Epidemiology of Chronic Shoulder Pain in the United Kingdom

Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

July, 2025

By Nouf Al-Otaibi, PT MSc
20109909

Supervisors: Dr. Michelle Hall (Principal supervisor), Prof. Weiya Zhang, Prof. Michael Doherty, Dr. Subhashisa Swain, Dr. Yana Vinogradova

School of Medicine, Academic Rheumatology
University of Nottingham

Declaration

I hereby declare that this thesis is the result of original research. It has been conducted by myself with the assistance of my supervisors. This work has not been submitted or accepted elsewhere for any degree, diploma or other qualification. All authors and works to which reference has been made are fully acknowledged.

Table of contents

Abstract

Background

Chronic shoulder pain (CSP) is a common musculoskeletal condition that can significantly affect a person's ability to work, sleep, and perform daily activities. It affects between 5% and 47% of the adult population annually worldwide. In the United Kingdom (UK), about 2.4% of adult people aged between 18 and 60 years old consulted their general practitioners (GPs) for CSP in 2006. However, whether the occurrence of CSP has changed in the past 20 years in the UK, whether it varies between geographical regions, and its associated comorbidities and consequences remain largely unknown.

Objectives

This research aimed to answer five objectives
[1] to systematically review the existing literature on the prevalence and incidence of CSP and its related risk factors, and associated comorbidities.
[2] to determine the current prevalence and incidence of CSP in the UK (2019).
[3] to determine the trends of prevalence and incidence of CSP in the UK over the past twenty years (2000 - 2020).
[4] to examine potential risk factors, and comorbidities that precede the diagnosis of CSP.
[5] to explore the outcomes of CSP including associated comorbidities, all-cause mortality, consultations and hospitalisations.

Methods

[1] a systematic review and meta-analysis were performed to summarise the literature on the prevalence and incidence of CSP and the associated risk factors in people aged 40 years and over.

The nationally representative UK primary care database, the Clinical Practice Research Datalink (CPRD) Aurum was used to determine:
[2&3] the cross-sectional prevalence, incidence, and trend of CSP in the UK
[4] risk factors and comorbidities occurring before the diagnosis of CSP using a case-control study design
[5] outcomes occurring after CSP diagnosis using a cohort study design.

Results

A total of 29 studies from 19 countries were identified in the systematic review. Of which, 20 had a high quality, and nine had moderate quality. The pooled prevalence of CSP in the included studies was 29% and higher in specific populations such as people with physically demanding occupations (36% prevalence), and people with diabetes (35% prevalence). The incidence of CSP was higher in females and in those aged over 40 years. In addition to age and sex, CSP was associated with smoking, lower educational level, manual labour, have been reported to associate with CSP. Also, CSP was found to be associated with a number of comorbidities, including arthritis, diabetes, angina, and other sites of musculoskeletal (MSK) pain.

In the UK, the prevalence of CSP in people aged 18 and above in 2019 was found to be 1.9 % and the incidence was 1.2 per 1000 person-years. The prevalence and incidence were more common in females than males and increased with age, especially after age 40 years. The prevalence was found to increase during the study period from 0.42% in 2000 to 1.83 in 2020, whereas the incidence increased significantly from 0.88 in 2000 to 2.00 per 1000-person year in 2011, then decreased afterwards. The significant decline of the incidence in 2020 resulted from the reduced consultations during the COVID-19 pandemic and lockdown. Smoking, low socioeconomic status, Asian and mixed ethnicity, and a high body mass index increased the risk of CSP, while current alcohol consumers had a significantly lower risk of having CSP.

People with CSP were more likely to have comorbidities prior to and post the diagnosis of CSP compared to the control group. Retrospectively, people with other MSK conditions (aOR 1.71, 95% CI 1.68 to1.75), osteoarthritis (OA) (aOR 1.76, 95% CI 1.70 to1.82), diabetes (aOR 1.48, 95% CI 1.43 to1.53), fibromyalgia (aOR 1.40, 95% CI 1.32 to 1.48), and insomnia (aOR 1.63, 95% CI 1.58 to1.69) were more likely to have CSP.

Prospectively, people with CSP were more likely to develop other long-term conditions compared to the control group. Of the twenty-two comorbidities studied, significant associations were seen with eighteen conditions. The strongest associations found were with sarcopenia (HR 1.74, 95% CI 1.11 to 2.71), fibromyalgia (HR 1.71, 95% CI 1.62,1.81), osteoarthritis (HR 1.60, 95% CI 1.55 to 1.64), other MSK conditions (HR 1.61, 95% CI 1.58 to1.64), and insomnia (HR 1.55, 95% CI 1.48 to1.63). Following their diagnosis, people with CSP had three times higher risk of GP consultations, 44% higher risk of hospitalisations, and 6% higher risk of all-cause mortality than those without CSP.

Conclusion

Chronic shoulder pain (CSP) affects around 2% of adults in the UK. The prevalence of this condition in primary care increased gradually in the past 20 years whereas the incidence has increased until 2011 then decreased afterwards (reasons to be investigated). The findings demonstrated that age, sex, smoking, socioeconomic deprivation, Asian or mixed ethnicity and higher BMI were associated with an increased risk of CSP. Alcohol consumption was associated with a decreased risk of CSP. People with CSP had a higher burden of comorbidities, higher risk of mortality, and increased healthcare utilisations. This study has provided essential background information/evidence of CSP in the UK for policymakers to allocate resources, healthcare providers to optimally manage CSP, and researchers to undertake further research such as the causality between shoulder pain and individual comorbidities.

List of publications

Published conference abstracts

Alotaibi N., Swain S., Vinogradova Y., Shuaib M., Doherty M. and Zhang W., Hall M. Epidemiology of chronic shoulder pain in people aged 40 or older- a systematic review and meta-analysis of observational studies. British Journal of Pain 2023; 17:1-36

Alotaibi N., Swain S., Vinogradova Y., Doherty M. and Zhang W., Hall M. POS1458-HPR. Trends of prevalence and incidence of chronic shoulder pain in the United Kingdom: findings from the Clinical Practice Research Datalink. Annals of the Rheumatic Diseases 2024; 83:1186.

Published conference abstract are presented in Appendix 1 (pages 316-320)

Presentations at National/International Conferences:

- The 56th Annual Scientific Meeting of the British Pain Society (Glasgow, May 2023). Epidemiology of chronic shoulder pain in people aged 40 or older – a systematic review and meta-analysis of observational studies. (Oral and poster presentation)
- UK-RIME Showcase (Manchester, June 2023). Epidemiology of chronic shoulder pain in the United Kingdom: a population-based study of UK primary care data using clinical practice research datalink (CPRD). (Oral presentation)

- The European Alliance of Associations for Rheumatology (EULAR) (Vienna, June 2024). Prevalence and incidence of chronic shoulder pain in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD) (poster presentation).

- UK-RIME Showcase (Keele, September 2024). Risk factors associated with chronic shoulder pain: a nested case-control study in the UK primary care setting using clinical practice research datalink (CPRD) (oral presentation).

Other meetings:

- Presentation of the "The frequency of chronic shoulder pain in the UK" in Versus Arthritis Pain Centre Internal Scientific Meeting (March 2023) and the annual School of Medicine Forum (June 2023).

Non-PhD collaborations:

- I have been involved in the Monirah Shuaib (PhD student) systematic review and meta-analysis ("Long-term conditions and related risk factors in professional footballers compared to the general population: a systematic review and meta-analysis of observational studies") as a second reviewer to extract and validate data and to assess the quality of all included studies.

Acknowledgments

I would firstly like to thank my supervisors Dr. Michelle Hall, Professor Weiya
Zhang, Professor Michael Doherty, Dr. Subhashisa Swain, and Dr.Yana Vinogradova for their generous assistance and encouragement throughout this project. The PhD journey could not have been accomplished without my supervisor's guidance, feedback and support, which made my experience at the University of Nottingham wonderful, unforgettable and inspiring. Their constructive feedback and advice enhanced my learning skills. I consider myself very lucky to develop my research skills under their supervision.

Further, I would like to thank all the amazing researchers and colleagues with whom I had the pleasure of working during this time. My sincere gratitude goes to Dr. Barbara Iyen for her constant, well-considered feedback on my work and for validating the codes used in this project. My thanks also to Professor Tony Avery, for his support in validating the comorbidity codes, and to Dr. Andrew Prayle, for technical assistance with big data. For all the staff of Academic Rheumatology in the University of Nottingham, I would like to say a big thank you.

I would also like to thank the government of the state of Kuwait scholarship program for financially supporting my PhD, and the University of Nottingham as the host institution for this project. Finally, my deepest gratitude goes to my mom, and my sister Maha, who have supported me physically and mentally every time it was needed. Your belief in me has

been a constant source of strength, and without your support and continuous guidance, this work would not have been accomplished. Thank you for always being there and I hope I made you all proud.. I would like to extend my heartfelt gratitude to my best friend, Monirah Shuaib, for her unwavering support, encouragement, and understanding throughout my PhD journey. Your belief in me, helped me through the most challenging times. Thank you for always being there. I would like also to thank my friend Badryah for being there for me and for her kind support throughout this journey.

List of Tables

List of Figures

List of abbreviations

AAPC	Average annual percentage change
AC	Acromioclavicular
BDRM	Basic Dementia Risk Model
BESS	British Elbow and Shoulder Society
BMI	Body mass index
BF	Body fat
CSP	Chronic shoulder pain
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CI	Confidence interval
CLBP	Chronic low back pain
CWP	Chronic widespread pain
CVD	Cardio-vascular disease
DLB	Dementia with Lewy bodies
EMIS	Egton Medical information system
EHRs	Electronic Health Records
FCP	First Contact Practitioner
FDR	False discovery rate
GP	General practice
GPs	General practitioners
GPRD	General Practice Research Datalink
GH	Glenohumeral
GAGs	glycosaminoglycans
HES	Hospital Episode Statistic
HR	Hazard ratio
ISAC	Independent Scientific Advisory Committee
IMD	Index of multiple deprivation
CES-D	Centre for Epidemiologic Studies-Depression
DASH	Disability of arm, shoulder, and hand questionnaire
QOF	Quality and Outcomes Framework
SD	standard deviation
SPHC	Stockholm Public Health Cohort
SE	Standard error
SNOMED CT	Systematized Nomenclature of Medicine Clinical Terms
SPADI	Shoulder pain and disability index
SC	Sternoclavicular
ST	Scapulothoracic
SOC	Standard Occupational Classification
THIN	The Health Improvement Network

MSK	Musculoskeletal
NSAIDS	Non-steroidal anti-inflammatory drugs
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
OA	Osteoarthritis
ONS	Office for National Statistics
UK	United Kingdom
UKUFF	United Kingdom rotator cuff
USA	United States of America
VAS	Visual analogue scale
VIF	Variance inflation factor

Chapter 1. Introduction

This chapter provides an introduction to chronic shoulder pain (CSP) regarding its background, definition, shoulder joint structures and biomechanics, epidemiology, associated risk factors and comorbidities. Some shoulder pathologies and management options for these pathologies are outlined. The chapter contains a literature review of previous studies relevant to the scope of this thesis. The chapter also lays out the rationale for the studies undertaken for this PhD.

1.1 Background

Chronic musculoskeletal (MSK) pain is defined as pain in bones, muscles, joints, tendons, or ligaments lasting more than three months (Cimmino et al., 2011, Coppieters et al., 2016). It affects many people worldwide and is considered to be one of the most common types of chronic pain. Common chronic MSK pain conditions include, osteoarthritis (OA), spine - related neck and low back pain, fibromyalgia/chronic widespread pain (CWP), and chronic shoulder pain (CSP) (Bergman, 2007, McBeth and Jones, 2007). In 2015, a United Kingdom (UK) Biobank study examined 503,325 participants aged between 40-69 and found a prevalence of chronic pain of 43%, the most common site-specific MSK pain being back (26.2%) followed by shoulder/neck (23.3%) and knee pain (20%) (Macfarlane et al., 2015). Chronic MSK pain can negatively affect an individual's physical, psychological, and social well-being status, and reduce their quality of life (Woolf and Pfleger, 2003). Additionally, it results in a major burden on

healthcare systems, resulting in substantial financial costs (Woolf and Pfleger, 2003).

CSP is one of the most common MSK conditions and affects between 5% to 47% of the adult population worldwide (Picavet and Schouten, 2003, Woolf, 2012, Noten et al., 2017, Djade et al., 2020). Shoulder pain can cause movement restrictions, sleeping problems and working difficulties (Noten et al., 2017, Djade et al., 2020) and can lead to functional limitations in daily activities such as driving, dressing, carrying and eating (Pribicevic, 2012, Greenberg, 2014, Noten et al., 2017, Djade et al., 2020). The overall prevalence of shoulder pain in the UK population aged between 18 and 60 was approximately 1.47% in 2006 (Linsell et al., 2006). The prevalence of shoulder pain among farmers on Jeju Island, South Korea was 17% (Lee et al., 2024). In Qatar, the prevalence of shoulder pain in the general population aged 15 years and above was 15.9% (Sarakbi et al., 2020). Variations in prevalence reported between studies might be due to the different definitions of shoulder pain and the different methodologies used in these studies (Picavet and Schouten, 2003, Woolf, 2012, Noten et al., 2017, Djade et al., 2020). For example, some studies asked patients whether they experienced shoulder pain or not, while others introduced specific questions, charts and diagrams to determine the exact site and characteristics of the pain (Pribicevic, 2012).

Most CSP conditions are managed in primary care (Mitchell et al., 2005, Artus et al., 2017). A national cross-sectional survey of 5000 UK GPs reported a wide range of management options for CSP (Artus et al., 2017). The survey included general questions about shoulder pain

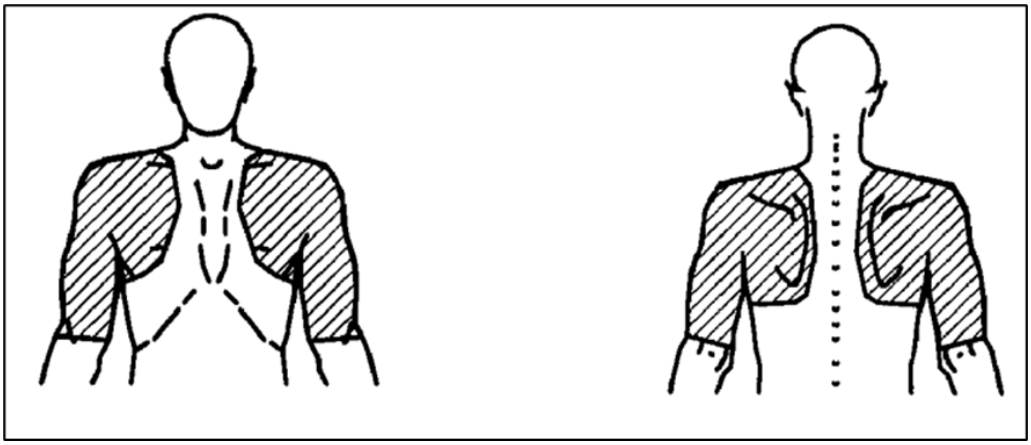
management options, and specific questions on the two most common shoulder pain conditions reported in primary care, specifically adhesive capsulitis and rotator (RC) tendinopathy. Of 2500 postal questionnaires, 542 were completed. Of 2471 online survey emails,182 online questionnaires were completed. Physiotherapy was the most common treatment option (71% adhesive capsulitis and 78% RC tendinopathy), followed by non-steroidal anti-inflammatory medications (NSAIDs) (74% adhesive capsulitis and 58% RC tendinopathy), and corticosteroid shoulder injection (adhesive capsulitis 49%, RC tendinopathy 48%). Most of the GPs selected more than one treatment option, the most common treatment combination being NSAIDs, and physiotherapy (45%) followed by corticosteroid injections and physiotherapy (36%) (Artus et al., 2017). Generally, surgery is recommended in the management of some conditions such as dislocation, end stage glenohumeral OA, and traumatic acute RC tear (Mitchell et al., 2005, Chaudhury et al., 2010). The National Institute for Health and Care Excellence (NICE) guidelines recommend several treatment options for shoulder pain conditions. NICE recommendations combine research evidence with expert opinion and also involve patients/public opinion of what constitutes good practice. Initial management of people with shoulder pain should include physiotherapy, prescription of analgesia, and activity modifications. If conservative management fails, corticosteroid injection and surgery can be considered (NICE, 2021).

