiol. 1999;28(12):670-8.
253. American College of Radiologists. ACR–SSRpractice guideline for the performance and interpretation of magnetic resonance imaging (MRI) of the shoulder. Practice guideline shoulder MRI 2015 [cited 2017 5/10/17]. Available from: http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/MRI_Shoulder.pdf.

254. Tuite MJ, Small KM. Imaging Evaluation of Nonacute Shoulder Pain. AJR Am J Roentgenol. 2017;209(3):525-33.
255. Wise JN, Daffner RH, Weissman BN, Bancroft L, Bennett DL, Blebea JS, et al. ACR Appropriateness Criteria(R) on acute shoulder pain. J Am Coll Radiol. 2011;8(9):602-9.
256. Goud A, Segal D, Hedayati P, Pan JJ, Weissman BN. Radiographic evaluation of the shoulder. Eur J Radiol. 2008;68(1):2-15.
257. Petje G, Manndorff P, Aigner N, Landsiedl F, Ganger R. Radiographic evaluation of the acromion in impingement syndrome: comparison with arthroscopic findings in 147 shoulders. Acta Orthop Scand. 2000;71(6):609-12.
258. Vanarthos WJ, Monu JU. Type 4 acromion: a new classification. Contemp Orthop. 1995;30(3):227-9.
259. Balke M, Schmidt C, Dedy N, Banerjee M, Bouillon B, Liem D. Correlation of acromial morphology with impingement syndrome and rotator cuff tears. Acta Orthop. 2013;84(2):178-83.
260. Nyffeler RW, Meyer DC. Acromion and glenoid shape: Why are they important predictive factors for the future of our shoulders? EFORT Open Rev. 2017;2(5):141-50.
261. Mayerhoefer ME, Breitenseher MJ, Roposch A, Treitl C, Wurnig C. Comparison of MRI and conventional radiography for assessment of acromial shape. AJR Am J Roentgenol. 2005;184(2):671-5.
262. Epstein RE, Schweitzer ME, Frieman BG, Fenlin JM, Jr., Mitchell DG. Hooked acromion: prevalence on MR images of painful shoulders. Radiology. 1993;187(2):479-81.
263. Sanders TG, Morrison WB, Miller MD. Imaging techniques for the evaluation of glenohumeral instability. Am J Sports Med. 2000;28(3):414-34.
264. Bright AS, Torpey B, Magid D, Codd T, McFarland EG. Reliability of radiographic evaluation for acromial morphology. Skeletal Radiol. 1997;26(12):718-21.
265. Tran G, Hensor EM, Ray A, Kingsbury SR, O'Connor P, Conaghan PG. Ultrasound-detected pathologies cluster into groups with different clinical outcomes: data from 3000 community referrals for shoulder pain. Arthritis Res Ther. 2017;19(1):30.
266. Lee MH, Sheehan SE, Orwin JF, Lee KS. Comprehensive Shoulder US Examination: A Standardized Approach with Multimodality Correlation for Common Shoulder Disease. Radiographics. 2016;36(6):1606-27.
267. Klauser AS, Tagliafico A, Allen GM, Boutry N, Campbell R, Court-Payen M, et al. Clinical indications for musculoskeletal ultrasound: a Delphi-based consensus paper of the European Society of Musculoskeletal Radiology. Eur Radiol. 2012;22(5):1140-8.
268. Homsi C, Bordalo-Rodrigues M, da Silva JJ, Stump XM. Ultrasound in adhesive capsulitis of the shoulder: is assessment of the coracohumeral ligament a valuable diagnostic tool? Skeletal Radiol. 2006;35(9):673-8.
269. Michelin P, Delarue Y, Duparc F, Dacher JN. Thickening of the inferior glenohumeral capsule: an ultrasound sign for shoulder capsular contracture. Eur Radiol. 2013;23(10):2802-6.

270. Lee JC, Sykes C, Saifuddin A, Connell D. Adhesive capsulitis: sonographic changes in the rotator cuff interval with arthroscopic correlation. Skeletal Radiol. 2005;34(9):522-7.
271. Tandon A, Dewan S, Bhatt S, Jain AK, Kumari R. Sonography in diagnosis of adhesive capsulitis of the shoulder: a case-control study. J Ultrasound. 2017;20(3):227-36.
272. Henderson RE, Walker BF, Young KJ. The accuracy of diagnostic ultrasound imaging for musculoskeletal soft tissue pathology of the extremities: a comprehensive review of the literature. Chiropr Man Therap. 2015;23:31.
273. Roy JS, Braen C, Leblond J, Desmeules F, Dionne CE, MacDermid JC, et al. Diagnostic accuracy of ultrasonography, MRI and MR arthrography in the characterisation of rotator cuff disorders: a systematic review and meta-analysis. Br J Sports Med. 2015;49(20):1316-28.
274. O'Connor PJ, Rankine J, Gibbon WW, Richardson A, Winter F, Miller JH. Interobserver variation in sonography of the painful shoulder. J Clin Ultrasound. 2005;33(2):53-6.
275. Beggs I, Bianchi S, Bueno A, Cohen M, Court-Payen M, Grainger A. Musculoskeletal Ultrasound Technical Guidelines. Shoulder 2017 [cited 2017 04/10/2017]. Available from: https://essr.org/content-essr/uploads/2016/10/shoulder.pdf.
276. Motamedi D, Everist BM, Mahanty SR, Steinbach LS. Pitfalls in shoulder MRI: part 2--biceps tendon, bursae and cysts, incidental and postsurgical findings, and artifacts. AJR Am J Roentgenol. 2014;203(3):508-15.
277. Motamedi D, Everist BM, Mahanty SR, Steinbach LS. Pitfalls in shoulder MRI: part 1--normal anatomy and anatomic variants. AJR Am J Roentgenol. 2014;203(3):501-7.
278. Freeman R, Khanna S, Ricketts D. Inappropriate requests for magnetic resonance scans of the shoulder. Int Orthop. 2013;37(11):2181-4.
279. Iannotti JP, Williams GR. Clinical impact of shoulder magnetic resonance imaging. Oper Tech Sports Med. 1997;5(1):15-8.
280. Symanski JS, Subhas N, Babb J, Nicholson J, Gyftopoulos S. Diagnosis of Superior Labrum Anterior-to-Posterior Tears by Using MR Imaging and MR Arthrography: A Systematic Review and Meta-Analysis. Radiology. 2017;285(1):101-13.
281. Razmjou H, Fournier-Gosselin S, Christakis M, Pennings A, ElMaraghy A, Holtby R. Accuracy of magnetic resonance imaging in detecting biceps pathology in patients with rotator cuff disorders: comparison with arthroscopy. J Shoulder Elbow Surg. 2016;25(1):38-44.
282. VanBeek C, Loeffler BJ, Narzikul A, Gordon V, Rasiej MJ, Kazam JK, et al. Diagnostic accuracy of noncontrast MRI for detection of glenohumeral cartilage lesions: a prospective comparison to arthroscopy. J Shoulder Elbow Surg. 2014;23(7):1010-6.
283. Ahn K-S, Kang CH, Oh Y-W, Jeong W-K. Correlation between magnetic resonance imaging and clinical impairment in patients with adhesive capsulitis. Skeletal Radiol. 2012;41(10):1301.
284. Ardic F, Kahraman Y, Kacar M, Kahraman MC, Findikoglu G, Yorgancioglu ZR. Shoulder impingement syndrome: relationships between