1.2 Definition of shoulder pain

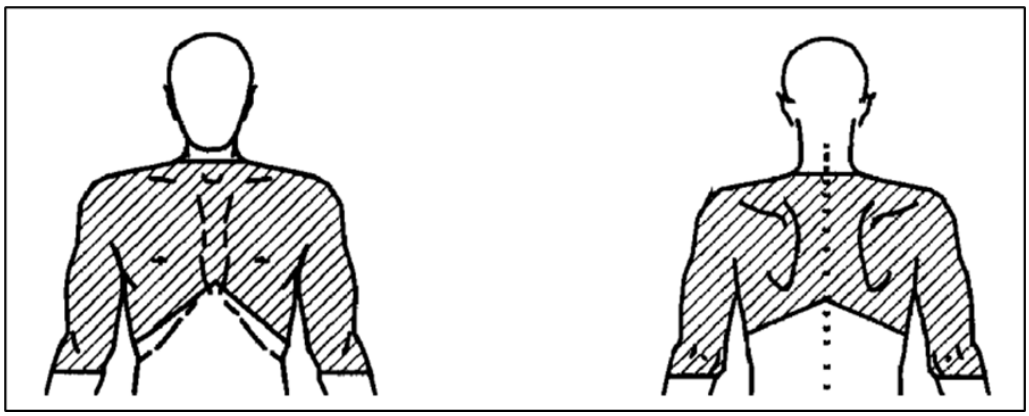
Shoulder pain is defined as pain which arises in or around the shoulder from its joints or the surrounding soft tissues (Murphy and Carr, 2010). Chronic shoulder pain refers to persistent shoulder pain that presents for more than 6 months (Burbank et al., 2008, Herin et al., 2012). There is no consensus in the literature regarding the definition of shoulder pain (Pope et al., 1997, Luime et al., 2004, Pribicevic, 2012). This may reflect the complex structure of the shoulder joint and the biomechanical association with other joints including the spine (Pribicevic, 2012). The majority of studies have asked the people directly whether they have shoulder pain or not, and this relies on the person's perception of the anatomical origins of their pain (Pope et al., 1997, Luime et al., 2004, Pribicevic, 2012). Pain can arise from structures around the shoulder joint and can be felt in a wider area such as the upper trunk and neck which might confuse the person's perception concerning the origin of their shoulder pain (Pribicevic, 2012). Such aspects might cause differences in reporting shoulder pain prevalence. Imprecise perceptions of anatomical regions can lead to inaccurate reporting when asked directly about symptoms (Silman and Hochberg, 1993). Pope et al. (1997) studied the influence of case definition using a cross-sectional survey. Four definitions of shoulder pain were identified from the answers to the questionnaire (Pope et al., 1997). The first definition was based on a direct question " During the past month have you experienced pain in your shoulder lasting more than 24 hours" (Pope et al., 1997). The second and third definition were based on line drawings on body manikin which the participants were asked to shade

any pain or aches experienced in the month before the questionnaire (Pope et al., 1997). Two definitions were derived from the areas shaded by participants : (1) pain in a restricted area in or around the shoulder complex (Figure 1.1), (2) pain felt in a broad area including the sternoclavicular region, anterior chest, and between the scapulae (upper trunk) (Figure 1.1).

(1) Pain in a restricted area in or around the shoulder complex



(2) pain felt in a broad area including the upper trunk region



Reproduced with permission from Pope et al.1997

Figure 1.1 Case definition of shoulder pain in the cross-sectional survey.

The fourth definition was based on a direct question about symptoms in a pre-shaded area including the upper trunk and neck on a separate body manikin (Pope et al., 1997) (Figure 1.2).

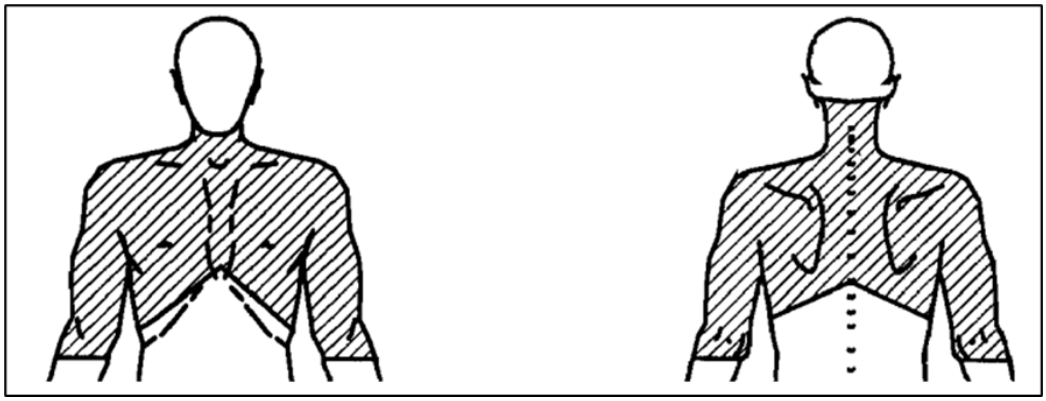


Figure 1.2 Case definition of shoulder pain in the cross-sectional survey.

They found that the prevalence estimates increased as the definition was broadened. The one-month prevalence of shoulder pain ranged from 31% to 48% across the four definitions (Pope et al., 1997). The direct question about shoulder symptoms yielded the lowest prevalence estimate among respondents (31%). The broadest definition, focussing on symptoms in a specific area on a manikin (upper trunk and neck), showed the highest prevalence (84%) (Pope et al., 1997). Limiting the definition to current symptoms (pain on interview day) and associated disability narrowed the prevalence estimate to 20% (Pope et al., 1997). An overlap was observed across the four definitions. 27% of all respondents answered positively to all four of the case definitions (Pope et al., 1997). Only seven respondents who answered positively when asked directly if they had symptoms in the shoulder (definition 1) did not mark symptoms on the body manikin drawing in the ‘restricted’ area (definition 2) (Figure 1.1) (Pope et al.,

1997). In contrast, 30% of those who answered negatively to the direct question either indicated symptoms on the pain drawing in the upper trunk area (definition 3) or positively to the question about symptoms in the upper or neck region (definition 4) (Figure 1.2) (Pope et al., 1997). Out of those who responded negatively to the direct question, only 9% reported symptoms in the 'restricted' area on the pain drawing (definition 2), while 18% reported symptoms in the upper trunk area (definition 3) and 27% in the upper trunk and neck area (definition 4). However, a number of methodological aspects might have influenced the prevalence estimate in this study. Firstly, the fact that the questions relating to all four definitions were included as part of the same questionnaire might have influenced the participants' responses and they expected that the various questions all related to the same definition. Secondly, the questions were asked in the same order for each definition, therefore, positive responses to initial questions might lead to positive answers to subsequent questions (Pope et al., 1997).

Additionally, Linsell et al. (2006) reported that often general practitioners (GPs) did not record a specific diagnosis for patients presenting with a shoulder complaint in primary care but instead described the symptoms in general terms such as shoulder pain and shoulder syndrome. Linsell et al. (2006) found that of 426 codes included in their study, GPs predominantly reported only ten of these. The most frequent diagnostic codes recorded were shoulder syndrome, sprained shoulder, RC syndrome, shoulder joint pain, and sprain shoulder/upper arm. This finding is expected due to several reasons. First, as mentioned in the previous section, the shoulder

articulation has a complex structure and there is no consensus about the diagnostic criteria for shoulder problems, which makes specific diagnosis difficult to reach (Pope et al., 1997, Luime et al., 2004, Pribicevic, 2012). A second reason is that GPs' often lack confidence and expertise in diagnosing MSK conditions, which in turn relates to their training and clinical interests (Speed and Crisp, 2005, Linsell et al., 2006). Speed and Crisp (2005) reported that 63.4% of GPs referrals to orthopaedics services were requested with no provisional diagnosis from the GP. Therefore, the diagnostic criteria for CSP remains a challenge for general practitioners and physicians and there is major discrepancy in the literature regarding diagnostic criteria.

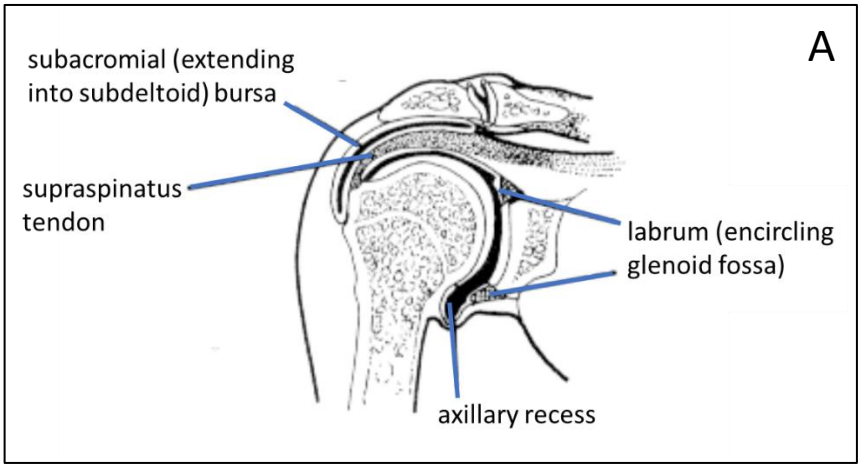
1.3 Shoulder joint structures and biomechanics

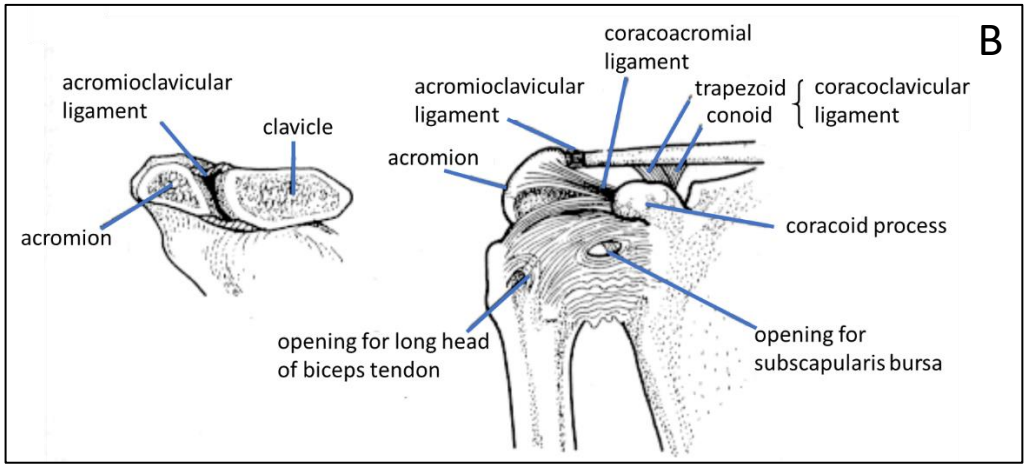
A comprehensive knowledge of the anatomy and biomechanics of the shoulder joint is crucial to diagnosing and managing shoulder disorders. The following section provides an overview of the structure of the shoulder joint and describes the role of biomechanics in people with shoulder pain.

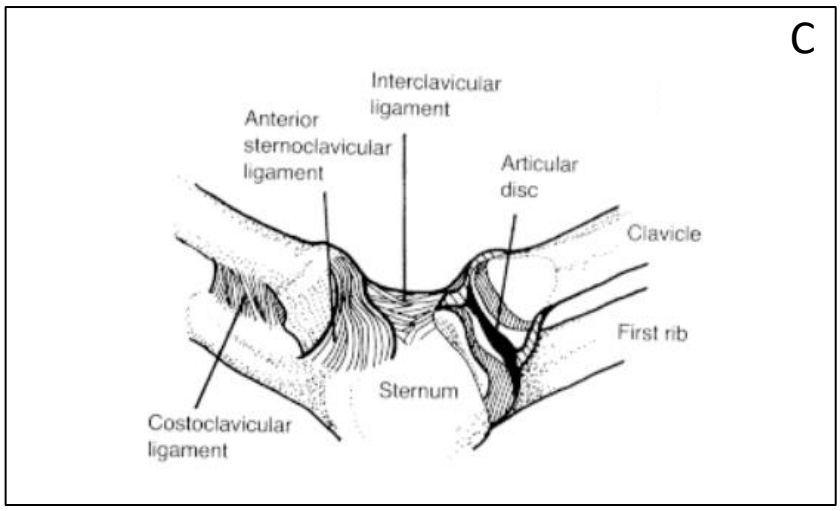
1.3.1 Shoulder anatomy

The shoulder glenohumeral (GH) synovial joint is the most mobile joint in the body and connects the upper limb to the trunk (Brox, 2003, Pandya et al., 2018). It is described as a "ball and socket" type joint and is formed by the articulation of the head of the humerus with the glenoid cavity of the scapula. The glenoid cavity is a shallow socket, which is surrounded by a fibrocartilaginous labrum (Figure 1.3a). The main functions of the labrum

are to increase the area and depth of the glenoid fossa by 50% to help stabilise the shoulder joint (Brox, 2003, Bakhsh and Nicandri, 2018). In addition to the GH joint, the shoulder complex also includes the two smaller joints, acromioclavicular (AC) (Figure 1.3b) and sternoclavicular (SC) (Figure 1.3c) synovial joints at the lateral and medial end of the clavicle, respectively, and the broad scapulothoracic (ST) articulation (Pandya et al., 2018, Bakhsh and Nicandri, 2018).





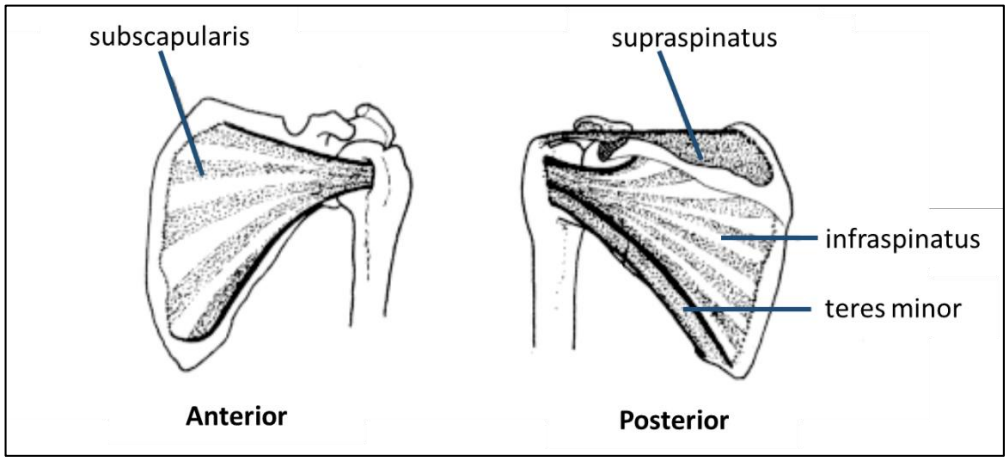


Reproduced with permission from Clinical Examination in Rheumatology, Doherty and Doherty, Wolfe 1992".

Figure 1.3 Anatomy of the shoulder girdle
(A) the glenohumeral joint, (B) the acromioclavicular joint, ligaments and glenohumeral capsule, and (C) the sternoclavicular joint.