clinical, functional, and radiologic findings. American journal of physical medicine & rehabilitation / Association of Academic Physiatrists. 2006;85(1):53.
285. Minagawa H, Yamamoto N, Abe H, Fukuda M, Seki N, Kikuchi K, et al. Prevalence of symptomatic and asymptomatic rotator cuff tears in the general population: From mass-screening in one village. Journal of Orthopaedics. 2013;10(1):8-12.
286. Bruyn GA, Pineda C, Hernandez-Diaz C, Ventura-Rios L, Moya C, Garrido J, et al. Validity of ultrasonography and measures of adult shoulder function and reliability of ultrasonography in detecting shoulder synovitis in patients with rheumatoid arthritis using magnetic resonance imaging as a gold standard. Arthritis Care Res (Hoboken). 2010;62(8):1079-86.
287. Makhni EC, Steinhaus ME, Morrow ZS, Jobin CM, Verma NN, Cole BJ, et al. Outcomes assessment in rotator cuff pathology: what are we measuring? J Shoulder Elbow Surg. 2015;24(12):2008-15.
288. Assuncao JH, Malavolta EA, Domingues VR, Gracitelli MEC, Ferreira Neto AA. Outcome assessment in the treatment of rotator cuff tear: what is utilized in Brazil? Rev Bras Ortop. 2017;52(5):561-8.
289. Yoo JC, Koh KH, Park WH, Park JC, Kim SM, Yoon YC. The outcome of ultrasound-guided needle decompression and steroid injection in calcific tendinitis. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]. 2010;19(4):596.
290. Kuhn JE. Exercise in the treatment of rotator cuff impingement: a systematic review and a synthesized evidence-based rehabilitation protocol. J Shoulder Elbow Surg. 2009;18(1):138-60.
291. Littlewood C, Malliaras P, Chance-Larsen K. Therapeutic exercise for rotator cuff tendinopathy: a systematic review of contextual factors and prescription parameters. Int J Rehabil Res. 2015;38(2):95-106.
292. Hanratty CE, McVeigh JG, Kerr DP, Basford JR, Finch MB, Pendleton A, et al. The effectiveness of physiotherapy exercises in subacromial impingement syndrome: a systematic review and meta-analysis. Semin Arthritis Rheum. 2012;42(3):297-316.
293. Gebremariam L, Hay EM, van der Sande R, Rinkel WD, Koes BW, Huisstede BM. Subacromial impingement syndrome--effectiveness of physiotherapy and manual therapy. Br J Sports Med. 2014;48(16):1202-8.
294. Kromer TO, Tautenhahn UG, de Bie RA, Staal JB, Bastiaenen CH. Effects of physiotherapy in patients with shoulder impingement syndrome: a systematic review of the literature. J Rehabil Med. 2009;41(11):870-80.
295. Haik MN, Alburquerque-Sendin F, Moreira RF, Pires ED, Camargo PR. Effectiveness of physical therapy treatment of clearly defined subacromial pain: a systematic review of randomised controlled trials. Br J Sports Med. 2016;50(18):1124-34.
296. Kelly SM, Wrightson PA, Meads CA. Clinical outcomes of exercise in the management of subacromial impingement syndrome: a systematic review. Clin Rehabil. 2010;24(2):99-109.
297. Braun C, Bularczyk M, Heintsch J, Hanchard NCA. Manual therapy and exercises for shoulder impingement revisited. Phys Ther Rev. 2013;18(4):263-84.

298. Desmeules F, Cote CH, Fremont P. Therapeutic exercise and orthopedic manual therapy for impingement syndrome: a systematic review. Clin J Sport Med. 2003;13(3):176-82.
299. Bury J, West M, Chamorro-Moriana G, Littlewood C. Effectiveness of scapula-focused approaches in patients with rotator cuff related shoulder pain: A systematic review and meta-analysis. Man Ther. 2016;25:35-42.
300. Green S, Buchbinder R, Hetrick S. Physiotherapy interventions for shoulder pain. Cochrane Database Syst Rev. 2003(2):CD004258.
301. Ho CY, Sole G, Munn J. The effectiveness of manual therapy in the management of musculoskeletal disorders of the shoulder: a systematic review. Man Ther. 2009;14(5):463-74.
302. Page MJ, Green S, McBain B, Surace SJ, Deitch J, Lyttle N, et al. Manual therapy and exercise for rotator cuff disease. Cochrane Database Syst Rev. 2016(6):CD012224.
303. Bronfort G, Haas M, Evans R, Leininger B, Triano J. Effectiveness of manual therapies: the UK evidence report. Chiropractic & Osteopathy. 2010;18:3-.
304. Page MJ, Green S, Kramer S, Johnston RV, McBain B, Chau M, et al. Manual therapy and exercise for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2014(8):CD011275.
305. Dong W, Goost H, Lin XB, Burger C, Paul C, Wang ZL, et al. Treatments for shoulder impingement syndrome: a PRISMA systematic review and network meta-analysis. Medicine (Baltimore). 2015;94(10):e510.
306. Littlewood C, Ashton J, Chance-Larsen K, May S, Sturrock B. Exercise for rotator cuff tendinopathy: a systematic review. Physiotherapy. 2012;98(2):101-9.
307. Carr AJ, Cooper CD, Campbell MK, Rees JL, Moser J, Beard DJ, et al. Clinical effectiveness and cost-effectiveness of open and arthroscopic rotator cuff repair [the UK Rotator Cuff Surgery (UKUFF) randomised trial]. Health Technol Assess. 2015;19(80):1-218.
308. van der Heijden GJ, van der Windt DA, Kleijnen J, Koes BW, Bouter LM. Steroid injections for shoulder disorders: a systematic review of randomized clinical trials. Br J Gen Pract. 1996;46(406):309-16.
309. Dean BJ, Lostis E, Oakley T, Rombach I, Morrey ME, Carr AJ. The risks and benefits of glucocorticoid treatment for tendinopathy: a systematic review of the effects of local glucocorticoid on tendon. Semin Arthritis Rheum. 2014;43(4):570-6.
310. van der Sande R, Rinkel WD, Gebremariam L, Hay EM, Koes BW, Huisstede BM. Subacromial impingement syndrome: effectiveness of pharmaceutical interventions-nonsteroidal anti-inflammatory drugs, corticosteroid, or other injections: a systematic review. Arch Phys Med Rehabil. 2013;94(5):961-76.
311. Johansson K, Oberg B, Adolfsson L, Foldevi M. A combination of systematic review and clinicians' beliefs in interventions for subacromial pain. Br J Gen Pract. 2002;52(475):145-52.
312. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: a meta-analysis. Br J Gen Pract. 2005;55(512):224-8.
313. Goupille P, Sibilia J. Local corticosteroid injections in the treatment of rotator cuff tendinitis (except for frozen shoulder and calcific tendinitis). Groupe

Rhumatologique Francais de l'Epaule (G.R.E.P.). Clin Exp Rheumatol. 1996;14(5):561-6.
314. Buchbinder R, Green S, Youd JM, Johnston RV. Oral steroids for adhesive capsulitis. Cochrane Database Syst Rev. 2006(4):CD006189.
315. Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. Cochrane Database Syst Rev. 2003(1):CD004016.
316. Favejee MM, Huisstede BM, Koes BW. Frozen shoulder: the effectiveness of conservative and surgical interventions--systematic review. Br J Sports Med. 2011;45(1):49-56.
317. Song A, Higgins LD, Newman J, Jain NB. Glenohumeral corticosteroid injections in adhesive capsulitis: a systematic search and review. PM R. 2014;6(12):1143-56.
318. Shah N, Lewis M. Shoulder adhesive capsulitis: systematic review of randomised trials using multiple corticosteroid injections. Br J Gen Pract. 2007;57(541):662-7.
319. Xiao RC, Walley KC, DeAngelis JP, Ramappa AJ. Corticosteroid Injections for Adhesive Capsulitis: A Review. Clin J Sport Med. 2017;27(3):308-20.
320. Sun Y, Lu S, Zhang P, Wang Z, Chen J. Steroid Injection Versus Physiotherapy for Patients With Adhesive Capsulitis of the Shoulder: A PRIMSA Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2016;95(20):e3469.
321. Griesser MJ, Harris JD, Campbell JE, Jones GL. Adhesive capsulitis of the shoulder: a systematic review of the effectiveness of intra-articular corticosteroid injections. J Bone Joint Surg Am. 2011;93(18):1727-33.
322. Blanchard V, Barr S, Cerisola FL. The effectiveness of corticosteroid injections compared with physiotherapeutic interventions for adhesive capsulitis: a systematic review. Physiotherapy. 2010;96(2):95-107.
323. Abdulla SY, Southerst D, Cote P, Shearer HM, Sutton D, Randhawa K, et al. Is exercise effective for the management of subacromial impingement syndrome and other soft tissue injuries of the shoulder? A systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Man Ther. 2015;20(5):646-56.
324. Maund E, Craig D, Suekarran S, Neilson A, Wright K, Brealey S, et al. Management of frozen shoulder: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2012;16(11):1-264.
325. Shin SJ, Lee SY. Efficacies of corticosteroid injection at different sites of the shoulder for the treatment of adhesive capsulitis. J Shoulder Elbow Surg. 2013;22(4):521-7.
326. Soh E, Li W, Ong KO, Chen W, Bautista D. Image-guided versus blind corticosteroid injections in adults with shoulder pain: a systematic review. BMC Musculoskelet Disord. 2011;12:137.
327. Bloom JE, Rischin A, Johnston RV, Buchbinder R. Image-guided versus blind glucocorticoid injection for shoulder pain. Cochrane Database Syst Rev. 2012(8):CD009147.
328. Oh JH, Oh CH, Choi JA, Kim SH, Kim JH, Yoon JP. Comparison of glenohumeral and subacromial steroid injection in primary frozen shoulder: a prospective, randomized short-term comparison study. J Shoulder Elbow Surg. 2011;20(7):1034-40.

329. Sun Y, Chen J, Li H, Jiang J, Chen S. Steroid Injection and Nonsteroidal Anti-inflammatory Agents for Shoulder Pain: A PRISMA Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2015;94(50):e2216.
330. Zheng XQ, Li K, Wei YD, Tie HT, Yi XY, Huang W. Nonsteroidal anti-inflammatory drugs versus corticosteroid for treatment of shoulder pain: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2014;95(10):1824-31.
331. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. Health Psychol. 2007;26(1):1-9.
332. Babatunde OO, Jordan JL, Van der Windt DA, Hill JC, Foster NE, Protheroe J. Effective treatment options for musculoskeletal pain in primary care: A systematic overview of current evidence. PLoS One. 2017;12(6):e0178621.
333. Karjalainen K, Malmivaara A, van Tulder M, Roine R, Jauhiainen M, Hurri H, et al. Multidisciplinary biopsychosocial rehabilitation for neck and shoulder pain among working age adults. Cochrane Database Syst Rev. 2003(2):CD002194.
334. Wu YC, Tsai WC, Tu YK, Yu TY. Comparative Effectiveness of Nonoperative Treatments for Chronic Calcific Tendinitis of the Shoulder: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Arch Phys Med Rehabil. 2017;98(8):1678-92 e6.
335. Page MJ, Green S, Mrocki MA, Surace SJ, Deitch J, McBain B, et al. Electrotherapy modalities for rotator cuff disease. Cochrane Database Syst Rev. 2016(6):CD012225.
336. Louwerens JK, Sierevelt IN, van Noort A, van den Bekerom MP. Evidence for minimally invasive therapies in the management of chronic calcific tendinopathy of the rotator cuff: a systematic review and meta-analysis. J Shoulder Elbow Surg. 2014;23(8):1240-9.
337. Ioppolo F, Tattoli M, Di Sante L, Venditto T, Tognolo L, Delicata M, et al. Clinical improvement and resorption of calcifications in calcific tendinitis of the shoulder after shock wave therapy at 6 months' follow-up: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2013;94(9):1699-706.
338. Louwerens JK, Veltman ES, van Noort A, van den Bekerom MP. The Effectiveness of High-Energy Extracorporeal Shockwave Therapy Versus Ultrasound-Guided Needling Versus Arthroscopic Surgery in the Management of Chronic Calcific Rotator Cuff Tendinopathy: A Systematic Review. Arthroscopy. 2016;32(1):165-75.
339. Page MJ, Green S, Kramer S, Johnston RV, McBain B, Buchbinder R. Electrotherapy modalities for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2014(10):CD011324.
340. Lee LC, Lieu FK, Lee HL, Tung TH. Effectiveness of hyaluronic acid administration in treating adhesive capsulitis of the shoulder: a systematic review of randomized controlled trials. Biomed Res Int. 2015;2015:314120.
341. Green S, Buchbinder R, Hetrick S. Acupuncture for shoulder pain. Cochrane Database Syst Rev. 2005(2):CD005319.

342. van der Heijden GJ, van der Windt DA, de Winter AF. Physiotherapy for patients with soft tissue shoulder disorders: a systematic review of randomised clinical trials. BMJ. 1997;315(7099):25-30.
343. Bull D, Tai Kie A, Hanusch B, Kulkarni R, Rees J, Rangan A. Is there sufficient evidence to support intervention to manage shoulder arthritis? Shoulder Elbow. 2016;8(2):77-89.
344. Sambandam SN, Khanna V, Gul A, Mounasamy V. Rotator cuff tears: An evidence based approach. World J Orthop. 2015;6(11):902-18.
345. Ghodadra NS, Provencher MT, Verma NN, Wilk KE, Romeo AA. Open, mini-open, and all-arthroscopic rotator cuff repair surgery: indications and implications for rehabilitation. J Orthop Sports Phys Ther. 2009;39(2):81-9.
346. Huang R, Wang S, Wang Y, Qin X, Sun Y. Systematic Review of All-Arthroscopic Versus Mini-Open Repair of Rotator Cuff Tears: A Meta-Analysis. Sci Rep. 2016;6:22857.
347. Lindley K, Jones GL. Outcomes of arthroscopic versus open rotator cuff repair: a systematic review of the literature. Am J Orthop (Belle Mead NJ). 2010;39(12):592-600.
348. Ji X, Bi C, Wang F, Wang Q. Arthroscopic versus mini-open rotator cuff repair: an up-to-date meta-analysis of randomized controlled trials. Arthroscopy. 2015;31(1):118-24.
349. Gebremariam L, Hay EM, Koes BW, Huisstede BM. Effectiveness of surgical and postsurgical interventions for the subacromial impingement syndrome: a systematic review. Arch Phys Med Rehabil. 2011;92(11):1900-13.
350. Coghlan JA, Buchbinder R, Green S, Johnston RV, Bell SN. Surgery for rotator cuff disease. Cochrane Database of Systematic Reviews. 2008(1).
351. Davis AD, Kakar S, Moros C, Kaye EK, Schepsis AA, Voloshin I. Arthroscopic versus open acromioplasty: a meta-analysis. Am J Sports Med. 2010;38(3):613-8.
352. Dorrestijn O, Stevens M, Winters JC, van der Meer K, Diercks RL. Conservative or surgical treatment for subacromial impingement syndrome? A systematic review. J Shoulder Elbow Surg. 2009;18(4):652-60.
353. Ketola S, Lehtinen J, Arnala I, Nissinen M, Westenius H, Sintonen H, et al. Does arthroscopic acromioplasty provide any additional value in the treatment of shoulder impingement syndrome?: a two-year randomised controlled trial. J Bone Joint Surg Br. 2009;91(10):1326-34.
354. Creech MJ, Yeung M, Denkers M, Simunovic N, Athwal GS, Ayeni OR. Surgical indications for long head biceps tenodesis: a systematic review. Knee Surg Sports Traumatol Arthrosc. 2016;24(7):2156-66.
355. Hsu AR, Ghodadra NS, Provencher MT, Lewis PB, Bach BR. Biceps tenotomy versus tenodesis: a review of clinical outcomes and biomechanical results. J Shoulder Elbow Surg. 2011;20(2):326-32.
356. Patel KV, Bravman J, Vidal A, Chrisman A, McCarty E. Biceps Tenotomy Versus Tenodesis. Clin Sports Med. 2016;35(1):93-111.
357. Slenker NR, Lawson K, Ciccotti MG, Dodson CC, Cohen SB. Biceps tenotomy versus tenodesis: clinical outcomes. Arthroscopy. 2012;28(4):576-82.