The soft tissue structures surrounding the shoulder joint play a substantial role in maintaining glenohumeral stability. These structures are described as static (fibrous) and dynamic (muscles) (Pandya et al., 2018). Static stabilisers include the glenohumeral ligaments and glenoid labrum, while dynamic stabilisers include the RC muscles (Figure 1.4), peri-scapular muscles and the long head of biceps (Menge et al., 2014, Pandya et al., 2018, Bakhsh and Nicandri, 2018). The RC muscles play a major role in stabilising the humeral head within the glenoid fossa through a compression force of the RC on the humeral head (Lewis, 2011). The deltoid muscle with the supraspinatus act as a force in the coronal plane, compressing the humeral head to the glenoid in abduction. On the other hand, subscapularis and infraspinatus provide a compressive joint reaction force in the axial plane (Parsons Iv et al., 2002). When they all contract together they bring the humeral head upwards and inwards (i.e.,

deeper into the glenoid labrum) – thus stabilising the head more securely (Bakhsh and Nicandri, 2018, Pandya et al., 2018).



Reproduced with permission from Clinical Examination in Rheumatology, Doherty and Doherty, Wolfe 1992".

Figure 1.4 Shoulder rotator cuff muscles.

1.3.2 Biomechanics

Kinetics and kinematics

The biomechanics of glenohumeral joint is complex compared to the hip and knee joint. The glenohumeral joint is the most mobile joint in the body and it has six mechanical degrees of movement, allowing the shoulder to move for greater range of motion (Akhtar et al., 2021). Shoulder movements represent coordinated motion of all the RC components (Lugo et al., 2008, Akhtar et al., 2021). For this movement to be completed, the humerus will rotate around the scapula at the glenohumeral joint (GH), the scapula rotates around the clavicle at the acromioclavicular (AC) joint, and the clavicle rotates around the sternum at the sternoclavicular joint (Akhtar et al., 2021). For the shoulder elevation to reach 180 degrees, all these

components need to move. During normal movement, up to 120 degrees of glenohumeral elevation is allowed within the glenoid fossa (Scibek and Carcia, 2012). After this point, the acromion and humerus neck impinge on each other, preventing the motion. For further humeral elevation, the scapula must rotate in a superior direction (Lugo et al., 2008). This rotation allows the humerus to elevate through an additional 60 degrees. This coordinated movement between humerus and scapula has been known as the scapulohumeral rhythm (Scibek and Carcia, 2012). The estimated ratio between the glenohumeral and scapulothoracic joint motion is approximately 2:1 (Inman et al., 1944). The scapula is the site of insertion for seventeen muscles. These muscles have a major role in the scapulothoracic movement, and include the trapezius, the serratus anterior, the levator scapulae, the pectoralis minor, the rhomboids, and the subclavius muscle (Lugo et al., 2008, Scibek and Carcia, 2012). The trapezius helps to rotate and elevate the scapula in synchrony with the glenohumeral movement, and the serratus anterior helps to maintain the medial angle against the chest wall (Lugo et al., 2008, Scibek and Carcia, 2012). Disruption of these muscles' activity can lead to scapular winging (Lugo et al., 2008).

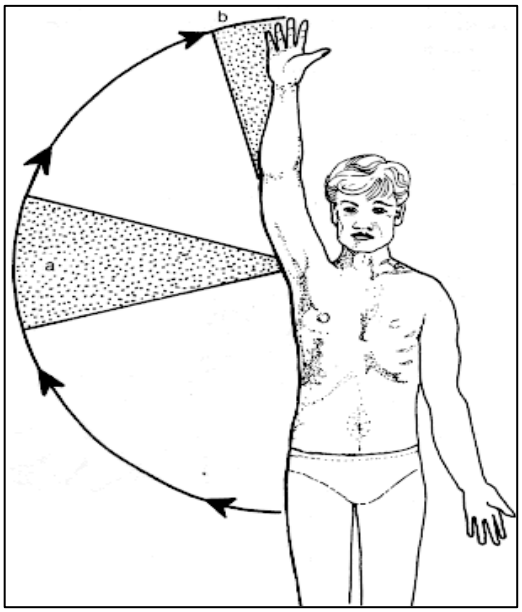
Shoulder Stability

As illustrated in the previous section (shoulder anatomy), the biomechanics of shoulder joint rely on the interaction of both dynamic and static structures (Lugo et al., 2008, Bakhsh and Nicandri, 2018). The RC muscles act to stabilise the humeral head in the neutral position (Akhtar et

al., 2021). They produce a force that compresses the glenohumeral joint, by keeping the humeral head further inside the glenoid concavity. Force couples occur when two opposing muscle groups produce a moment around a fulcrum (Huegel et al., 2015, Akhtar et al., 2021). The RC muscles produce a force couple around the joint, with coordinated activation and inactivation of agonist and antagonist muscles (Lugo et al., 2008, Akhtar et al., 2021). The deltoid and supraspinatus act as a force couple in the frontal plane, thus compressing the humeral head to the glenoid in abduction (Lugo et al., 2008, Akhtar et al., 2021). Whereas subscapularis and infraspinatus provide a compressive force in the horizontal plane (Parsons Iv et al., 2002, Lugo et al., 2008). Therefore, disturbance in the RC muscles' coupled activity can impact the force couples produced and thereby contribute to instability (Lugo et al., 2008). Rupture of RC muscles can cause anterior dislocation of the humeral head on an intact anterior soft tissue surface (Lugo et al., 2008).

The bony stability of the shoulder is insufficient, because the glenoid fossa is only 25% the size of the articular surface of the humeral head (Akhtar et al., 2021). Therefore, the shoulder stability is largely supported by the glenoid labrum, the joint capsule and glenohumeral ligaments (Lugo et al., 2008). The labral tissue adds 50% to the glenoid' depth, in addition to the RC 's compressive force, which provide a concave compression on the humeral head into the glenoid (Lugo et al., 2008, Akhtar et al., 2021). The scapulothoracic joint also provide stability to the shoulder joint (Brox, 2003, Lugo et al., 2008, Scibek and Carcia, 2012). It allows for an additional range of motion beyond the initial 120 degrees provided by the

glenohumeral joint (Lugo et al., 2008, Scibek and Carcia, 2012). The scapular motion contributes to the shoulder abduction from 80 to 140 degrees (Brox, 2003). This might explain the painful arc in patients with subacromial impingement syndrome and suggests that the subacromial space might be compromised at this range of motion (Figure 1.5) (Brox, 2003).



Reproduced with permission from Clinical Examination in Rheumatology, Doherty and Doherty, Wolfe 1992".

Figure 1.5 Painful arcs:(a) painful middle arc (supraspinatus/subacromial bursitis), and (b) painful superior arc (acromioclavicular joint).

Disruption of scapulohumeral rhythm

Disruption of the normal scapulohumeral rhythm can cause glenohumeral joint pathology (Lugo et al., 2008). In people with instability, the ratio between the glenohumeral and scapulothoracic joint motion is increased, while in those with RC tears and impingement it is decreased (Inman et al., 1944, Halder et al., 2000). A study from the Kerlan-Jobe Clinic showed

that subscapularis weakness and/or serratus anterior muscles led to symptoms of RC tendinitis in young baseball players (Glousman et al., 1988). Therefore, in the rehabilitation for people with subacromial impingement syndrome and RC tendinitis it is important to focus mainly on scapulothoracic stabilisation by strengthening the scapular muscles (Lugo et al., 2008, Brox, 2003).

1.4 Pain mechanisms and pathology of the shoulder

This section describes pain mechanisms in people with CSP and provides an overview of the different pathologies of the shoulder joint.

1.4.1 Pain mechanisms

It is important to understand why some individuals with MSK pain develop a chronic pain syndrome. Pain may arise from different tissues including tendons, bursae, ligaments, and muscles. The threshold for experiencing pain depends on several factors such as sex, genetic factors, and psychological factors (Sanchis et al., 2015, Noten et al., 2017). Shoulder movement may be affected by pain, fear of pain or structural abnormality. Fear of pain means that expectation or fear of pain affects the patient's behaviour and the neuromuscular function (Brox, 2003). It has also been found that depression and anxiety mediate central sensitisation and predict prognosis in people with MSK pain (Orenius et al., 2013). Specifically, people with shoulder pain appear to have higher rates of anxiety and depression compared to healthy controls (Cho et al., 2013). In recent years, the presence of central sensitisation has been demonstrated

in some people with shoulder pain. Central sensitisation is defined as the development of neural signalling within the central nervous system that provokes pain hypersensitivity (Sanchis et al., 2015, Noten et al., 2017). Central sensitisation is a broad term that includes sensory processing distortion in the central nervous system (Staud et al., 2007), dysfunction of descending pain inhibitory mechanisms (Meeus et al., 2008), and increased pain facilitatory mechanisms (Meeus and Nijs, 2007).

Recent systematic literature reviews have highlighted that central sensitisation plays a major role in many chronic pain conditions such as OA (Lluch et al., 2014), chronic fatigue syndrome (Nijs et al., 2012), and rheumatoid arthritis (Meeus et al., 2012). Furthermore, some studies have demonstrated the role of the central nervous system in pain experienced by people with chronic RC tendinopathy (Littlewood et al., 2013), and adhesive capsulitis (Struyf and Meeus, 2014). A systematic review by Sanchis et al. (2015) was conducted to evaluate the current evidence on the presence of central sensitisation in people with unilateral shoulder pain of different causes including RC tendinopathy and chronic subacromial impingement syndrome. A total of 10 studies were included, 7 were categorised as case-control and the other three were cross-sectional. Of the 10 studies, eight supported the presence of a key role of central sensitisation in people with unilateral shoulder pain and RC tendinopathy. This was confirmed through a variety of different objective (e.g., widespread hyperalgesia, suprathreshold heat pain response) and subjective (e.g., enlarged radiation of pain down the arm) parameters. However, two studies in this review did not find any evidence regarding

the presence of central sensitisation in people with unilateral shoulder pain or RC tendinopathy. Although the results suggested that peripheral mechanisms are involved and hypersensitivity of the central nervous system might play a substantial role in a subgroup within the shoulder pain population, this has been poorly investigated in the literature and needs further investigations (Sanchis et al., 2015).

1.4.2 Shoulder pathologies

CSP can result from one or more of the following pathologies: adhesive capsulitis, glenohumeral OA, subacromial pain, RC tendinopathy, RC tears, and bursitis. This section explains some shoulder pathologies and their symptoms, and some management options.

1.4.2.1 Adhesive capsulitis (frozen shoulder)

Adhesive capsulitis, also known as “frozen shoulder”, is a common condition that is characterised by a painful and progressive loss of active and passive range of motion (leading to fixed internal rotation and adduction) resulting from contracture and progressive fibrosis of the joint capsule (Neviaser and Hannafin, 2010, Ramirez, 2019). The pathophysiology of adhesive capsulitis in not completely clear and is regarded generally as an idiopathic condition (Ryan et al., 2016, Ramirez, 2019, Redler and Dennis, 2019). Several studies have shown that it appears to start as an inflammation with associated synovitis that progresses to fibrosis formation and contracture of the shoulder capsule (Brox, 2003, Ramirez, 2019, Redler and Dennis, 2019).

The prevalence of adhesive capsulitis in the United States (USA) in 2019 was between 2% to 5% in the general population aged between 40 and 60 years old (Ramirez, 2019). In the UK, a large primary care study found that adhesive capsulitis affected 10% of females and 8% of males aged between 35 and 66 years (Walker-Bone et al., 2004). Most people with adhesive capsulitis are females, often with diabetes and aged between 40 and 60 years (Brox, 2003, D'Orsi et al., 2012, Zreik et al., 2016, Ramirez, 2019). A meta-analysis conducted by Zreik et al. (2016) found that people with diabetes were five times more likely to have adhesive capsulitis compared to those without diabetes. The prevalence of adhesive capsulitis in the population with diabetes was 13.4%, and the prevalence of diabetes in people with adhesive capsulitis was estimated to be 30% (Zreik et al., 2016).

The clinical course of adhesive capsulitis consists of 4 stages, specifically: stage 1, the pre-adhesive stage; stage 2, acute adhesive capsulitis; stage 3, the maturation phase and stage 4, the chronic stage (Neviaser and Hannafin, 2010, Ramirez, 2019). The pre-adhesive phase is characterised by an inflammatory reaction without adhesion. At this phase, people typically report pain that is worse at night but without limitation in the range of motion. Phase 2 is the acute phase during the adhesive capsulitis clinical course, which is marked by formation of adhesions and maximum pain that might radiate to the arm and hand. The most common symptoms at this time are pain and slight loss of range of motion. Phase 3, the maturation phase, involves more fibrosis formation and less synovitis. Pain might be less severe in this phase, but the range of motion

is significantly limited (Neviaser and Hannafin, 2010). In phase 4, also known as the chronic stage and sometimes termed the “thawing” stage (Neviaser and Neviaser, 1987), the adhesions will be fully mature, the movement is severely reduced, and shoulder pain is often only mild or absent (Neviaser and Hannafin, 2010, Ramirez, 2019). Although the amount of improvement seen in this phase is controversial, a gradual improvement in motion can occur in this stage. With time the movement of the shoulder can slowly improve back to or close to the person’s normal range (Neviaser and Hannafin, 2010).

The management of adhesive capsulitis initially includes nonsurgical approaches such as physiotherapy, oral NSAIDS and intra-articular steroid injections (Neviaser and Hannafin, 2010, Ramirez, 2019). If there is insufficient improvement with nonsurgical approaches, arthroscopic capsular release and manipulation under anaesthesia may be considered (Neviaser and Hannafin, 2010, Yip et al., 2018, Ramirez, 2019).

1.4.2.2 Glenohumeral osteoarthritis

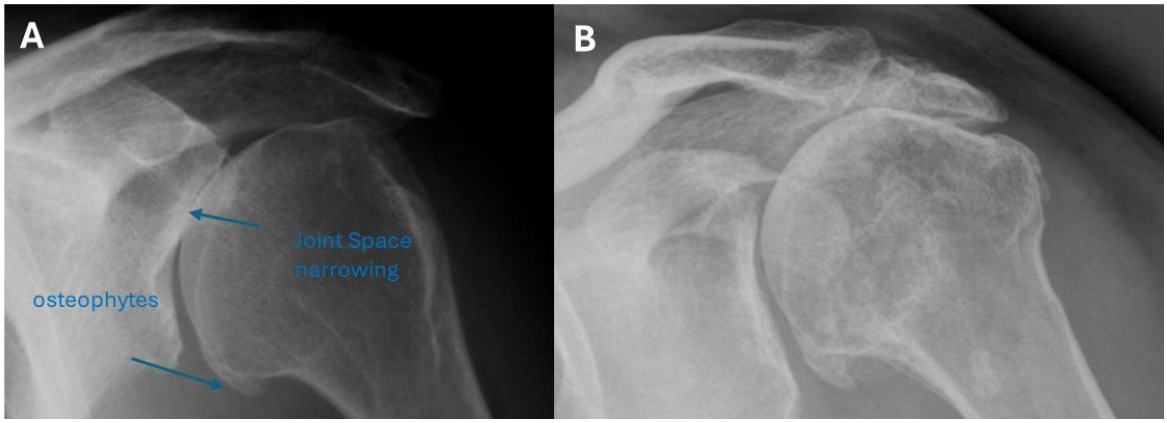
Osteoarthrosis (OA) is “a common complex disorder with multiple risk factors and varied phenotypic expression” (Lafeber et al., 2016). Shoulder OA is sometimes described as either primary or secondary. Primary OA in the glenohumeral joint occurs when there are no specific causes that could lead to joint damage and malfunction (Chillemi and Franceschini, 2013). Primary OA is relatively uncommon compared to other sites such as the knee or hand and mainly occurs in people aged 60 years or more (Millett et al., 2008, Silva et al., 2023). Secondary OA refers to OA due to

traumatic injury to the joint or from recurrent dislocations, severe RC injury and chronic instability (Millett et al., 2008, Silva et al., 2023). Several theories have been proposed in the literature regarding etiological factors leading to glenohumeral OA, such as advanced age, genetic factors, excessive mechanical loading, RC arthropathy, previous fracture and inflammatory arthritis (Lehtinen et al., 2000, Ecklund et al., 2007, Kopec et al., 2007, Fernández-Moreno et al., 2008, Sanchez-Adams et al., 2014, Kobayashi et al., 2014, Ibounig et al., 2021). Ageing is considered to be the principal risk factor for glenohumeral OA. As people age, their hyaline cartilage's chondrocyte density and responsiveness to growth factor decrease, making the joint cartilage more susceptible to damage (Martin and Buckwalter, 2003). The prevalence of glenohumeral OA increases with age, rising from 1.8% in people in their 40s to 27.5% in those in their 80s (Kopec et al., 2007, Kobayashi et al., 2014). Degenerative joint damage has been recognised to be largely influenced by genetic factors (Fernández-Moreno et al., 2008). It is estimated that between 35% and 65% of OA is due to genetic influence, and inheritance patterns are complex and polygenic (Fernández-Moreno et al., 2008). Some genetic variations and risk loci have been directly associated with OA in recent studies, while others have been associated with contributing factors like obesity, congenital joint malalignment, and excessive inflammation (Chapman and Valdes, 2012, Loughlin, 2015).