358. Ge H, Zhang Q, Sun Y, Li J, Sun L, Cheng B. Tenotomy or tenodesis for the long head of biceps lesions in shoulders: a systematic review and meta-analysis. PLoS One. 2015;10(3):e0121286.
359. Bryant D, Litchfield R, Sandow M, Gartsman GM, Guyatt G, Kirkley A. A comparison of pain, strength, range of motion, and functional outcomes after hemiarthroplasty and total shoulder arthroplasty in patients with osteoarthritis of the shoulder. A systematic review and meta-analysis. J Bone Joint Surg Am. 2005;87(9):1947-56.
360. Radnay CS, Setter KJ, Chambers L, Levine WN, Bigliani LU, Ahmad CS. Total shoulder replacement compared with humeral head replacement for the treatment of primary glenohumeral osteoarthritis: a systematic review. J Shoulder Elbow Surg. 2007;16(4):396-402.
361. Singh JA, Sperling J, Buchbinder R, McMaken K. Surgery for shoulder osteoarthritis: a Cochrane systematic review. J Rheumatol. 2011;38(4):598-605.
362. Buchbinder R, Green S, Youd JM, Johnston RV, Cumpston M. Arthrographic distension for adhesive capsulitis (frozen shoulder). Cochrane Database Syst Rev. 2008(1):CD007005.
363. Wu WT, Chang KV, Han DS, Chang CH, Yang FS, Lin CP. Effectiveness of Glenohumeral Joint Dilatation for Treatment of Frozen Shoulder: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Sci Rep. 2017;7(1):10507.
364. Grant JA, Schroeder N, Miller BS, Carpenter JE. Comparison of manipulation and arthroscopic capsular release for adhesive capsulitis: a systematic review. J Shoulder Elbow Surg. 2013;22(8):1135-45.
365. Fabricant PD, Taylor SA, McCarthy MM, Gausden EB, Moran CJ, Kang RW, et al. Open and Arthroscopic Anterior Shoulder Stabilization. JBJS Rev. 2015;3(2).
366. Cowling PD, Akhtar MA, Liow RY. What is a Bristow-Latarjet procedure? A review of the described operative techniques and outcomes. Bone Joint J. 2016;98-B(9):1208-14.
367. Harris JD, Gupta AK, Mall NA, Abrams GD, McCormick FM, Cole BJ, et al. Long-term outcomes after Bankart shoulder stabilization. Arthroscopy. 2013;29(5):920-33.
368. Griesser MJ, Harris JD, McCoy BW, Hussain WM, Jones MH, Bishop JY, et al. Complications and re-operations after Bristow-Latarjet shoulder stabilization: a systematic review. J Shoulder Elbow Surg. 2013;22(2):286-92.
369. Robinson R. Economic evaluation and health care. What does it mean? BMJ. 1993;307(6905):670-3.
370. Kuye IO, Jain NB, Warner L, Herndon JH, Warner JJ. Economic evaluations in shoulder pathologies: a systematic review of the literature. J Shoulder Elbow Surg. 2012;21(3):367-75.
371. Jowett S, Crawshaw DP, Helliwell PS, Hensor EM, Hay EM, Conaghan PG. Cost-effectiveness of exercise therapy after corticosteroid injection for moderate to severe shoulder pain due to subacromial impingement syndrome: a trial-based analysis. Rheumatology (Oxford). 2013;52(8):1485-91.
372. Nazarian LN, Jacobson JA, Benson CB, Bancroft LW, Bedi A, McShane JM, et al. Imaging algorithms for evaluating suspected rotator cuff disease:

Society of Radiologists in Ultrasound consensus conference statement. Radiology. 2013;267(2):589-95.
373. Dinnes J, Loveman E, McIntyre L, Waugh N. The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review. Health Technol Assess. 2003;7(29):iii, 1-166.
374. Academy of Medical Royal Colleges. Protecting resource, promoting value: a doctor's guide to cutting waste in clinical care. 2014.
375. Ottenheijm RP, Cals JW, Winkens B, Weijers RE, de Bie RA, Dinant GJ. Ultrasound imaging to tailor the treatment of acute shoulder pain: a randomised controlled trial in general practice. BMJ Open. 2016;6(11):e011048.
376. Bureau NJ, Ziegler D. Economics of Musculoskeletal Ultrasound. Curr Radiol Rep. 2016;4:44.
377. Hendee WR, Becker GJ, Borgstede JP, Bosma J, Casarella WJ, Erickson BA, et al. Addressing overutilization in medical imaging. Radiology. 2010;257(1):240-5.
378. Kulkarni R, Gibson J, Brownson P, Thomas M, Rangan A, Carr AJ, et al. Subacromial shoulder pain. Shoulder Elbow. 2015;7(2):135-43.
379. Brownson P, Donaldson O, Fox M, Rees JL, Rangan A, Jaggi A, et al. BESS/BOA Patient Care Pathways: Traumatic anterior shoulder instability. Shoulder Elbow. 2015;7(3):214-26.
380. Hearst Health International. Map of Medicine 2017 [cited 2017 30/11/17]. Available from: http://mapofmedicine.com/.
381. NICE. Clinical Knowledge Summary 2017 [cited 2017 30/11/17]. Available from: https://cks.nice.org.uk/shoulder-pain#!topicsummary). .
382. New Zealand Guidelines Group. The diagnosis and management of soft tissue shoulder injuries and related disorders: New Zealand Guidelines Group; 2004 [cited 2016 Accessed 22 November 2016]. Available from: www.health.govt.nz.
383. American Academy of Orthopaedic Surgeons. Optimizing the management of rotator cuff problems. 2010.
384. Diercks R, Bron C, Dorrestijn O, Meskers C, Naber R, de Ruiter T, et al. Guideline for diagnosis and treatment of subacromial pain syndrome: a multidisciplinary review by the Dutch Orthopaedic Association. Acta Orthop. 2014;85(3):314-22.
385. Klintberg IH, Cools AM, Holmgren TM, Holzhausen AC, Johansson K, Maenhout AG, et al. Consensus for physiotherapy for shoulder pain. Int Orthop. 2015;39(4):715-20.
386. Beaudreuil J, Dhenain M, Coudane H, Mlika-Cabanne N. Clinical practice guidelines for the surgical management of rotator cuff tears in adults. Orthop Traumatol Surg Res. 2010;96(2):175-9.
387. Johansson K, Adolfsson L, Foldevi M. Attitudes toward management of patients with subacromial pain in Swedish primary care. Fam Pract. 1999;16(3):233-7.
388. Ottenheijm RP, Jansen MJ, Staal JB, van den Bruel A, Weijers RE, de Bie RA, et al. Accuracy of diagnostic ultrasound in patients with suspected subacromial disorders: a systematic review and meta-analysis. Arch Phys Med Rehabil. 2010;91(10):1616-25.

389. Connor PM, Banks DM, Tyson AB, Coumas JS, D'Alessandro DF. Magnetic resonance imaging of the asymptomatic shoulder of overhead athletes: a 5-year follow-up study. Am J Sports Med. 2003;31(5):724-7.
390. Sher JS, Uribe JW, Posada A, Murphy BJ, Zlatkin MB. Abnormal findings on magnetic resonance images of asymptomatic shoulders. J Bone Joint Surg Am. 1995;77(1):10-5.
391. Academy of Medical Royal Colleges. Protecting resources, promoting value: a doctor's guide to cutting waste in clinical care: Academy of Medical Royal Colleges; 2014.
392. Lievense AM, Bierma-Zeinstra SM, Verhagen AP, van Baar ME, Verhaar JA, Koes BW. Influence of obesity on the development of osteoarthritis of the hip: a systematic review. Rheumatology (Oxford). 2002;41(10):1155-62.
393. Barr AJ, Campbell TM, Hopkinson D, Kingsbury SR, Bowes MA, Conaghan PG. A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis. Arthritis Res Ther. 2015;17:228.
394. Slavin RE. Best evidence synthesis: an intelligent alternative to meta-analysis. J Clin Epidemiol. 1995;48(1):9-18.
395. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
396. Chiou HJ, Chou YH, Wu JJ, Hsu CC, Huang DY, Chang CY. Evaluation of calcific tendonitis of the rotator cuff: role of color Doppler ultrasonography. J Ultrasound Med. 2002;21(3):289-95; quiz 96-7.
397. Cholewinski JJ, Kusz DJ, Wojciechowski P, Cielinski LS, Zoladz MP. Ultrasound measurement of rotator cuff thickness and acromio-humeral distance in the diagnosis of subacromial impingement syndrome of the shoulder. Knee Surg Sports Traumatol Arthrosc. 2008;16(4):408-14.
398. Daghir AA, Sookur PA, Shah S, Watson M. Dynamic ultrasound of the subacromial-subdeltoid bursa in patients with shoulder impingement: A comparison with normal volunteers. Skeletal Radiol. 2012;41(9):1047-53.
399. Draghi F, Scudeller L, Draghi AG, Bortolotto C. Prevalence of subacromial-subdeltoid bursitis in shoulder pain: an ultrasonographic study. Journal of ultrasound. 2015;18(2):151.
400. Fehringer EV, Sun J, VanOeveren LS, Keller BK, Matsen IIIFA. Full-thickness rotator cuff tear prevalence and correlation with function and co-morbidities in patients sixty-five years and older. J Shoulder Elbow Surg. 2008;17(6):881-5.
401. Hamid N, Omid R, Yamaguchi K, Steger-May K, Stobbs G, Keener D. Relationship of radiographic acromial characteristics and rotator cuff disease: a prospective investigation of clinical, radiographic, and sonographic findings. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]. 2012;21(10):1289.
402. Joensen J, Couppe C, Bjordal JM. Increased palpation tenderness and muscle strength deficit in the prediction of tendon hypertrophy in symptomatic unilateral shoulder tendinopathy: an ultrasonographic study. Physiotherapy. 2009;95(2):83.

403. Keener JD, Steger-May K, Stobbs G, Yamaguchi K. Asymptomatic rotator cuff tears: Patient demographics and baseline shoulder function. J Shoulder Elbow Surg. 2010;19(8):1191-8.
404. Keener JD, Wei AS, Kim HM, Steger-May K, Yamaguchi K. Proximal humeral migration in shoulders with symptomatic and asymptomatic rotator cuff tears. Journal of Bone and Joint Surgery - Series A. 2009;91(6):1405-13.
405. Le B, Berthelot JM, Guillot P, Glemarec J, Maugars Y. Assessment of calcific tendonitis of rotator cuff by ultrasonography: Comparison between symptomatic and asymptomatic shoulders. Joint Bone Spine. 2010;77(3):258-63.
406. McMahon J, Prasad A, Francis A. What is the prevalence of senior-athlete rotator cuff injuries and are they associated with pain and dysfunction? Clin Orthop Relat Res. 2014;472(8):2427.
407. Tracy MR, Trella TA, Nazarian LN, Tuohy CJ, Williams GR. Sonography of the coracohumeral interval: a potential technique for diagnosing coracoid impingement. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine. 2010;29(3):337-41.
408. Wu C-H, Wang Y-C, Wang H-K, Chen W-S, Wang T-G. Evaluating displacement of the coracoacromial ligament in painful shoulders of overhead athletes through dynamic ultrasonographic examination. Arch Phys Med Rehabil. 2010;91(2):278.
409. Chiou HJ, Chou YH, Wu JJ, Huang TF, Ma HL, Hsu CC, et al. The role of high-resolution ultrasonography in management of calcific tendonitis of the rotator cuff. Ultrasound Med Biol. 2001;27(6):735.
410. Couanis G, Breidahl W, Burnham S. The relationship between subacromial bursa thickness on ultrasound and shoulder pain in open water endurance swimmers over time. Journal of science and medicine in sport / Sports Medicine Australia. 2015;18(4):373.
411. Desmeules F, Minville L, Riederer B, Cote CH, Fremont P. Acromio-humeral distance variation measured by ultrasonography and its association with the outcome of rehabilitation for shoulder impingement syndrome. Clin J Sport Med. 2004;14(4):197-205.
412. Keener D, Galatz M, Teefey A, Middleton D, Steger-May K, Stobbs-Cucchi G, et al. A prospective evaluation of survivorship of asymptomatic degenerative rotator cuff tears. The Journal of bone and joint surgery American volume. 2015;97(2):89.
413. Mall NA, Kim HM, Keener JD, Steger-May K, Teefey SA, Middleton WD, et al. Symptomatic progression of asymptomatic rotator cuff tears: a prospective study of clinical and sonographic variables. J Bone Joint Surg Am. 2010;92(16):2623-33.
414. Moosmayer S, Tariq R, Stiris M, Smith HJ. The natural history of asymptomatic rotator cuff tears: A three-year follow-up of fifty cases. Journal of Bone and Joint Surgery - Series A. 2013;95(14):1249-55.
415. Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WD. Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]. 2001;10(3):199.

416. Safran O, Schroeder J, Bloom R, Weil Y, Milgrom C. Natural history of nonoperatively treated symptomatic rotator cuff tears in patients 60 years old or younger. The American journal of sports medicine. 2011;39(4):710-4.
417. Moosmayer S, Gartner AV, Tariq R. The natural course of nonoperatively treated rotator cuff tears: an 8.8-year follow-up of tear anatomy and clinical outcome in 49 patients. J Shoulder Elbow Surg. 2017;26(4):627-34.
418. Curry EJ, Matzkin EE, Dong Y, Higgins LD, Katz JN, Jain NB. Structural characteristics are not associated with pain and function in rotator cuff tears: The row cohort study. Orthopaedic Journal of Sports Medicine. 2015;3(5).
419. Di MM, Fraracci L. MR study of the intrinsic acromial angle in 74 symptomatic patients. Radiol Med. 2005;110(3):273.
420. Epstein RE, Schweitzer ME, Frieman BG, Fenlin JM, Mitchell DG. Hooked acromion: prevalence on MR images of painful shoulders. Radiology. 1993;187(2):479.
421. Frost P, Andersen JH, Lundorf E. Is supraspinatus pathology as defined by magnetic resonance imaging associated with clinical sign of shoulder impingement? Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]. 1999;8(6):565.
422. Gill TK, Shanahan EM, Allison D, Alcorn D, Hill CL. Prevalence of abnormalities on shoulder MRI in symptomatic and asymptomatic older adults. Int J Rheum Dis. 2014;17(8):863-71.
423. Graichen H, Bonel H, Stammberger T, Haubner M, Rohrer H, Englmeier KH, et al. Three-dimensional analysis of the width of the subacromial space in healthy subjects and patients with impingement syndrome. AJR American journal of roentgenology. 1999;172(4):1081.
424. Jung JY, Yoon YC, Cha DI, Yoo J-C, Jung JY. The "bridging sign": a MR finding for combined full-thickness tears of the subscapularis tendon and the supraspinatus tendon. Acta radiologica (Stockholm, Sweden : 1987). 2013;54(1):83.
425. Kanatli U, Gemalmaz HC, Ozturk BY, Voyvoda NK, Tokgoz N, Bolukbasi S. The role of radiological subacromial distance measurements in the subacromial impingement syndrome. European journal of orthopaedic surgery & traumatology : orthopédie traumatologie. 2013;23(3):317.
426. Krief P, Huguet D. Shoulder pain and disability: comparison with MR findings. AJR American journal of roentgenology. 2006;186(5):1234.
427. Mayerhoefer ME, Breitenseher MJ, Wurnig C, Roposch A. Shoulder impingement: Relationship of clinical symptoms and imaging criteria. Clin J Sport Med. 2009;19(2):83-9.
428. Moon MOONG, Unruh P, Kuhn E, Sanders R, An Q, Baumgarten M, et al. The duration of symptoms does not correlate with rotator cuff tear severity or other patient-related features: a cross-sectional study of patients with atraumatic, full-thickness rotator cuff tears. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]. 2014;23(7):1052.
429. Moses DA, Chang EY, Schweitzer ME. The scapuloacromial angle: A 3D analysis of acromial slope and its relationship with shoulder impingement. J Magn Reson Imaging. 2006;24(6):1371-7.