Although glenohumeral OA is not as prevalent as knee and hip OA, the prevalence of radiographic glenohumeral OA in the UK was approximately 21% in people with shoulder pain in primary care (Tran et al., 2022). The

prevalence increased with age, with prevalence peaking in the 80–89 age group (37.4%) (Tran et al., 2022). Radiographic glenohumeral OA was detected in 17.4% of the residents of a single village in Japan, and the prevalence of shoulder OA among people aged 65 years or older was 20.3% (Kobayashi et al., 2014). In Korea, the prevalence of primary glenohumeral OA was 16%, and the prevalence of secondary glenohumeral OA was estimated to be 1.3% in people aged between 65-97 years (Oh et al., 2011).

The most common presenting complaint in glenohumeral OA is persistent deep joint pain that is activity-related and slowly progressive (Ibounig et al., 2021). This pain is frequently localised to the posterior aspect of the shoulder. As it worsens it may associate also with night and rest pain and decreases in range of motion and function (Brox, 2003, Pandya et al., 2018, Ibounig et al., 2021). The diagnosis of glenohumeral OA is based usually on clinical and radiographic findings. Clinical examination findings in people with glenohumeral OA may include a reduced range of movement, especially external rotation and abduction, equal pain and restriction on active or passive movement, anterior-joint line tenderness, anterior-joint line crepitus, and effusion (Ibounig et al., 2020, Silva et al., 2023). Radiographic findings may include osteophyte formation, sub-chondral sclerosis, cysts, and predominantly focal joint space narrowing (Silva et al., 2023) (Figure 1.6).



Courtesy of Prof. Michael Doherty

Figure 1.6 Radiograph showing osteoarthritis of the glenohumeral joint in (A), someone without a rotator cuff tear, and (B) someone with a rotator cuff tear (shown by superior humeral head migration and sclerosis of the inferior acromion and superior humeral head)

The management of glenohumeral OA aims to reduce pain, to improve and maintain function, and to improve quality of life (NICE, 2021, NICE, 2022, Wood et al., 2023). The management approaches can be classified as conservative and surgical (Brox, 2003, Ansok and Muh, 2018). Conservative approaches include rest, oral NSAIDs with a COX inhibitor for gut prophylaxis, intra-articular steroid injection, physiotherapy and modifications of the activities of daily living (Millett et al., 2008, Pandya et al., 2018, Ansok and Muh, 2018). In severe cases and if conservative approaches fail, surgery may be considered. Surgical strategies include total shoulder arthroplasty, reverse shoulder arthroplasty and hemiarthroplasty (Brox, 2003, Millett et al., 2008, Pandya et al., 2018).

1.4.2.3 RC tendinopathy (subacromial impingement syndrome)

Disorders of the RC muscles or associated soft tissues are the most common cause of CSP (Lewis et al., 2009, Lewis, 2009, Seitz et al., 2011) (Hsiao et al., 2015, Consigliere et al., 2018, Creech and Silver, 2021), accounting for 44% to 65% of all shoulder complaints (Consigliere et al., 2018, Creech and Silver, 2021). RC disorders has been described as a progressive disorders of RC tendons. It starts with an acute inflammation, pain and weakness and progresses to degeneration with partial thickness tear and potentially a full thickness tear (Seitz et al., 2011, Lewis et al., 2015). It is a debilitating problem that can cause functional limitation and sleeping difficulties. In the Netherlands, a Dutch study found that impingement syndrome was the most frequent shoulder disorder (29%) in the general population, specifically between the ages of 25 and 64 years (van der Windt et al., 1995). More recently, in the UK, of the 20% to 50% of people who have shoulder pain and seek medical treatment, 25% are diagnosed with RC disorders (Consigliere et al., 2018, Creech and Silver, 2021). The incidence of shoulder impingement syndrome was found to increase with age and to associate with lifting heavy loads, repetitive activities and some sports that require repetitive overhead arm activities such as swimming, handball and volleyball (van der Windt et al., 1995, Garving et al., 2017, Consigliere et al., 2018, Creech and Silver, 2021). The definitive cause of RC tendinopathy remains uncertain, but several proposed mechanisms have been described. The pathophysiology of RC tendinopathy may be divided into intrinsic, extrinsic (external) and combined mechanisms (Seitz et al., 2011).

Extrinsic mechanisms of RC tendinopathy include anatomical factors, biomechanical factors, or a combination of both that originate external to tendon, shear force or compression (Seitz et al., 2011). Anatomical factors that may significantly narrow the subacromial space and compress the RC tendons include variations in shape of the acromion or orientation of the slope/angle of the acromion (Vaz et al., 2000, Ogawa et al., 2005). One suggestion is that RC tendinopathy involves narrowing of the subacromial space due to coracoacromial ligament hypertrophy and subacromial osteophyte formation, which reduce the space for the RC tendons (Neer and Welsh, 1977). The subacromial space is formed by the acromion, coracoacromial ligament, and the acromioclavicular joint superiorly, and the humeral head inferiorly (Consigliere et al., 2018). The space between the acromion and the humeral head normally ranges from 1.0 to 1.5 cm (Consigliere et al., 2018, Creech and Silver, 2021). When the shoulder is abducted at 90 degrees and rotated internally at 45 degrees, the subacromial space width is at its lowest and the humerus comes closer to the acromion (Consigliere et al., 2018). If shoulder biomechanics are compromised, the soft tissues and the RC tendons between the acromion and the humeral head will be irritated and compressed increasingly. The repetitive compression and degeneration of the RC tendons contribute to the narrowing of the subacromial space (Creech and Silver, 2021, Consigliere et al., 2018). Another explanation proposed is that subacromial impingement syndrome involves inflammation of the subacromial bursa in response to RC injury (Brox, 2003, Hsiao et al., 2015). The constitutional shape of the acromion might contribute also to

the development of impingement syndrome as an external compressive force (Creech and Silver, 2021, Varacallo et al., 2021). The shape of the acromion is classified by its three common morphologies into flat, curved, and hooked (Varacallo et al., 2021). Several studies have found an association between the hooked type of acromion and the presence of impingement syndrome symptoms (Gill et al., 2002, Inderhaug et al., 2018, Varacallo et al., 2021). Biomechanical factors include postural abnormalities, RC and scapular muscle dysfunction, aberrant scapular and humeral kinematics, and reduced extensibility of the posterior shoulder tissues or pectoralis minor (Seitz et al., 2011).

Extrinsic theories have suggested that RC tendinopathy might be a consequence of friction of the RC tendons with structures such as the humeral head below and the coracoacromial arch above and this is probably due to poor function and weakness of the RC and scapular muscles (Lewis et al., 2009, Lewis et al., 2015). Neer (1983) claimed that the majority of RC pathology was caused by irritation between the superior part of the RC and the anteroinferior surface of the acromion (Neer, 1972, Neer, 1983). On the other hand, intrinsic mechanisms are characterised by tendon pathology that originates mainly within the tendon (Seitz et al., 2011). Intrinsic mechanisms are factors that directly affect tendon health and quality, including ageing (Neer, 1983, Kumagai et al., 1994, Milgrom et al., 1995, Woo, 2000), genetics (Harvie et al., 2004), and poor vascularity (Biberthaler et al., 2003). Overload also has been known to be one of the major causes of RC tendinopathy. Excessive loading occurs predominantly in dominant limbs, physically demanding manual

work and in some sports with upper limb loading including swimming (Sein et al., 2010). Several studies have suggested that intrinsic degeneration within the RC tendon is the major factor in RC pathology. Hashimoto et al. (2003) clarified the pathological mechanism of the RC tear by analysing the distribution of pathologic lesions in the torn tendons. Histopathologic examination revealed degenerative changes within RC tendons that included disorientation of collagen fibres, tendon thinning, hyaline degeneration, vascular proliferation, calcification, and fatty infiltration (Hashimoto et al., 2003).

Comprehensive history-taking and physical examination are fundamental to the diagnosis of RC tendinopathy. Other diagnostic approaches include imaging such as magnetic resonance imaging (MRI) and ultrasound (Garving et al., 2017). MRI allows evaluation of soft tissue and bony structures within the shoulder girdle, while ultrasound enables the assessment of bursitis tendinopathy, and tendon ruptures (Jaggi and Lambert, 2010, Creech and Silver, 2021).

1.4.2.4 RC tears

RC tear is the last stage of RC tendinopathy, which is characterised by rupture of the RC tendons (Brox, 2003, May and Garmel, 2021). It starts initially as tendinopathy and progress to partial tear, and finally to complete tear (May and Garmel, 2021). RC tear accounts for approximately 50% of major shoulder disorders (Murrell and Walton, 2001) (Brox, 2003). In the UK, the ultrasonographic prevalence of symptomatic and asymptomatic full-thickness tears was 22% in the

population aged between 64 and 87 in a large general practice in Chingford, North London (Hinsley et al., 2022). The reported ultrasonographic prevalence of symptomatic and asymptomatic RC tears in the population aged over 60 and over 80 ranges between 30% and 60% respectively in Japan (Dang and Davies, 2018). In Germany, a prospective cohort study found that the prevalence of RC tear increased from 30% in people aged 70 to 50% in those aged 80 (Tempelhof et al., 1999). Furthermore, a large observational study demonstrated a significant increase in RC repair surgery in the years 2008 and 2009 (4.7/100 000, 95% CI 4.5 to 4.8) in 152 local health areas across England (Judge et al., 2014). The growing awareness of the availability of such surgical intervention among patients and GPs may be the cause of this increase. Additionally, the number of specialist shoulder surgeons qualified to carry out these operations has increased, as indicated by the BESS (British Elbow and Shoulder Society), which demonstrated a 164% rise over this period (Judge et al., 2014). After 2010, the rate of RC surgery in the UK had fallen dramatically returning to rates for this type of surgery seen ten years earlier. One possible reason for the observed decrease is that it occurred at the same time that the United Kingdom RC (UKUFF) trial started. UKUFF is a multicentre randomised controlled trial with approximately 90 surgeons from around the UK, evaluating the cost-effectiveness and clinical results of various RC surgery options (Judge et al., 2014).

The causes of RC tears are multifactorial, and it appears to be a combination of microtrauma and age-related degenerative changes

(Tashjian, 2012, May and Garmel, 2021). Additionally, there are several risk factors associated with RC tears such as age, smoking, poor posture, hypercholesterolemia, and activities that require repetitive overhead arm activity (Tashjian, 2012, May and Garmel, 2021, Varacallo et al., 2021). Again, the history and physical examination are the key elements in diagnosing RC tear. Most people with RC tear will complain of pain that commonly radiates down the deltoid muscle region (Dang and Davies, 2018). The pain can be acute due to obvious trauma, or gradual in onset and increasing with time and activity. Traditionally, patients will report pain and difficulty with performing overhead arm tasks, lifting heavy objects and sleeping on the affected side. On physical examination, patients may show muscle weakness

to resisted arm elevation in the Jobe position (supraspinatus muscle), or at 90 degrees of abduction (teres minor muscle), or weakness of internal rotation (subscapularis muscle) or resisted external rotation at 0 degrees of abduction (infraspinatus muscle)(Dang and Davies, 2018). There may be tenderness of the supraspinatus, infraspinatus, or teres minor muscles. Additionally, they commonly have pain in the mid-range of active, but not passive, movement between 60 and 120 degrees of abduction (i.e., the painful arch) (Hermans et al., 2013) (Figure 1.5).

1.4.2.5 Shoulder bursitis

Subacromial-subdeltoid bursa inflammation has been proposed recently as a primary cause for persistent shoulder pain and limitation of range of motion (Draghi et al., 2015, Kennedy et al., 2017, Faruqi and Rizvi, 2021).

Bursae are synovial lined sacs between MSK structures that function to reduce friction and facilitate normal movement (Draghi et al., 2015, Faruqi and Rizvi, 2021). The subacromial bursa is the main bursa of the shoulder, and it composed of three parts, the subacromial, subdeltoid, and subcoracoid portions (Draghi et al., 2015, Kennedy et al., 2017). The subacromial bursa, along with the RC muscles are considered to be the primary source of pain in the shoulder (Henkus et al., 2006, Lewis et al., 2015). Bursitis accounts for approximately 0.4% of primary care shoulder pain consultations (Faruqi and Rizvi, 2021). It is common in people who are involved in repetitive overhead arm activities such as athletes and manual workers (Faruqi and Rizvi, 2021). Subacromial bursitis is more common in older people due to age-related wear and degeneration process leading to subacromial impingement (Faruqi and Rizvi, 2021). Subacromial bursitis can be caused by several pathologies including acromioclavicular joint disorders, RC tendinopathy, subacromial impingement syndrome, calcific periarthritis, infection, pigmented villonodular synovitis, rheumatoid arthritis and acute shoulder trauma (Blaine et al., 2005, Faruqi and Rizvi, 2021). These causes lead to inflammation of the subacromial bursa, which increases the production of fluid and collagen by the bursa's synovial cells (Hirji et al., 2011). This bursal effusion might become haemorrhagic and is frequently fibrin-rich (Blaine et al., 2005). Bursitis is divided into three stages, specifically acute, chronic, and recurrent. The acute phase is characterised by localised inflammation, which results in pain during movement, particularly with overhead arm activities, whereas the chronic phase is characterised

by a chronic inflammatory process, resulting in more constant pain, weakness and tears of the surrounding tendons and ligaments. Patients exposed to overhead arm activities and repetitive trauma may develop recurrent bursitis (Kennedy et al., 2017, Faruqi and Rizvi, 2021).

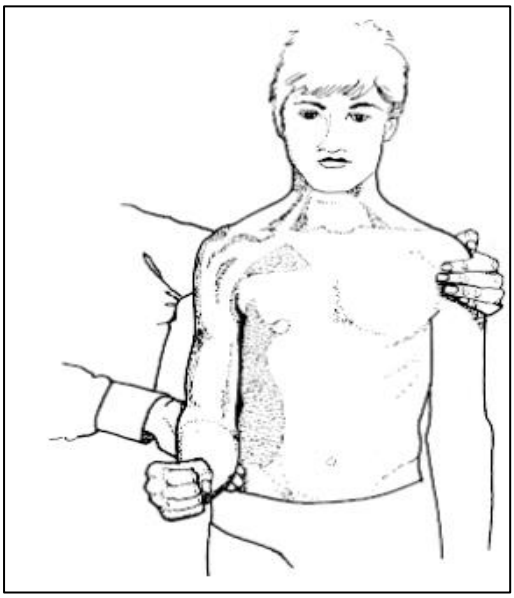
1.4.3 Clinical diagnosis

A comprehensive and systematic clinical examination is the keystone for evaluation of patients with shoulder pain (Brox, 2003, Yang et al., 2021). Having an accurate diagnosis leads to better targeted management. The clinical examination consists of taking a history, inspection, at rest and during movement, palpation, range of motion and muscle strength testing, and special tests (Tennent et al., 2003, Brox, 2003, Yang et al., 2021). History taking is the first essential step in the patient's assessment as it gathers important information for effective clinical decision making (Brox, 2003, Tennent et al., 2003). Common questions in history taking to assess the characteristics of shoulder pain should including the onset, duration, associated symptoms, radiation, and aggravating and alleviating factors. The next step is observation, which involves looking at the shoulder anteriorly and posteriorly. The examiner needs to look for asymmetry between the two shoulders, presence of muscle atrophy, winged scapula, swelling, deformity or redness. Following observation, palpation of the shoulder may reveal tenderness, soft-tissue mass, and muscle spasm (Brox, 2003, Yang et al., 2021). For example, pain triggered by deep palpation of the lateral deltoid may indicate supraspinatus tendinitis or RC tear (Burbank et al., 2008). The next steps are range of motion and

muscle strength assessment, which allows determination of limitation in movement and muscle weakness (Brox, 2003). Assessing range of motion includes both active and passive movement. Loss of both may indicate frozen shoulder, whereas loss of only active range of motion may reflect RC tendinopathy (Yang et al., 2021).