430. Reuter RM, Hiller WD, Ainge GR, Brown DW, Dierenfield L, Shellock FG, et al. Ironman triathletes: MRI assessment of the shoulder. Skeletal Radiol. 2008;37(8):737-41.
431. Schweitzer ME, Magbalon MJ, Fenlin JM, Frieman BG, Ehrlich S, Epstein RE. Effusion criteria and clinical importance of glenohumeral joint fluid: MR imaging evaluation. Radiology. 1995;194(3):821.
432. White EA, Schweitzer ME, Haims AH. Range of normal and abnormal subacromial/subdeltoid bursa fluid. J Comput Assist Tomogr. 2006;30(2):316-20.
433. Williamson MP, Chandnani VP, Baird DE, Reeves TQ, Deberardino TM, Swenson GW, et al. Shoulder impingement syndrome: Diagnostic accuracy of magnetic resonarace imaging and radiographic signs. Australas Radiol. 1994;38(4):265-71.
434. Ertan S, Ayhan E, Guven MF, Kesmezacar H, Akgun K, Babacan M. Medium-term natural history of subacromial impingement syndrome. J Shoulder Elbow Surg. 2015;24(10):1512-8.
435. Birtane M, Calis M, Akgun K. The diagnostic value of magnetic resonance imaging in subacromial impingement syndrome. Yonsei Med J. 2001;42(4):418-24.
436. Binder AI, Bulgen DY, Hazleman BL, Tudor J, Wraight P. Frozen shoulder: an arthrographic and radionuclear scan assessment. Ann Rheum Dis. 1984;43(3):365.
437. Endo K, Ikata T, Katoh S, Takeda Y. Radiographic assessment of scapular rotational tilt in chronic shoulder impingement syndrome. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association. 2001;6(1):3.
438. Kircher J, Morhard M, Magosch P, Ebinger N, Lichtenberg S, Habermeyer P. How much are radiological parameters related to clinical symptoms and function in osteoarthritis of the shoulder? Int Orthop. 2010;34(5):677-81.
439. Kircher J, Morhard M, Patzer T, Magosch P, Lichtenberg S, Habermeyer P. Do anatomic variants of the acromion shape in the frontal plane influence pain and function in calcifying tendinitis of the shoulder? Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA. 2012;20(2):368.
440. Yamaguchi K, Sher JS, Andersen WK, Garretson R, Uribe JW, Hechtman K, et al. Glenohumeral motion in patients with rotator cuff tears: a comparison of asymptomatic and symptomatic shoulders. Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons [et al]. 2000;9(1):6.
441. Cho NS, Lee BG, Rhee YG. Radiologic course of the calcific deposits in calcific tendinitis of the shoulder: does the initial radiologic aspect affect the final results? J Shoulder Elbow Surg. 2010;19(2):267.
442. Clunie GPR, Bomanji J, Renton P, Edwards JCW, Ell PJ. Technetium-99m human immunoglobulin imaging in patients with subacromial impingement or adhesive capsulitis. Clin Rheumatol. 1998;17(5):419-21.
443. Koike Y, Sano H, Kita A, Itoi E. Symptomatic rotator cuff tears show higher radioisotope uptake on bone scintigraphy compared with asymptomatic tears. The American journal of sports medicine. 2013;41(9):2028-33.

444. Kim DH, Sung DH, Ga HY, Choi JY. Metabolic patterns of the shoulder joint on (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in adhesive capsulitis. Ann Nucl Med. 2014;28(2):136.
445. Sridharan R, Engle MP, Garg N, Wei W, Amini B. Focal uptake at the rotator interval or inferior capsule of shoulder on 18F-FDG PET/CT is associated with adhesive capsulitis. Skeletal Radiol. 2017;46(4):533-8.
446. Ottenheijm RP, van't Klooster IG, Starmans LM, Vanderdood K, de Bie RA, Dinant GJ, et al. Ultrasound-diagnosed disorders in shoulder patients in daily general practice: a retrospective observational study. BMC Fam Pract. 2014;15:115.
447. Hill JC, Whitehurst DG, Lewis M, Bryan S, Dunn KM, Foster NE, et al. Comparison of stratified primary care management for low back pain with current best practice (STarT Back): a randomised controlled trial. Lancet. 2011;378(9802):1560-71.
448. May S, Chance-Larsen K, Littlewood C, Lomas D, Saad M. Reliability of physical examination tests used in the assessment of patients with shoulder problems: a systematic review. Physiotherapy. 2010;96(3):179-90.
449. Ottenheijm RP, Hesselmans NJ, Kemper A, Moser A, de Bie RA, Dinant GJ, et al. GPs' perspectives on the diagnostic work-up in patients with shoulder pain: a qualitative study. J Eval Clin Pract. 2014;20(3):239-45.
450. Lenza M, Buchbinder R, Takwoingi Y, Johnston V, Hanchard NC, Faloppa F. Magnetic resonance imaging, magnetic resonance arthrography and ultrasonography for assessing rotator cuff tears in people with shoulder pain for whom surgery is being considered. The Cochrane database of systematic reviews. 2013;9.
451. Leeds NHS Trust IT data (unpublished).
452. Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WD. Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. J Shoulder Elbow Surg. 2001;10(3):199-203.
453. Schibany N, Zehetgruber H, Kainberger F, Kainberger F, Wurnig C, Ba-Ssalamah A, et al. Rotator cuff tears in asymptomatic individuals: a clinical and ultrasonographic screening study. Eur J Radiol. 2004;51(3):263-8.
454. Whitehurst DG, Bryan S, Lewis M, Hay EM, Mullis R, Foster NE. Implementing stratified primary care management for low back pain: cost-utility analysis alongside a prospective, population-based, sequential comparison study. Spine (Phila Pa 1976). 2015;40(6):405-14.
455. O'Connor PJ, Rankine J, Gibbon WW, Richardson A, Winter F, Miller JH. Interobserver variation in sonography of the painful shoulder. J Clin Ultrasound. 2005;33(2):53-6.
456. Nylund KL, Asparouhov T, Muthen BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study (vol 14, pg 535, 2007). Structural Equation Modeling-a Multidisciplinary Journal. 2008;15(1):182-.
457. Wilson MW, Richards JS, Klapow JC, DeVivo MJ, Greene P. Cluster Analysis and Chronic Pain: An Empirical Classification of Pain Subgroups in a Spinal Cord Injury Sample. Rehabil Psychol. 2005;50(4):381-8.
458. Flynn T, Fritz J, Whitman J, Wainner R, Magel J, Rendeiro D, et al. A clinical prediction rule for classifying patients with low back pain who

demonstrate short-term improvement with spinal manipulation. Spine (Phila Pa 1976). 2002;27(24):2835-43.
459. Magidson J. Latent class models for clustering: A comparison with K-means. Canadian Journal of Marketing Research. 2002;20:37-44.
460. Kent P, Jensen RK, Kongsted A. A comparison of three clustering methods for finding subgroups in MRI, SMS or clinical data: SPSS TwoStep Cluster analysis, Latent Gold and SNOB. BMC Med Res Methodol. 2014;14:113.
461. Ottenheijm RPG, Cals JWL, Winkens B, Weijers RE, de Bie RA, Dinant G-J. Ultrasound imaging to tailor the treatment of acute shoulder pain: a randomised controlled trial in general practice. BMJ Open. 2016;6(11).
462. Crawshaw DP, Helliwell PS, Hensor EM, Hay EM, Aldous SJ, Conaghan PG. Exercise therapy after corticosteroid injection for moderate to severe shoulder pain: large pragmatic randomised trial. BMJ. 2010;340:c3037.
463. Moosmayer S, Tariq R, Stiris M, Smith HJ. The natural history of asymptomatic rotator cuff tears: a three-year follow-up of fifty cases. J Bone Joint Surg Am. 2013;95(14):1249-55.
464. Kuhn JE, Dunn WR, Sanders R, An Q, Baumgarten KM, Bishop JY, et al. Effectiveness of physical therapy in treating atraumatic full-thickness rotator cuff tears: a multicenter prospective cohort study. J Shoulder Elbow Surg. 2013;22(10):1371-9.
465. Slabaugh MA, Nho SJ, Grumet RC, Wilson JB, Seroyer ST, Frank RM, et al. Does the literature confirm superior clinical results in radiographically healed rotator cuffs after rotator cuff repair? Arthroscopy. 2010;26(3):393-403.
466. Carr AJ, Rees JL, Ramsay CR, Fitzpatrick R, Gray A, Moser J, et al. Protocol for the United Kingdom Rotator Cuff Study (UKUFF): a randomised controlled trial of open and arthroscopic rotator cuff repair. Bone Joint Res. 2014;3(5):155-60.
467. Weber SC, Martin DF, Seiler JG, 3rd, Harrast JJ. Superior labrum anterior and posterior lesions of the shoulder: incidence rates, complications, and outcomes as reported by American Board of Orthopedic Surgery. Part II candidates. Am J Sports Med. 2012;40(7):1538-43.
468. Schwartzberg R, Reuss BL, Burkhart BG, Butterfield M, Wu JY, McLean KW. High Prevalence of Superior Labral Tears Diagnosed by MRI in Middle-Aged Patients With Asymptomatic Shoulders. Orthop J Sports Med. 2016;4(1):2325967115623212.
469. Roh YH, Lee BK, Noh JH, Oh JH, Gong HS, Baek GH. Effect of depressive symptoms on perceived disability in patients with chronic shoulder pain. Arch Orthop Trauma Surg. 2012;132(9):1251-7.
470. Unruh KP, Kuhn JE, Sanders R, An Q, Baumgarten KM, Bishop JY, et al. The duration of symptoms does not correlate with rotator cuff tear severity or other patient-related features: a cross-sectional study of patients with atraumatic, full-thickness rotator cuff tears. J Shoulder Elbow Surg. 2014;23(7):1052-8.
471. Jordan KP, Kadam UT, Hayward R, Porcheret M, Young C, Croft P. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. BMC Musculoskelet Disord. 2010;11:144.