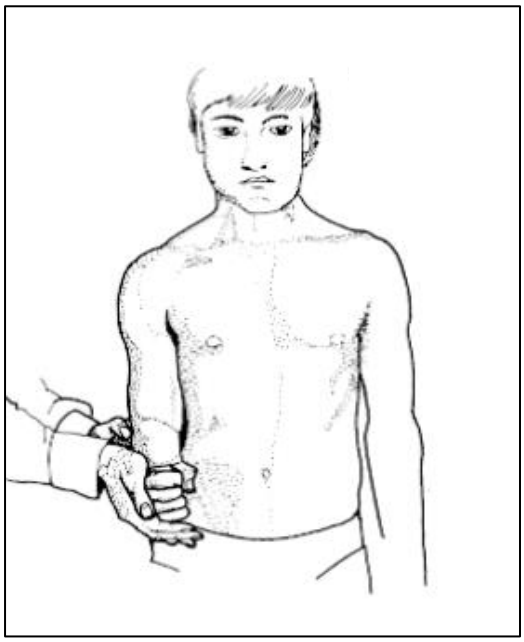
Following these initial steps of the shoulder assessment, physical examination tests need to be performed, which include muscular strength tests and provocative tests. Muscle strength tests, or resisted active movements, are usually performed by comparing the shoulder muscles of the affected side and contralateral side (Jain et al., 2013). Resisted active movements are used to detect RC lesions (Woodward and Best, 2000, Jain et al., 2013). The following movements are tested: (1) Resisted active abduction when the patient is asked to push their elbow outwards against the examiner's hand (Figure 1.7). If the patient has a painful middle arc and resisted active abduction reproduces the same pain then a supraspinatus lesion is the likely cause (Woodward and Best, 2000). If, however, they have a painful arc and resisted active abduction is pain-free then the likely problem is subacromial bursitis. (2) In resisted active external rotation, the patient's elbow is at their side, steadied by one of the examiners hands, the hand is pointing forwards, and the examiner asks the patient to push the hand outwards against the examiner's other restraining hand (Figure 1.8). Pain experienced in the upper arm suggests an infraspinatus/teres minor lesion (Jain et al., 2013). (3) In resisted active internal rotation, the patient's elbow and arm are placed in the same position as in the previous test and the examiner asks them to push the

hand inwards against the examiner's restraining hand (Figure1.9). Pain experienced in the upper arm suggests a subscapularis muscle/tendon lesion (Woodward and Best, 2000, Jain et al., 2013).



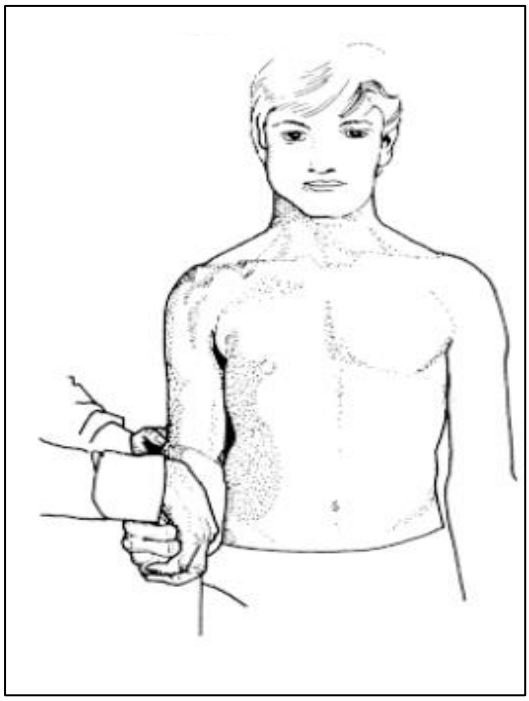
Reproduced with permission from Clinical Examination in Rheumatology, Doherty and Doherty, Wolfe 1992".

Figure 1.7 Resisted active abduction



Reproduced with permission from Clinical Examination in Rheumatology, Doherty and Doherty, Wolfe 1992".

Figure 1.8 Resisted active external rotation



Reproduced with permission from Clinical Examination in Rheumatology, Doherty and Doherty, Wolfe 1992".

Figure 1.9 Resisted active internal rotation

Provocative or special tests can be considered after history taking and physical examination. A large number of special tests that aid in specific shoulder diagnosis have been described in the literature such as Neer's sign, which suggests RC tendinopathy, Hawkins' test which suggests supraspinatus lesion, and drop arm test which might indicate RC tear (Liu et al., 1996, Caliş et al., 2000, Tennent et al., 2003, Brox, 2003, Hegedus et al., 2008, Arnander and Tennent, 2014). In some cases, the combination of special tests may improve the diagnostic accuracy of the physical examination of the shoulder. Michener et al. (2003) suggested that more than three positive results in the painful arc, Neer sign, empty

can test, Hawkins-Kennedy test, or resisted active external rotation can confirm the diagnosis of RC tendinopathy (Michener et al., 2003).

Imaging tests, including radiography, ultrasound, and MRI are often used for the examinations for shoulder pathologies (Gimarc and Lee, 2020). Radiographs may show changes of the bone, osteophytes, and focal/ asymmetrical loss of normal space between the head of the humerus and the glenoid and superior subluxation of the humeral head (Millett et al., 2008, Pandya et al., 2018). It can be useful for diagnosing pathologies of the shoulder joint such as glenohumeral arthritis, fractures and calcific tendinitis (Brox, 2003, Ramirez, 2019). In more advanced cases, severe changes with deformity may appear in the x-ray (Millett et al., 2008, Pandya et al., 2018). However, several studies have found that MRI and ultrasound are more helpful compared to radiographs in diagnosing joint capsule pathologies such as RC tear and labrum tear as these pathologies compromise soft tissue, which will not be visible on radiographs (Dinnes et al., 2003, Shahabpour et al., 2008, Ramirez, 2019, Yang et al., 2021). An example of that is adhesive capsulitis, which can be accurately diagnosed with MRI in conjunction with appropriate clinical examination (Brox, 2003, Shahabpour et al., 2008, Ramirez, 2019). In conclusion, focused history taking, comprehensive physical examination and appropriate diagnostic imaging methods together are important key elements to reach a confident diagnosis and provide the optimal management for the patients.

In the context of CSP, as described in the previous paragraph, a range of physical clinical tests are used to support the specific diagnosis. However, their diagnostic accuracy varies, which can influence the accuracy and precision of clinical coding in primary care (O'Kane and Toresdahl, 2014, Yang et al., 2021). The Neer impingement test, commonly used to identify subacromial impingement, has demonstrated only moderate sensitivity (72%) and specificity (60%), which limits its utility as a standalone diagnostic tool (Hegedus et al., 2012, Yang et al., 2021). Similarly, the Hawkins-Kennedy test, another provocative test for impingement, is reported to have high sensitivity (80%) but moderate specificity (65%), making it more suitable for ruling out impingement when negative, rather than definitively confirming it when positive (Hegedus et al., 2012, O'Kane and Toresdahl, 2014, Yang et al., 2021). Therefore, when used in isolation, the physical examinations associated with impingement provide limited diagnostic value. The empty can test, commonly used to detect supraspinatus tendon involvement, demonstrates high specificity (90%) but low sensitivity (44%), which may limit its effectiveness as a standalone screening tool and suggests that it is more useful for confirming rather than excluding supraspinatus pathology (Park et al., 2005).

These findings align with recent literature questioning the effectiveness of orthopaedic tests in diagnosing shoulder pain (Gismervik et al., 2017, Salamh and Lewis, 2020, Requejo-Salinas et al., 2022). Most orthopaedic tests for diagnosing shoulder pain have low accuracy (Hegedus et al., 2012, Hegedus et al., 2015, Gismervik et al., 2017). This is likely due to the difficulty of isolating and stressing a single anatomical structure

(Lewis, 2016), the presence of multiple altered structures (Dean et al., 2013), and changes in local tissue mechanosensitivity (Struyf et al., 2015). In some cases, the combination of special tests (test clusters) may improve the diagnostic accuracy of physical examination of the shoulder conditions (Park et al., 2005, Hegedus et al., 2015, Requejo-Salinas et al., 2022). For example, Michener et al. (2009) suggested that ≥ 3 positive results using the following tests - painful arc, Neer impingement, Hawkins-Kennedy impingement, external rotation resistance, or empty can test - can confirm the diagnosis of subacromial impingement syndrome (Michener et al., 2009). Similarly, Litaker et al. (2000) identified three findings that may indicate a RC tear, specifically age ≥65, night pain, and weakness on external rotation (Litaker et al., 2000, Yang et al., 2021).

These limitations highlight the need to interpret these tests within a broader clinical context, incorporating patient history, symptoms, and additional diagnostic measures to ensure accurate identification and coding of shoulder conditions. Despite the widespread clinical use of these shoulder orthopaedic tests to inform a diagnosis, there is little evidence to support their clinical utility (Hegedus, 2008, Lewis, 2009, Hegedus et al., 2012). Given that many people have identifiable structural pathology on imaging without shoulder symptoms (Girish et al., 2011), reliance on physical tests with inconsistent diagnostic validity alone could result in misclassification and an underestimation of certain shoulder conditions in epidemiological datasets.

Proper diagnostic coding requires accurate clinical differentiation, particularly when using systems such as ICD-10 or Read Codes, or SNOMED codes, which frequently require a clear diagnostic label (e.g., “RC syndrome” vs. “adhesive capsulitis”). Misclassification resulting from inconsistent or ambiguous clinical findings can impact patient care as well as the accuracy of diagnostic coding systems used in research and the epidemiological data. Therefore, greater standardisation in clinical assessment, potentially supported by clustering tests, imaging or consensus-based diagnostic criteria, may help to improve the reliability of CSP coding and data quality in primary care settings.

1.4.4 Management of chronic shoulder pain

As discussed previously, effective treatment depends on the cause of shoulder pain. Currently, there is a paucity of evidence on the optimal treatment for shoulder complaints in primary care, and information on the actual management by the GP is limited (Mitchell et al., 2005, Doorn et al., 2021). Most management options focus on controlling pain and restoring full shoulder function (Mitchell et al., 2005, Burbank et al., 2008). Table 1-1 outlines the management options of some conditions associated with CSP. In addition to these options, cognitive behavioural therapy is considered an effective management approach. Cognitive behavioural therapy is a psychological treatment reported to improve quality of life and pain-related distress and disability in people with chronic pain (Morley et al., 1999, Wetherell et al., 2011). The cognitive behavioural model of pain acknowledges the role of underlying pathology as a source of pain and

emphasises the crucial role of psychological factors in pain (Keefe and Somers, 2010). Emotional factors such as depression and anxiety, cognitive factors such as perceived helplessness and self-efficacy, and behavioural factors can influence the pain perception and how the person adapts to pain (Keefe and Somers, 2010, Linton and Shaw, 2011). Cognitive behavioural therapy approaches have been increasingly studied in people with low back pain (Hoffman et al., 2007), however the extent to which this has been incorporated into the management of CSP is limited. A scoping review by Farzad et al. (2021) identified ten studies (seven randomised trials and three cohorts) that addressed the psychological aspects of shoulder pain. Out of seven randomised trials, four compared psychological interventions with usual MSK care. Eight studies used cognitive approaches, including face-to-face cognitive-behavioural treatment, physical-cognitive-mindfulness training, emotional freedom techniques, pain coping strategies, and psychological flexibility. Three studies used the behavioural approaches as their main intervention, including graded exercise therapy and behavioural therapy (Farzad et al., 2021). Only one study used one approach (either behavioural or cognitive) in its evaluation and management. Two studies examined pain intensity as a primary outcome, and five studies examined it as a secondary outcome. Cognitive factors were assessed in 50% of the studies using nine different outcome measures. Emotional factors were examined in 80% of studies using ten outcome measures (Farzad et al., 2021). Most studies (70%) that used a biopsychosocial approach found reduction in pain intensity and catastrophising thinking related to pain. Additionally, there was a

positive association between cognitive approaches and reductions in the emotional aspect of pain (Farzad et al., 2021). However, none of the studies provided a comprehensive explanation on how the three psychological factors (cognition, emotion, and behavioural) were addressed in evaluation, and treatment.

Table 1-1 Management of chronic shoulder pain

Condition	**Initial management**	**Further treatment options if no improvement with initial management**
Adhesive capsulitis	Physiotherapy, activity modification, NSAIDs, intra-articular injections	Intra-articular corticosteroid injection, surgery
Glenohumeral OA	Physiotherapy, activity modification, NSAIDs	Intra-articular corticosteroid injection, possible surgery
Acromioclavicular joint OA	NSAIDs, activity modification	Corticosteroid /local anaesthetic injection, surgery
Glenohumeral instability	Physiotherapy, activity modification	Surgery
RC pathology	For small RC tear (physiotherapy, activity modification, NSAIDs) For large RC tear, conservative management as listed above	Subacromial corticosteroid injection, surgery

NSAIDs- nonsteroidal anti-inflammatory drugs, RC-rotator cuff

1.5 Epidemiology of chronic shoulder pain

Epidemiology is defined as " the study of the occurrence and distribution of disease in populations and the factors that account for this distribution" (Shy, 1986, Frérot et al., 2018). Prevalence and incidence are the most common measures of disease frequency in epidemiology (Noordzij et al., 2010). Prevalence is a measure of the total burden of a disease within a population. It is defined as the total number of people with a specific condition at or within a specific time period. Incidence is defined as the number of newly developed cases in a population during a specified time period and can be expressed as a risk or an incidence rate (Noordzij et al., 2010).

Understanding the burden of CSP is crucial for clinicians and policy makers when providing healthcare services, and management options. Shoulder pain has been estimated to be the third most common MSK condition in primary care (Urwin et al., 1998). A number of studies examining the epidemiology of shoulder pain have been cited in the literature, and the prevalence and incidence estimates varied across these studies (Urwin et al., 1998, Tekavec et al., 2012, Cho et al., 2015, Sarakbi et al., 2020). Lucas et al. (2022) carried out a systematic review including 61 observational studies which summarised the evidence on the prevalence and incidence of shoulder pain and explored the influence of different case definitions of shoulder pain on prevalence estimates. The case definition for shoulder pain in that review was restricted to pain in the shoulder region not incorporating the neck or upper limb areas. The majority (84%) of the studies used a questionnaire or interview method to

collect data on shoulder pain, while the remaining studies analysed primary care health records. Of the 61 included studies, 16 had an overall moderate risk of bias, 45 had an overall low risk of bias, and none had a high risk of bias. Results showed that the overall prevalence of shoulder pain in primary care (healthcare database) ranged from 1.0% to 4.8%. The prevalence of shoulder pain in the general population varied widely, from 0.67% to 55.2% in the population aged between 15 and 85 years. Females were found to be more likely to have shoulder pain than males, and studies undertaken in higher income countries had higher prevalence than those from lower income countries, specifically 16.9% and 0.7%, respectively. One explanation for that might be because of the easier healthcare accessibility and availability in the higher income countries compared to lower income countries. Eight studies reported the incidence of shoulder pain, of which seven were conducted in high income countries. The overall annual incidence rates for shoulder pain ranged from 7.7 to 62 per 1000 person-years. Only two studies focused on the general population, presenting an incidence of shoulder pain of 11.4 per 1000 person-years in Kuwait and 62 per 1000 person-years in residents of a village in Bangladesh. A subgroup analysis was undertaken stratified by the duration of pain symptoms (1 week or less; 2 to 6 weeks; 12 months or longer), and the case definition of shoulder pain that was used. Prevalence estimates ranged from 10.8 – 55% for a reference period of 12-months or more, 2.0 – 34 % for a reference period of 7 days, 12 – 42 % for a period of 2 – 6 weeks, and 20.9 – 26% for point-prevalence (Lucas et al., 2022). Prevalence estimates stratified according to case definition

show that studies using a restricted case definition reported similar prevalence estimates. As expected, studies using healthcare records reported a consistently lower prevalence of shoulder pain. However, there are several caveats to this study. The common limitation across the included studies was the use of a target population that was not representative of the general population. This was particularly apparent in countries where the socioeconomic status varied considerably across the country, such as between rural areas and urban centres. Additionally, there was a lack of standardised case definitions and data collection methods across the included studies. Some studies used a body map to identify areas of pain, swelling, or stiffness in the shoulder region, while others used a more restricted case definition including frequency and duration of shoulder pain symptoms, which might explain the considerable variations in prevalence estimates among studies. In contrast to the previous studies, a broader definition for shoulder pain has been introduced by Takala (1982), which included ache or stiffness or difficulty of movement in the shoulder or upper arm. The prevalence estimate according to this definition was 17% in adults aged between 40 and 64 years (Takala, 1982) .

Cho et al. (2015) conducted a cross-sectional study to determine the prevalence of radiographic OA in the spine, shoulder, hand, hip, and knee in the Korean population over the age of 65 years. Of the 1118 invited participants, 696 (females 398, males 298) participated in the study (response rate 62%). The mean age of respondents ranged from 65 to 99 years. Radiographs of the spine, shoulder, hand, hip, and knee were

taken and examined for radiographic OA. Results revealed that the highest prevalence of radiographic OA was seen in the lumbar spine (66%) followed by the hand (60%), knee (38%), shoulder (5%), and hip (2%) (Cho et al., 2015). However, the findings of this study need to be interpreted with caution due to several limitations. First, there may have been recruitment bias in terms of participant selection since the respondents were younger than the non-respondents. Furthermore, people who were symptomatic might have been more likely to participate in the study to obtain radiographic examination and a diagnosis. Therefore, the true prevalence of OA among Koreans could be underestimated or overestimated as a result of these potential biases. Recently, Khosravi et al. (2019) examined the prevalence of shoulder pain in middle aged females in Iran. A total of 511 females aged between 45 and 65 years old were selected through a cluster-sampling method (Khosravi et al., 2019). The case definition of shoulder pain was having pain lasting for more than one week and localised to the proximal anterolateral shoulder area. Presence of shoulder pain was determined from the following question: “Have you ever had shoulder disorder in the present time or long lasting?”. The point and lifetime prevalence of shoulder pain was 18.6% and 27.6%, respectively (Khosravi et al., 2019). However, 10% of the participants reported cervical radiculopathy (Khosravi et al., 2019). Thus, the prevalence estimates might not indicate the true estimate of shoulder pain in the population, because cervical disorders can mimic shoulder pathologies. Additionally, sometimes it is hard for people to differentiate between shoulder and neck pain.

1.5.1 Epidemiology of chronic shoulder pain in the UK

Several studies in the literature have explored the epidemiology of MSK pain in the UK, but few have focused on CSP. In 1998, Urwin et al. conducted a cross-sectional study to determine the prevalence of MSK pain at multiple anatomical regions. A sample of 6000 adults aged between 16 and 75 from three general practices were mailed a questionnaire that collected data on demographic factors, physical disability, and MSK pain in the last month in the neck, back, shoulder, elbow, hand, hip, knee, or multiple sites. The most common site with MSK pain in the community was the back (23%; 95% CI 21 to 25) followed by the knee (19%; 95% CI 18 to 21), and the shoulder (16%; 95% CI 14 to 17) (Urwin et al., 1998). However, the definition of shoulder pain was not clarified if it was chronic or acute in this study. In another study in Manchester, UK, Pope et al. (1997) explored the prevalence of shoulder pain according to four different shoulder pain definitions and restricted the definition to only those with associated disability (Pope et al., 1997). Two definitions were based on questions asking directly about pain in the shoulder and neck and the upper trunk areas, and two were based on marking the pain sites on a body chart of the shoulder region and the upper trunk. Postal questionnaires were sent to a sample of 500 people registered with a general practice in Manchester (Pope et al., 1997). The results showed that in total 160 (51%) people reported shoulder pain based on at least one definition. The one-month prevalence ranged from 31% to 48% across the four definitions. The lowest prevalence was found

for the question asking directly about shoulder symptoms (31%). The highest prevalence was found for the broadest definition asking about pain in pre-defined areas on a body map (neck and trunk) (48%). In total, 27% of all respondents answered positively to all four definitions (Pope et al., 1997). Only seven people who answered positively when asked directly about shoulder pain did not indicate symptoms on the body map for the shoulder region (Pope et al., 1997). On the other hand, 30% of those answering negatively to the direct question about shoulder pain pointed out symptoms on the body map for the upper trunk area or answered positively to the direct question about pain in the neck or upper trunk areas (Pope et al., 1997). It is clear that imprecise perceptions of anatomical areas by the participants often leads to inaccurate reporting of shoulder pain. However, the results of this study might not be generalisable as the population sample was taken from a single general practice in South Manchester (Pope et al., 1997). Additionally, the respondents were more likely to be people who had consulted their general practitioners for shoulder pain before the survey, which suggests that prevalence of shoulder pain based on the respondents to the questionnaire might have overestimated the prevalence in the general population.

A prospective cohort study by Linsell et al. (2006) assessed the prevalence and incidence of shoulder pain in the UK population aged between 18 and 60 using a primary healthcare record database (the IMS Disease Analyzer-Mediplus UK) (Linsell et al., 2006). As far as is known, this was the only study that has examined the incidence of shoulder pain

in the UK. The overall prevalence and incidence of shoulder pain were 2.4% and 14.7 per 1000 person years, respectively.

Table 1-2 summarises the existing evidence regarding the general population burden of shoulder pain in the UK. Overall, the studies conducted in the UK highlighted that there are significant differences in reported prevalence and incidence rates of shoulder pain in the literature (Chard et al., 1991, Urwin et al., 1998, Lock et al., 1999, Badcock et al., 2002, Walker-Bone et al., 2004, Linsell et al., 2006, Adamson et al., 2006, Jordan et al., 2010, Duncan et al., 2011, Docking et al., 2015a, Sanchez Santos et al., 2020). These differences might be explained by different case definitions of shoulder pain, population age and characteristics, variations in research and sampling methods used in these studies, and differences in reference periods which clearly led to discrepancy in results. However, there are several caveats to these studies, such as a lack of standardised case definition and data ascertainment methods. For example, in the study by Badcock et al. (2002), although the focus was on shoulder pain, the neck region was included which might not provide an accurate estimate for shoulder pain prevalence (Badcock et al., 2002), whereas Duncan et al. (2011) examined only the diagnosis of arthritis (Duncan et al., 2011). Many studies used questionnaires but the application of these was not consistent across studies. Also, Several studies did not obtain an adequate response rate, which can increase the risk of selection bias (Sanchez Santos et al., 2020). Furthermore, some studies did not report numerators and denominators with the prevalence or incidence estimate. The use of a selected target population might not

be representative of the UK general population, because socioeconomic status varies across areas of the UK, such as between rural areas and urban centres (Urwin et al., 1998, Jordan et al., 2010). For example, in the study by Sanchez Santos et al. (2020), although the population was broadly representative of the English population in terms of demographic and health-related characteristics, people living in more deprived area were less likely to participate in the study (Sanchez Santos et al., 2020). Only one study examined the incidence of shoulder pain in the UK using electronic medical records and found the incidence to be 14.7 per 1000 person-years (Linsell et al., 2006). Finally, none of these studies specifically focused on the burden of CSP .

Table 1-2 Summary of reported prevalence of shoulder pain in the UK

Study	Year	Country	Data ascertainment	Study setting	Sample Size	Study population / Age group	Case definition	Prevalence period	Prevalence
Chard	1991	England	Face-to-face questionnaire and physical examination	Community	644	Age ≥ 70. Residents of Cambridge	Shoulder pain or disability More specific definition Shoulder condition by physical examination	Point prevalence Prevalence of shoulder disorder	26% 21%
Urwin	1998	England	Face-to-face questionnaire	Community	5752	Adults. Urban. Residents of Tameside and Glossop Area.	Pain in the area of the shoulder for more than one week	1 month	16%
Lock	1999	England	Postal questionnaire	Community	1546	Age >= 17 Urban. Residents of Newcastle-upon-Tyne	Shoulder pain restricted daily activities for more than 1 week	1 year	19.98%
Badcock	2002	England	Face-to-face questionnaire	Community	2606	Age 18-75.	Ache or pain in the shoulder area. Marked on body map	1 month	11.7%
Walker-Bone	2004	England	Face-to-Face questionnaire and physical examination	Community	9696	Age 25-64. Southampton.	Symptoms of pain, numbness, or tingling in the shoulder lasting at least one day	7 days	7.4%
Linsell	2006	UK	Medical Records	Primary care	658469	Age ≥ 18. Registered with a practice.	Read codes from GP records - musculoskeletal	1 year	2.36%

							codes allocated to shoulder region		
Adamson	2006	Scotland	Face-to-face questionnaire	Community	858	Three cohorts aged around 15, 35 and 55 years. Urban. Residents of Glasgow	Reported regular swelling, pain or stiffness in either shoulder. Marked on body map	Unclear	25.52%
Jordan	2010	UK	Medical Records	Primary care	100758	Residents of North Staffordshire	Read codes from GP records - musculoskeletal codes allocated to shoulder region	1 year	1.99%
Duncan	2011	England	Face-to-face questionnaire	Community	1029	Age ≥ 85 Residents of Newcastle	Pain of the shoulder on most days during the last month	1 month	30.7%
Docking	2015	Scotland	Face-to-face questionnaire	Community	6013	Age ≥ 55 registered in general practices	Any aches or pain that lasted for one day or longer in the shoulder	1 month	27%
Sanchez Santos	2020	England	Face-to-face questionnaire	Community	5409	Age ≥ 65 Elderly residents in Merseyside, West-Yorkshire, West Midlands, Cambridgeshire, Gloucestershire, Dorset, Wiltshire,	Any trouble (ache, pain, discomfort) in the shoulder	6 weeks	29.80%

						London or Oxfordshire.			

1.5.2 Epidemiology of chronic shoulder pain in workers

Work-related MSK conditions of the upper limb area is considered a major problem worldwide. Several epidemiological studies conducted in working populations have highlighted that there is a high prevalence of neck and shoulder pain disorders among workers with physically demanding jobs (Cassou et al., 2002, Feveile et al., 2002). Alipour et al. (2008) conducted a cross-sectional study to examine the prevalence of neck and shoulder pain in the largest Iranian car manufacturer workforce. Shoulder pain was defined as having complaints (aches, pain, and discomfort) in the shoulder region during the last year (Alipour et al., 2008). A total of 14,384 (79.8%) of all employees completed the questionnaire. Most of the employees were less than 30 years of age (59%), with low duration of employment (less than 6 years) (69%) (Alipour et al., 2008). Approximately 6.1% had self-reported shoulder pain (Alipour et al., 2008). However, in comparison to other studies of working populations comprising older workers in developed countries, the study by Alipour et al. (2008) focused on younger working population, and the prevalence of pain was relatively low. Several studies (Allander, 1974, Holmström et al., 1992, Daigneault and Cooney Jr, 1998) demonstrated that the prevalence of work-related neck and shoulder pain increases with age.

In a prospective cohort study, Harkness et al. (2003) studied the new onset of shoulder pain in newly employed workers in different occupations in the UK. Participants were recruited from 12 occupational groups including firefighters, police officers, army officers, army infantry, dentists,

nurses, shipbuilders, postal workers, and forestry workers (Harkness et al., 2003). At baseline, a questionnaire was distributed to 1186 workers, and 1081 (91%) completed it. A body manikin was used to identify shoulder pain lasting at least 24 hours in the past month (Harkness et al., 2003). Those participants identified at baseline as being free from shoulder pain (803, 74%) were eligible for follow-up. Follow-up questionnaires were sent to the participants at 12 and 24 months. Of 803 at baseline, 638 (79%) responded at 12 months and 476 (88%) at 24 months. Participants who reported shoulder pain for the first time were 93 (15%) and 73 (15%), in the period 12 months and 24 months, respectively (Harkness et al., 2003). The prevalence estimates of shoulder pain varied largely according to the occupational group. For example, the prevalence in the army infantry was 35%, whereas in forestry workers, and shipbuilders the prevalence was 10% (Harkness et al., 2003).

Recently in 2023, Yanik et al. (2023) conducted a population-based prospective cohort study to examine the relationship between occupational exposures and the risk of symptomatic RC diseases requiring surgery using UK Biobank data. Jobs and UK Standard Occupational Classification (SOC) codes were recorded during the UK Biobank verbal interview (Yanik et al., 2023) and lifetime job history was obtained through an online survey. Data on surgery for RC diseases were derived from the linked national hospital inpatient records. Yanik et al. (2023) linked UK SOC codes to the US SOC 2010 system to allow use of the recent job exposure matrix (JEM) based on the US occupational Information Network (O*NET) database. In brief, O*NET is an available

resource including scores rating the physical and mental requirements of over 800 jobs (Yanik et al., 2023). Approximately, 421,850 people aged between 40 and 69 were enrolled in this study. Of these, no job title was provided by 143,918 (34%) people, and 124 (0.03%) people had jobs that could not be scored with O*NET (Yanik et al., 2023). Results showed that of 277,808 people who reported their jobs, 1997 (0.7%) had RC disease operation, and 6.3% of these reported that their jobs often involved heavy manual work (Yanik et al., 2023). Additionally, it was found that more than 10 years of exposure was significantly associated with increased risk of surgery for RC disease with an adjusted HR of 2.06 (95% CI 1.39 to 3.04, $p < 0.003$) (Yanik et al., 2023).

In summary, occupations that require high physical demands on the arm are associated with shoulder disorders (Miranda et al., 2008, Svendsen et al., 2013, Seidler et al., 2020). Shoulder pain in workers might be due to mechanical exposures involving work load, repetitive work, heavy weights, lifting objects at or above shoulder level, carrying objects on one shoulder, and heavy pushing or pulling (Bernard and Putz-Anderson, 1997, van der Windt et al., 2000, Harkness et al., 2003). Previous studies clearly show that shoulder pain is considered to be one of the most frequent MSK conditions in the population. Knowledge of the determinants of shoulder pain is very important for the development of strategies to prevent shoulder pain. Thus, in the next paragraph, the potential risk factors for shoulder pain will be discussed.

1.5.3 Risk factors for chronic shoulder pain

The aetiology of shoulder pain is thought to be multifactorial. Risk factors that have been associated with shoulder pain include personal risk factors such as female sex, older age, high body mass index (BMI) and smoking, and occupational risk factors such as activities that frequently require high force demands such as carrying heavy loads, packaging and working in industry (Bernard and Putz-Anderson, 1997, Luime et al., 2004, Ryall et al., 2007, Pribicevic, 2012, Sansone et al., 2014, Noten et al., 2017).