472. Martinoli C. Musculoskeletal ultrasound: technical guidelines. Insights Imaging. 2010;1(3):99-141.
473. Laslett M, Steele M, Hing W, McNair P, Cadogan A. Shoulder pain in primary care--part 2: predictors of clinical outcome to 12 months. J Rehabil Med. 2015;47(1):66-71.
474. Feleus A, Bierma-Zeinstra SM, Miedema HS, Verhagen AP, Nauta AP, Burdorf A, et al. Prognostic indicators for non-recovery of non-traumatic complaints at arm, neck and shoulder in general practice--6 months follow-up. Rheumatology (Oxford). 2007;46(1):169-76.
475. Chester R, Shepstone L, Lewis JS, Jerosch-Herold C. Predicting response to physiotherapy treatment for musculoskeletal shoulder pain: protocol for a longitudinal cohort study. BMC Musculoskelet Disord. 2013;14:192.
476. Kuijpers T, van der Windt DA, Boeke AJ, Twisk JW, Vergouwe Y, Bouter LM, et al. Clinical prediction rules for the prognosis of shoulder pain in general practice. Pain. 2006;120(3):276-85.
477. Bruls VE, Bastiaenen CH, de Bie RA. Prognostic factors of complaints of arm, neck, and/or shoulder: a systematic review of prospective cohort studies. Pain. 2015;156(5):765-88.
478. Vergouw D, Heymans MW, de Vet HC, van der Windt DA, van der Horst HE. Prediction of persistent shoulder pain in general practice: comparing clinical consensus from a Delphi procedure with a statistical scoring system. BMC Fam Pract. 2011;12:63.
479. West SL, Savitz DA, Koch G, Strom BL, Guess HA, Hartzema A. Recall accuracy for prescription medications: self-report compared with database information. Am J Epidemiol. 1995;142(10):1103-12.
480. Green SB. How Many Subjects Does It Take to Do a Regression-Analysis. Multivar Behav Res. 1991;26(3):499-510.
481. Baruch Y, Holtom BC. Survey response rate levels and trends in organizational research. Human Relations. 2008;61(8):1139-60.
482. Bray BC, Lanza ST, Tan X. Eliminating Bias in Classify-Analyze Approaches for Latent Class Analysis. Struct Equ Modeling. 2015;22(1):1-11.
483. Tennant A, Conaghan PG. The Rasch measurement model in rheumatology: what is it and why use it? When should it be applied, and what should one look for in a Rasch paper? Arthritis Rheum. 2007;57(8):1358-62.
484. Wainer H, Kiely GL. Item Clusters and Computerized Adaptive Testing: A Case for Testlets. Journal of Educational Measurement. 1987;24(3):185-201.
485. Nylund KL, Asparoutiov T, Muthen BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. Structural Equation Modeling-a Multidisciplinary Journal. 2007;14(4):535-69.
486. Gialanella B, Prometti P. Effects of corticosteroids injection in rotator cuff tears. Pain Med. 2011;12(10):1559-65.
487. Bhatia M, Singh B, Nicolaou N, Ravikumar KJ. Correlation between rotator cuff tears and repeated subacromial steroid injections: a case-controlled study. Ann R Coll Surg Engl. 2009;91(5):414-6.
488. Beard DJ, Rees JL, Cook JA, Rombach I, Cooper C, Merritt N, et al. Arthroscopic subacromial decompression for subacromial shoulder pain

(CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial. Lancet. 2018;391(10118):329-38.
489. Paavola M, Malmivaara A, Taimela S, Kanto K, Inkinen J, Kalske J, et al. Subacromial decompression versus diagnostic arthroscopy for shoulder impingement: randomised, placebo surgery controlled clinical trial. BMJ. 2018;362:k2860.
490. Ryosa A, Laimi K, Aarimaa V, Lehtimaki K, Kukkonen J, Saltychev M. Surgery or conservative treatment for rotator cuff tear: a meta-analysis. Disabil Rehabil. 2017;39(14):1357-63.
491. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, et al. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis. 2005;64(1):34-7.
492. Maksymowych WP, Richardson R, Mallon C, van der Heijde D, Boonen A. Evaluation and validation of the patient acceptable symptom state (PASS) in patients with ankylosing spondylitis. Arthritis Rheum. 2007;57(1):133-9.
493. Tubach F, Wells GA, Ravaud P, Dougados M. Minimal clinically important difference, low disease activity state, and patient acceptable symptom state: methodological issues. J Rheumatol. 2005;32(10):2025-9.
494. Christie A, Dagfinrud H, Garratt AM, Ringen Osnes H, Hagen KB. Identification of shoulder-specific patient acceptable symptom state in patients with rheumatic diseases undergoing shoulder surgery. J Hand Ther. 2011;24(1):53-60; quiz 1.
495. Maksymowych WP, Gooch K, Dougados M, Wong RL, Chen N, Kupper H, et al. Thresholds of patient-reported outcomes that define the patient acceptable symptom state in ankylosing spondylitis vary over time and by treatment and patient characteristics. Arthritis Care Res (Hoboken). 2010;62(6):826-34.
496. Escobar A, Gonzalez M, Quintana JM, Vrotsou K, Bilbao A, Herrera-Espineira C, et al. Patient acceptable symptom state and OMERACT-OARSI set of responder criteria in joint replacement. Identification of cut-off values. Osteoarthritis Cartilage. 2012;20(2):87-92.
497. Heiberg T, Kvien TK, Mowinckel P, Aletaha D, Smolen JS, Hagen KB. Identification of disease activity and health status cut-off points for the symptom state acceptable to patients with rheumatoid arthritis. Ann Rheum Dis. 2008;67(7):967-71.
498. Tubach F, Pham T, Skomsvoll JF, Mikkelsen K, Bjorneboe O, Ravaud P, et al. Stability of the patient acceptable symptomatic state over time in outcome criteria in ankylosing spondylitis. Arthritis Rheum. 2006;55(6):960-3.
499. Tubach F, Dougados M, Falissard B, Baron G, Logeart I, Ravaud P. Feeling good rather than feeling better matters more to patients. Arthritis Rheum. 2006;55(4):526-30.
500. Tashjian RZ, Hung M, Keener JD, Bowen RC, McAllister J, Chen W, et al. Determining the minimal clinically important difference for the American Shoulder and Elbow Surgeons score, Simple Shoulder Test, and visual analog scale (VAS) measuring pain after shoulder arthroplasty. J Shoulder Elbow Surg. 2017;26(1):144-8.

501. Bodin J, Garlantezec R, Costet N, Descatha A, Viel JF, Roquelaure Y. Risk factors for shoulder pain in a cohort of French workers: A Structural Equation Model. Am J Epidemiol. 2017.
502. van der Molen HF, Foresti C, Daams JG, Frings-Dresen MHW, Kuijer P. Work-related risk factors for specific shoulder disorders: a systematic review and meta-analysis. Occup Environ Med. 2017;74(10):745-55.
503. Dabija DI, Gao C, Edwards TL, Kuhn JE, Jain NB. Genetic and familial predisposition to rotator cuff disease: a systematic review. J Shoulder Elbow Surg. 2017;26(6):1103-12.
504. Tashjian RZ, Farnham JM, Albright FS, Teerlink CC, Cannon-Albright LA. Evidence for an inherited predisposition contributing to the risk for rotator cuff disease. J Bone Joint Surg Am. 2009;91(5):1136-42.
505. Kvalvaag E, Anvar M, Karlberg AC, Brox JI, Engebretsen KB, Soberg HL, et al. Shoulder MRI features with clinical correlations in subacromial pain syndrome: a cross-sectional and prognostic study. BMC Musculoskelet Disord. 2017;18(1):469.
506. Steuri R, Sattelmayer M, Elsig S, Kolly C, Tal A, Taeymans J, et al. Effectiveness of conservative interventions including exercise, manual therapy and medical management in adults with shoulder impingement: a systematic review and meta-analysis of RCTs. Br J Sports Med. 2017;51(18):1340-7.
507. Shire AR, Staehr TAB, Overby JB, Bastholm Dahl M, Sandell Jacobsen J, Hoyrup Christiansen D. Specific or general exercise strategy for subacromial impingement syndrome-does it matter? A systematic literature review and meta analysis. BMC Musculoskelet Disord. 2017;18(1):158.
508. Hawk C, Minkalis AL, Khorsan R, Daniels CJ, Homack D, Gliedt JA, et al. Systematic Review of Nondrug, Nonsurgical Treatment of Shoulder Conditions. J Manipulative Physiol Ther. 2017;40(5):293-319.
509. Cook T, Minns Lowe C, Maybury M, Lewis JS. Are corticosteroid injections more beneficial than anaesthetic injections alone in the management of rotator cuff-related shoulder pain? A systematic review. Br J Sports Med. 2018;52(8):497-504.
510. Wang W, Shi M, Zhou C, Shi Z, Cai X, Lin T, et al. Effectiveness of corticosteroid injections in adhesive capsulitis of shoulder: A meta-analysis. Medicine (Baltimore). 2017;96(28):e7529.
511. Farfaras S, Sernert N, Rostgard Christensen L, Hallstrom EK, Kartus JT. Subacromial Decompression Yields a Better Clinical Outcome Than Therapy Alone: A Prospective Randomized Study of Patients With a Minimum 10-Year Follow-up. Am J Sports Med. 2018;46(6):1397-407.
512. Verstraelen FU, Fievez E, Janssen L, Morrenhof W. Surgery for calcifying tendinitis of the shoulder: A systematic review. World J Orthop. 2017;8(5):424-30.
513. Brealey S, Armstrong AL, Brooksbank A, Carr AJ, Charalambous CP, Cooper C, et al. United Kingdom Frozen Shoulder Trial (UK FROST), multi-centre, randomised, 12 month, parallel group, superiority study to compare the clinical and cost-effectiveness of Early Structured Physiotherapy versus manipulation under anaesthesia versus arthroscopic capsular release for patients referred to secondary care with a primary frozen shoulder: study protocol for a randomised controlled trial. Trials. 2017;18(1):614.

514. NHS. Evidence review 2017 [cited 2017 07/12/17]. Available from: (https://www.evidence.nhs.uk/Search?om=[%7B%22srn%22:[%22UK%20Database%20of%20Uncertainties%20about%20the%20Effects%20of%20Treatments%20-%20UK%20DUETS%22]%7D]&q=shoulder+impingement&sp=on). .
515. Rangan A, Upadhaya S, Regan S, Toye F, Rees JL. Research priorities for shoulder surgery: results of the 2015 James Lind Alliance patient and clinician priority setting partnership. BMJ Open. 2016;6(4):e010412.
516. Buchbinder R, Page MJ, Huang H, Verhagen AP, Beaton D, Kopkow C, et al. A Preliminary Core Domain Set for Clinical Trials of Shoulder Disorders: A Report from the OMERACT 2016 Shoulder Core Outcome Set Special Interest Group. J Rheumatol. 2017;44(12):1880-3.
517. Sconfienza LM, Albano D, Allen G, Bazzocchi A, Bignotti B, Chianca V, et al. Clinical indications for musculoskeletal ultrasound updated in 2017 by European Society of Musculoskeletal Radiology (ESSR) consensus. Eur Radiol. 2018.
518. Neogi T. Structural correlates of pain in osteoarthritis. Clin Exp Rheumatol. 2017;35 Suppl 107(5):75-8.
519. Zhang Y, Niu J, Felson DT, Choi HK, Nevitt M, Neogi T. Methodologic challenges in studying risk factors for progression of knee osteoarthritis. Arthritis Care Res (Hoboken). 2010;62(11):1527-32.
520. Hunter DJ, Guermazi A, Roemer F, Zhang Y, Neogi T. Structural correlates of pain in joints with osteoarthritis. Osteoarthritis Cartilage. 2013;21(9):1170-8.
521. Cole SR, Platt RW, Schisterman EF, Chu H, Westreich D, Richardson D, et al. Illustrating bias due to conditioning on a collider. Int J Epidemiol. 2010;39(2):417-20.
522. Osteoarthritis Initiative. [cited 2018 19/10/2018]. Available from: https://oai.epi-ucsf.org/datarelease/StudyOverview.asp.
523. Bowes MA, Vincent GR, Wolstenholme CB, Conaghan PG. A novel method for bone area measurement provides new insights into osteoarthritis and its progression. Ann Rheum Dis. 2015;74(3):519-25.
524. Collinger JL, Fullerton B, Impink BG, Koontz AM, Boninger ML. Validation of grayscale-based quantitative ultrasound in manual wheelchair users: relationship to established clinical measures of shoulder pathology. Am J Phys Med Rehabil. 2010;89(5):390-400.
525. Cole BF, Peters KS, Hackett L, Murrell GA. Ultrasound-Guided Versus Blind Subacromial Corticosteroid Injections for Subacromial Impingement Syndrome: A Randomized, Double-Blind Clinical Trial. Am J Sports Med. 2016;44(3):702-7.
526. Arendt-Nielsen L. Pain sensitisation in osteoarthritis. Clin Exp Rheumatol. 2017;35 Suppl 107(5):68-74.
527. Boettger MK, Weber K, Grossmann D, Gajda M, Bauer R, Bar KJ, et al. Spinal tumor necrosis factor alpha neutralization reduces peripheral inflammation and hyperalgesia and suppresses autonomic responses in experimental arthritis: a role for spinal tumor necrosis factor alpha during induction and maintenance of peripheral inflammation. Arthritis Rheum. 2010;62(5):1308-18.

528. Chang DS, Hsu E, Hottinger DG, Cohen SP. Anti-nerve growth factor in pain management: current evidence. J Pain Res. 2016;9:373-83.
529. Brady B, Veljanova I, Schabrun S, Chipchase L. Integrating culturally informed approaches into physiotherapy assessment and treatment of chronic pain: a pilot randomised controlled trial. BMJ Open. 2018;8(7).
530. Escape-Pain. 2018 [cited 2018 31/10/18]. Available from: http://escape-pain.org/about-escape/evidence.
531. Skou ST, Roos EM. Good Life with osteoArthritis in Denmark (GLA:D): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. BMC Musculoskelet Disord. 2017;18(1):72.
532. Laslett L, Otahal P, Hensor E, Kingsbury S, Conaghan P. Understanding the biomechanical spread of joint pain: knee pain predicts subsequent shoulder pain and this is mediated by leg weakness. Data from the osteoarthritis initiative. Osteoarthritis Cartilage. 2015;23:A353.
533. Chou R, Fu R, Carrino JA, Deyo RA. Imaging strategies for low-back pain: systematic review and meta-analysis. Lancet. 2009;373(9662):463-72.
534. Maitino AJ, Levin DC, Parker L, Rao VM, Sunshine JH. Nationwide trends in rates of utilization of noninvasive diagnostic imaging among the Medicare population between 1993 and 1999. Radiology. 2003;227(1):113-7.
535. Jarvik JG, Deyo RA. Diagnostic evaluation of low back pain with emphasis on imaging. Ann Intern Med. 2002;137(7):586-97.
536. Hill JC, Dunn KM, Lewis M, Mullis R, Main CJ, Foster NE, et al. A primary care back pain screening tool: identifying patient subgroups for initial treatment. Arthritis Rheum. 2008;59(5):632-41.
537. Foster NE, Mullis R, Hill JC, Lewis M, Whitehurst DG, Doyle C, et al. Effect of stratified care for low back pain in family practice (IMPaCT Back): a prospective population-based sequential comparison. Ann Fam Med. 2014;12(2):102-11.