1.5.3.1 Person specific risk factors

Female sex

Evidence shows that females are significantly more likely to experience shoulder pain compared to males (Andersen et al., 2003, Mitchell et al., 2005, Straker et al., 2009), and that shoulder pain is almost twice as common in females as in males (Pribicevic, 2012, Djade et al., 2020). In a cross-sectional study conducted among a worker population in Denmark, being a female was found to be associated with neck and shoulder pain with an OR of 1.8 (95% CI 1.2 to 2.8) (Andersen et al., 2003). A prospective longitudinal cohort study by Hill et al. (2010) studied risk factors associated with shoulder pain in people aged 18 years old and above from the north-west region of Adelaide, South Australia (Hill et al., 2010). At stage 1 of the study (2000), the sample was randomly recruited by telephone interview. At stage 2 (2002-2003), around 3206 participants attended the clinic to fill in a questionnaire and/or a clinical assessment (Hill et al., 2010). In total, 88% of the participants completed the self-report

questionnaire, 81% completed the telephone survey, and 81% attended the follow-up clinical evaluation. Results showed that females were significantly more likely to report shoulder pain, with an OR of 1.4 (95% CI 1.2 to 1.7) (Hill et al., 2010).

This could be explained by the biological differences in anatomy, strength and hormones that increase females' tendency to develop certain MSK conditions (Razmjou et al., 2016, Shultz and Fegley, 2023). Additionally, differences in pain thresholds between sexes and increased pain sensitivity in females could explain this higher prevalence (Razmjou et al., 2016). Kindler et al. (2006) investigated the differences between males and females with shoulder pain in terms of their experience of experimental and clinical pain. Fifty-nine patients with shoulder pain requiring surgery were enrolled in the study. Information captured included demographics, clinical pain, catastrophising trait or state, and psychological status (Kindler et al., 2011). A series of experimental pain tests were conducted, which included pressure pain threshold, thermal pain, and thermal temporal summation (Kindler et al., 2011).They found that females reported greater pain severity (effect size 0.77, p-value, 0.005) and showed enhanced sensitivity to experimental pain (masseter pressure pain effect size 0.92, p-value 0.001/ acromion pressure pain effect size 1.23, p-value <0.001/ Tolerance 1.23, p-value <0.001) (Kindler et al., 2011). However, the findings of this study might not be generalisable to other populations with pain, because the study population was a homogenous group of patients with marked CSP recruited prior to surgery, and excluded patients with less severe CSP (Kindler et al., 2011).

Age

Most studies have reported that age is a strong risk factor for shoulder pain (Miranda et al., 2001, Luime et al., 2004, Jonasson et al., 2011). The reported increase of shoulder pain with age could result from degenerative changes of the shoulder and RC tendon which are associated with the ageing process (Pribicevic, 2012). Presumably, ageing-related physiological characteristics, such as joint and muscle degeneration, and decreased tissue healing, are thought to increase the risk of MSK conditions (Squires et al., 2003, Musumeci et al., 2015). Age has been shown to have a negative influence on tendon properties (Seitz et al., 2011). Evidence from biomechanical studies suggest that there is a decrease in tendon elasticity, reduction in the number and functionality of tendon stem/progenitor cells, disorganised collagen content, and an increased deposition of glycosaminoglycans (GAGs), which may lead to inflammation, pain and impaired mobility. Also, with ageing, the total glycosaminoglycan and proteoglycans content in the supraspinatus tendon decreases (Riley et al., 1994). In older people, the number of microvessels in the tendon found to be significantly reduced, which makes the RC tissue more prone to adiposis, fibrovascular hyperplasia, calcification, and atrophy, which could be associated with RC tears (da Rocha Motta et al., 2014).The prevalence of CSP was found to increase from 23% in the 18-24 age group to 50% in the 55-64 age group in Australia (Pribicevic, 2012). Other studies have shown that those over age 40 years are more likely to experience shoulder joint conditions such as

adhesive capsulitis, RC tears, RC tendinopathy, and glenohumeral OA (Woodward and Best, 2000, Murrell and Walton, 2001, Iannotti and Kwon, 2005). Interestingly, several studies have reported the highest prevalence of shoulder pain in the middle aged population (40-64 years), which could relate to occupational activities, with a subsequent decrease of pain in older people that may result from reduced biomechanical stress following retirement (Chard and Hazleman, 1987, Picavet and Schouten, 2003, Parsons et al., 2007, Pribicevic, 2012).

Obesity

Obesity is considered a risk factor for shoulder pain. Two studies (Hill et al., 2010; Rechardt et al., 2010) found that shoulder pain was more common in females aged > 50 years, in smokers and in those classified as having high BMI (approximately 28 Kg/m^2) (Hill et al., 2010) and a high waist circumference (Hill et al., 2010, Rechardt et al., 2010). Recently, Gumina et al (2014) studied the association between body fat and RC tear in a cross-sectional study. Approximately, 381 patients (180 males and 201 females) who underwent RC repair were included (Gumina et al., 2014). The control group included 220 participants with no RC repair. BMI and the percentage of body fat (BF%) were assessed for all the participants. They found that patients with RC tear had a higher BMI compared to subjects with no RC tear. Interestingly, patients with a small RC tear had lower BMI (27.85) and BF% (37.63) than patients with a massive tear (BMI, 29.93; BF%, 39.43) with significant differences between the two groups (p-value = 0.004; p-value =0.031) (Gumina et al.,

2014). While this study presents strong evidence regarding the association between obesity and RC tear, other potential risk factors for RC tear which might have affected the results, such as smoking, genetic factors, physical activity level, diabetes and body habits were not considered or adjusted for in this study. It would be valuable to compare these findings with studies that took these factors into account.

Smoking

Shoulder pain has been associated also with smoking (D'Onise et al., 2010, Gill et al., 2013). In a longitudinal cohort study conducted by Gill et al. (2013), current smoking was found to be associated with recurrent shoulder pain compared to people who did not smoke (p-value = 0.011). Smokers are more likely to complain of chronic MSK conditions in general (D'Onise et al., 2010, Gill et al., 2013). Barton et al. (1989) hypothesised that nicotine has a major effect on pain processing and may decrease pain threshold by sensitising pain receptors. This hypothesis is supported by an association found between tobacco and both chronic MSK pain and poor sleep quality (Averina et al., 2005, Mitchell et al., 2011). Mitchell et al. (2011) undertook a cross-sectional study of the Kentucky females' Health Registry from 2006 to 2008 to determine the relationship between smoking and chronic MSK pain. They found that females who were daily smokers reported more pain compared to females who never smoked (adjusted odds ratio [aOR] = 2.04 and 95% confidence interval [CI] 1.67 to 2.49) (Mitchell et al., 2011). While this study provides evidence of the association between smoking and chronic MSK pain, it has some

limitations. For example, there is the possibility of selection bias since females not included in the registry may have differed from the females who participated in it (Mitchell et al., 2011).

Socioeconomic status

Socioeconomic status and education level are also considered a well-known predictors of MSK pain in the literature (McBeth and Jones, 2007, Engebretsen et al., 2010, Putrik et al., 2015, Hansen et al., 2023), however, few studies explored this in people with shoulder pain. The term "socioeconomic status" refers to differences in relative deprivation and is usually classified by factors such as levels of unemployment, home ownership and education (McBeth and Jones, 2007). Low socioeconomic status has consistently been associated with poor healthcare quality (Andresen and Miller, 2005). Macfarlane et al. (2009) found that people in the lowest social class experienced approximately a threefold increase in the risk of chronic widespread pain compared to the highest social class (RR 2.9, 95% CI 1.8 to 4.6). This might be explained by several factors such as lifestyle and psychological distress. There is evidence supporting the association between socioeconomic status and chronic pain, and two studies included area-level measures such as the Townsend Index (a combination of home ownership, car ownership, unemployment and over-crowding) (Urwin et al., 1998, Eachus et al., 1999). Wilkinson (2010) proposed that social comparison, which has previously been shown to explain the link between poor health and low job status, might be a key mechanism by which inequality leads to poorer health (De Vogli et al.,

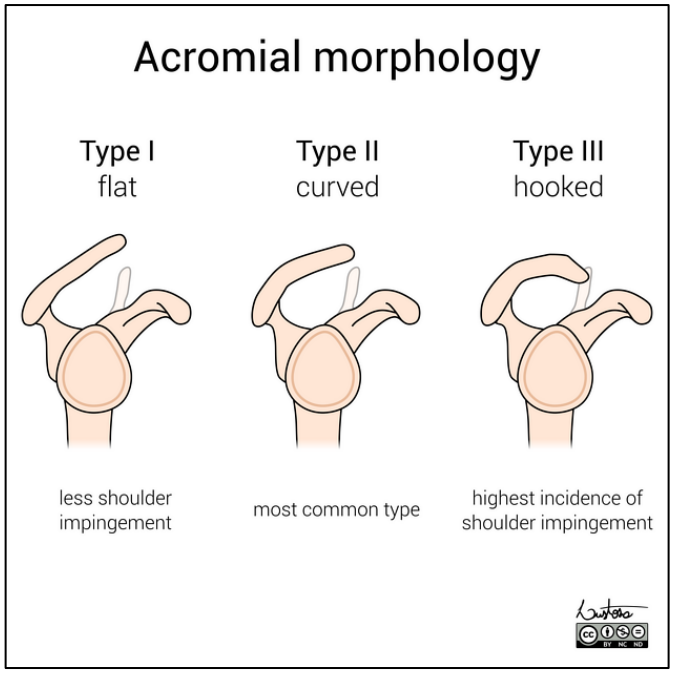
2007). Additionally, social threats can cause anxiety and depression, which are involved in the development of chronic pain (Keefe et al., 2001). Socioeconomic factors such as low level of education was found to be associated with higher rates of chronic and disabling pain (McBeth and Jones, 2007). Engebretsen et al. (2010) studied the predictors of pain and disability (SPADI) and work status in 104 people with subacromial shoulder pain. Low education (≤ 12 years at school), was a significant risk factor for shoulder pain and disability at one year follow-up (aβ-14.3, 95% CI -23.5 to -5.2; p-value = 0.003) (Engebretsen et al., 2010). High education levels found to be linked to improved personal economy, socio-psychological resources, and a healthier lifestyle (Bot et al., 2005, Hagen et al., 2006, Furnée et al., 2008). Furthermore, low level of education found to be associated with low socioeconomic status, which has been suggested to associate with MSK pain (Bergman et al., 2001). One possible explanation for such association could be that people with low level of education could be more exposed to risk factors such as low level of physical activity, manual work, and nutritional deficits (Diderichsen et al., 2001). The clustering of these risk factors among people with lower educational level may increase their risk to the development of MSK conditions, and pain (Diderichsen et al., 2001).

Another study by Kim et al. (2014) conducted a cross-sectional study to identify factors affecting the satisfaction and shoulder function of people with a recurrent RC tear. Education level was categorised to as high school graduate, college graduate, or postgraduate. The multivariable analysis showed that lower education level was one of the significant

predictors of poorer scores in the functional limitations and pain scale (β= 0.39, p-value=0.003), Simple Shoulder test form (β= 0.59, p-value=0.001), and pain visual analogue scale (VAS) (β=0.33, p-value =0.01) of the shoulder in patients with RC muscle retear. However, this study has some limitations. First, the study is cross-sectional design which might not confirm the association between education level and MSK symptoms. Second, the VAS, as a one-dimensional linear scale, may not accurately reflect the multidimensional psychometric nature of patient satisfaction. In addition, only 48% of the included population were examined, therefore the data obtained may not reflect the entire population.

Other risk factors

There are other factors found to be key risk factors for RC tear such as type of acromion, and dominant side (Zhao et al., 2022, Xu et al., 2024). Acromion type was categorised based on the morphology observed in MRI using a common established classification system (Bigliani, 1986, Xu et al., 2024). This system identifies three types: Type I (flat), Type II (arc-shaped), and Type III (hooked) (Figure 1.10) (Bigliani, 1986). Variations in acromion morphology found to be associated to mechanical impingement and RC disorders (Epstein et al., 1993, Gill et al., 2002, Varacallo et al., 2021, Xu et al., 2024).



The material is free to use for non-commercial use, Case contributed by Lustosa L, Radiopaedia.org, rID 180351

Figure 1.10 Illustrations of the acromial types according to the Bigliani classification.

Acromion type 3 was significantly associated with greater risk of RC tear (Bigliani et al., 1991, Epstein et al., 1993, Worland et al., 2003, Morelli et al., 2019). Bigliani et al. (1991) proposed that a down-sloping acromion in the sagittal plane may cause impingement of the RC muscles, which could progressively lead to tear. People with a type-III acromion were found to have approximately three times higher odds of RC tear compared to people with a type-I or -II acromion (Morelli et al., 2019), however, not all authors have confirmed this (Ozaki et al., 1988, Balke et al., 2013).

1.5.3.2 Occupational risk factors

Heavy, manual workload and repetitive shoulder movements have been associated with shoulder pain (Pribicevic, 2012, Noten et al., 2017) and prolonged durations of sustained shoulder or neck positions have also been found to be a major risk factor for RC tendon pain (Pribicevic, 2012, Noten et al., 2017). For example, dental hygienists and dentists undergo prolonged static postures, involving bilateral submaximal contractions of their muscles, with few intervals for rest (Hayes et al., 2014) and this might contribute for the high incidence of shoulder pain reported in dental professionals (Hayes et al., 2014). Previous research on samples of overhead athletes such as baseball players, as well as symptomatic and asymptomatic populations, has shown that repetitive loading increases tendon thickness (Malanga et al., 2012, Michener et al., 2015, McCreesh et al., 2017, Popchak et al., 2017, Porter et al., 2020). Repetitive loading during tasks can increase thickening of the supraspinatus tendon due to constant tendon remodelling (Wang et al., 2005). Repetitive loading causes thickness of the RC tendon (Leong et al., 2012, Malanga et al., 2012, McCreesh et al., 2017). It has been demonstrated that people with tendinopathy have thicker supraspinatus tendons, which suggests an increase in tendon dimension (Joensen et al., 2009, Michener et al., 2015). An increased thickness of the supraspinatus tendon causes the tendon to occupy a greater space of the subacromial space, which increase the likelihood of tendon compression and potentially pain (Michener et al., 2015, McCreesh et al., 2017).

In 2006, Sim et al. found that approximately 44% of manual workers experienced shoulder pain due to repetitive lifting of heavy objects and working in positions with their arms above shoulder height (Sim et al., 2006). Another cross-sectional study involving 598 workers in occupations requiring repetitive movement such as supermarket cashiers, people working in packaging and people working in the food industry, especially meet cutting, found that in 18 different companies, repetitive working with arms above shoulder level was associated with shoulder pain (Leclerc et al., 2004). A recent systematic review by Wærsted et al. (2020) focused on the association and the exposure–response relationship between work above shoulder level and shoulder pain. 34 articles were included in which 15 were cross-sectional, 16 were prospective cohort and 3 case-control. Of the 20 studies using questionnaires or interviews to assess self-reported work with elevated arms, 15 used self-report approach only, four used a diagnosis of RC syndrome, and one study used partial or total supraspinatus tendon tears (Wærsted et al., 2020). Five studies used video recording to assess work exposure, five studies used technical measures (inclinometer) to measure arm elevation >90°, and four studies assessed work with elevated arms using expert ratings. Eighteen out of the 34 included studies presented a possible exposure–response relationship, with an increasing exposure to arm elevation associated with an increased reporting of shoulder pain and disorders.

The findings demonstrated that, compared to studies with lower effect estimates, studies with large effect estimates (OR ≥ 2) have a higher quality score, include analyses of severe arm elevation, use clinical

outcomes, and report an exposure-response relationship (Wærsted et al., 2020). There was moderate evidence for an association between severe arm elevation with elbows above shoulder level (>90°) and shoulder disorders (Wærsted et al., 2020). However, 15 of the 34 included studies were of cross-sectional design, which makes it difficult to evaluate causality. The mechanisms for the pathophysiology, relating arm elevation at work and MSK pain have been extensively explored. Multiple proposed mechanisms could be involved, including muscular fatigue (Armstrong et al., 1993, Kumar, 2001), prolonged muscle activity (Hagg, 1991, Visser and van Dieën, 2006), cumulative trauma disorder (Kumar, 2001), reduced microcirculation (Visser and van Dieën, 2006) and mechanical static or repetitive pressure on tendons (Seitz et al., 2011). Elevated shoulder, particularly between 60° and 120°, can cause pressure on the RC tendons by the undersurface of the acromion (Levitz and Iannotti, 1995).

Bodin et al. (2012a) assessed work-related risk factors on the incidence of shoulder pain in a large working population in France. Between 2002 and 2005, 3,710 workers were randomly selected from a French region to participate in a cross-sectional survey (Bodin et al., 2012a). They completed a self-administered questionnaire about MSK conditions, demographic factors, and exposure to workplace difficulties. In 2007, 2,332 people responded to a follow-up questionnaire. The analysis included 946 males and 709 females who did not have shoulder pain at baseline (Bodin et al., 2012a). At the follow-up, 11% males and 20.5% females reported shoulder pain. For males, working with arms above the

shoulder level (aOR 1.5, 95% CI 1.0 to 2.3), and high perceived physical exertion (aOR 1.6, 95% CI 1.0 to 2.5) increased the risk of shoulder pain. For females, temporary employment (a OR 2.1, 95% CI 1.1 to 3.7), high perceived physical exertion (aOR 2.2, 95% CI 1.4 to 3.5), and low decision latitude (the extent to which someone is allowed to make decision independently) (aOR 1.6, 95% CI 1.0 to 2.3) were risk factors for incident shoulder pain (Bodin et al., 2012a). This study demonstrated that beside physical exertion and working with arm above shoulder height , psychosocial factors can also be involved in shoulder pain. However, some methodological issues in this study need to be considered. The shoulder pain was defined as pain occurring during the preceding seven days (Bodin et al., 2012b). For the group without shoulder pain at baseline, workers with shoulder pain for more than eight days during the preceding 12 months were excluded, which could narrow the inclusion criteria and might omit people with shoulder pain at baseline. In summary, mechanical and psychosocial risk factors need to be a key focus for shoulder pain prevention strategies in the workplace.

The prevalence of shoulder pain is expected to increase due to several reasons such as ageing, work load, lifestyle and the long-term use of computer and phone (Djade et al., 2020). Therefore, it is important to identify the modifiable risk factors that might contribute to shoulder pain in order to prevent its development and reduce healthcare costs. There is little information about determinants of shoulder pain in the existing literature. A recent systematic review conducted by da Costa and Vieira (2010), found only three studies that focused on shoulder pain, and these

only explored occupational risk factors and did not include personal risk factors and the older population. The majority of studies that have explored risk factors for shoulder pain have been cross-sectional so could not examine temporal associations between potential risk factors and the incidence of shoulder pain (Luime et al., 2004, Djade et al., 2020). A systematic review by Luime et al. (2004), investigated the incidence and prevalence of shoulder pain in the general population. They found that of 18 studies identified, only one provided information about incidence of shoulder pain, the others reporting on prevalence alone (Luime et al., 2004). The incidence of shoulder pain increased with ageing, from 0.9 for those aged 31-35 to 2.5% for those aged 70-74. Prevalence differed from 6.9 to 26% for point prevalence, 18.6-31% for 1- month prevalence, 4.7-46.7 for 1 year prevalence (Luime et al., 2004). However, this study did not investigate the risk factors associated with shoulder pain.

Recently, Djade et al. (2020) conducted a systematic review to review cohort studies that studied the incidence of shoulder pain in people aged ≥ 40 and to explore the associated risk factors. Of the six studies included, five were prospective cohort studies and one was retrospective (Djade et al., 2020). The overall annual incidence of shoulder pain in this review was 2.4%. Of the six studies, only two explored both occupational and non-occupational risk factors (Djade et al., 2020) and these reported that psychosocial stressors, repetitive manual work and awkward positions were associated with the incidence of shoulder pain. One study found that sleeping problems also were linked to shoulder pain. This systematic review has some limitations as there were few longitudinal

studies that estimated the incidence and the potential risk factors of shoulder pain for people aged ≥ 40. Also, the definition of shoulder pain was heterogenous in all the included studies, which might affect the results and make it difficult to draw specific conclusions (Djade et al., 2020).

1.6 Comorbidities

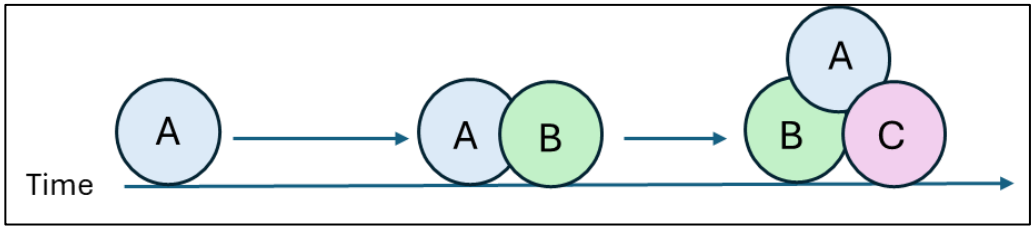
Comorbidity is defined as the co-existence of another medical condition during the clinical course of a patient who has the index disease under study (Feinstein, 1970). Comorbidity is important to consider when estimating patient outcomes, because death or hospitalisation may be due to a comorbidity rather than the index disease alone (Valderas et al., 2009). Comorbidity can alter the clinical course of people with the same diagnosis by affecting the time of detection, prognosis, management plan, and post-management outcome of the index disease (Feinstein, 1970).

1.6.1 Types of comorbidities

1.6.1.1 Primary versus Secondary

Based on chronological sequence and causal inference, Feinstein proposed that comorbidities can be classified as primary or secondary (Feinstein, 1970). Chronological comorbidity (Figure 1.11) is time dependent and develops in sequence. For example, if an individual with chronic condition A develops condition B later in life and then condition C even later in life, there could be a linkage between the three conditions. In this case, B is the primary comorbidity of A and C is the secondary

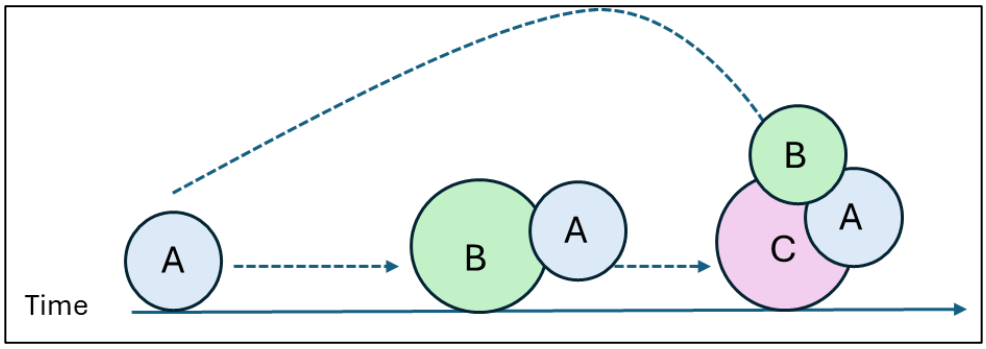
comorbidity of A, but C can also be the primary comorbidity of B (Feinstein, 1970).



Reproduced with permission from Subhashisa Swain (2020)

Figure 1.11 Chronological comorbidity model.

In causal inference, condition B developed later than A but occurs because of A. Similarly, C can develop later in life which is caused by A or B or both. The causal linkage could be because of the disease; the side effect of drugs used for one condition or other factors. (Figure 1.12)



Reproduced with permission from Subhashisa Swain (2020)

Figure 1.12 Causal inference comorbidity model.

1.6.1.2 Concordant and discordant comorbidity (Piette and Kerr, 2006)

Concordant comorbidities share characteristics of the same overall pathophysiologic risk profile. For example, metabolic syndrome is a

cluster of conditions that include hypertension, high blood sugar, excess body fat around the waist, abnormal cholesterol or triglyceride levels, and hyperuricaemia that occur together and increase the risk of heart disease, stroke and type 2 diabetes. On the other hand, discordant comorbidities are those that are not directly related in either their pathogenesis or management and do not share an underlying predisposing factor for example diabetes and irritable bowel syndrome (Piette and Kerr, 2006).

1.6.2 Musculoskeletal conditions and comorbidities

The existence of additional comorbidities may increase disease severity and increase demand on healthcare services and require more complex management guidelines. The majority of comorbidity patterns have a direct association with advanced age and are strongly associated with poor health outcomes such as frequent healthcare utilization, limitation in functional status, poor quality of life, and higher mortality (Menotti et al., 2001, Loza et al., 2009, Nikiphorou et al., 2020, Muckelt et al., 2020) . Hudon et al. (2008) reported that among patients with chronic MSK conditions (58%), the number of comorbidities ranged from 0 to 11, and the average was four comorbidities, especially hypertension, urinary diseases, cardiovascular disease and stomach ulcer. Approximately, 49% of patients had hypertension, 31% had urinary disease, 31% had cardiovascular disease, and 17% had stomach ulcers (Hudon et al., 2008). Around 70% of patients with chronic MSK conditions had at least one of the four comorbidities reported above (Hudon et al., 2008). Swain et al. (2021) determined the burden of 49 comorbidities in people with OA

in the UK. A combined case-control and cohort study was conducted using the Clinical Practice Research Datalink (CPRD, GOLD) database (Swain et al., 2021). Results showed that 38 comorbidities were associated with OA both prior to and following the diagnosis of OA (Swain et al., 2021). People with OA were at greater risk of developing heart failure (adjusted hazard ratio aHR 1.63, 95% CI 1.56 to 1.71), dementia (aHR 1.62, 95% CI 1.56 to 1.68), liver diseases (aHR 1.51, 95% CI 1.37 to 1.67), gastrointestinal bleeding (aHR 1.49, 95% CI 1.39 to 1.59), and irritable bowel syndrome (aHR 1.51, 95% CI 1.45 to 1.58) (Swain et al., 2021). These comorbidities might be mediated through drug use for OA, for example oral NSAIDS, systemic inflammation associated with joint damage, or shared risk factors (e.g., ageing, high BMI) or be explained by other comorbidities in people with OA (Muckelt et al., 2020, Swain et al., 2021).

1.6.3 Chronic shoulder pain and comorbidities

Few studies have examined the association between shoulder complaints and comorbidities, such as diabetes, lung problems, cardiovascular conditions, depression and other MSK conditions (Vogt et al., 2003, Luime et al., 2004, Wright et al., 2015) and very few have been carried out in the UK. Based on existing evidence, there was only one cohort study in the United States that reported associations between neck and shoulder pain and cardiovascular diseases, arthritis and neurological conditions in the older population (70 to 79 years old) (Vogt et al., 2003). In Finland, shoulder pain was found to be associated with low back pain and OA of

the knee, hip and hand in people aged 30 and older (Mäkelä et al., 1999). As far as is known, only one case-control study in the UK examined the comorbidities associated with RC tendinopathy using the THIN database (Titchener et al., 2014). That study identified a number of comorbidities and risk factors for RC tendinopathy. The study included 5000 patients with RC tendinopathy who were matched with a single control by age, sex, and practice (Titchener et al., 2014). Multivariate analysis showed that the comorbidities associated with RC tendinopathy were Achilles tendinitis (OR 1.78), trigger finger (OR 1.99), lateral epicondylitis (OR 1.71) and carpal tunnel syndrome (OR 1.55), and that oral corticosteroid therapy (OR 2.03) was a further association, whereas medial epicondylitis, cubital tunnel syndrome, de Quervain syndrome, and rheumatoid arthritis were not found to be associated with RC tendinopathy. However, the list of comorbidities examined in this study might be limited. An additional limitation of this study was the level of missing data and the exclusion of any individuals with missing values in the analysis, which might have introduced some bias into the result (Titchener et al., 2014).

1.6.3.1 Chronic shoulder pain and diabetes

Diabetes has been associated with several MSK conditions such as adhesive capsulitis, periarthritis of the shoulder, shoulder calcific tendinopathy, and flexor tenosynovitis (Cole et al., 2009, Shah et al., 2015, Su et al., 2021). Several studies have reported a higher prevalence of shoulder pain in people with diabetes with a prevalence ranging from 11% to 35% compared to 2% to 17% in people without diabetes (Cagliero

et al., 2002, Thomas et al., 2007, Laslett et al., 2007, Cole et al., 2009, Gill et al., 2013). These findings might be due to the relationship between poor glycaemic control or chronic hyperglycaemia and increased risk of developing microvascular complications around the shoulder joint and synovium in people with diabetes. Decreased circulation around the shoulder joint causes tissue hypoxia and overproduction of free radicals, which may result in apoptosis. This might lead to enhancement of degenerative changes and joint tissue damage (Hsu and Sheu, 2016). Most of this evidence has shown an association between MSK pain and diabetes, but the strength of this association is still debatable. Cole et al. (2009) conducted a cohort study to assess the relationship between shoulder pain and diabetes. Approximately 3128 patients were evaluated for diabetes and shoulder complaints through questionnaires, self-reported shoulder pain and disability index (SPADI), physical examination and blood samples. Of the 3128 participants included in the study, 21.8% complained of shoulder pain and 221 (7.1%) had diabetes (Cole et al., 2009). Participants with diabetes had a higher prevalence of shoulder pain (27.9% vs 21.3%; p-value = 0.025) and poorer total SPADI score (p-value = 0.02) (Cole et al., 2009). However, this association was no longer apparent when the data were adjusted for obesity. The definition of shoulder pain in this study was narrow as people with short-term muscle or ligament pain were excluded, which might have led to an underestimation of the prevalence of shoulder pain and thus reduced the probability of finding an association between shoulder pain and diabetes.

Recently, a population-based matched cohort study investigated the risk of calcific tendinopathy of the shoulder in people with diabetes in Taiwan (Su et al., 2021). A total of 42,915 people with diabetes (type 1and type 2) and 171,660 matched people without diabetes were included in this study (Su et al., 2021). A total of 122 (0.284%) of people with diabetes, and 340 (0.198%) of people in the non-diabetic group developed shoulder calcific tendinopathy. They found that people with diabetes had a 27% increased risk of developing shoulder calcific tendinopathy after eight years of follow-up. Several theories have been proposed about the pathologic mechanism of shoulder calcific tendinopathy, including ageing-related degeneration, repetitive injury, reactive calcification, ischaemic degeneration, and tenocyte necrosis (Rathbun and Macnab, 1970, Brewer, 1979, Uhthoff and Loehr, 1997, Sansone et al., 2018). In people with poorly controlled diabetes, angiopathy is one of the most common long-term complications, which may result in nephropathy, retinopathy, peripheral neuropathy, and atherosclerosis (Xu et al., 2012). Diabetes-related impaired vascularity may lead to a reduction in the amount of oxygen and nutrients supplied to connective tissues, which can lead to degeneration and slow tendon wound healing, all of which may facilitate ectopic calcific deposition (Rathbun and Macnab, 1970). Additionally, various extracellular proteins may become glycosylated when connective tissue is exposed to high blood sugar levels. This can alter the biomechanical environment and accelerate ectopic calcification of the connective tissue (Rathbun and Macnab, 1970, Su et al., 2021). A recent matched cohort study in UK was conducted to determine if frozen

shoulder diagnosis is associated with a subsequent type 2 diabetes diagnosis using primary care electronic medical records (CPRD GOLD) (Dyer et al., 2024). The study included 31, 226 people with frozen shoulders matched with 31, 226 people without frozen shoulder. They found that people with frozen shoulder were more likely to be diagnosed with type 2 diabetes than people without frozen shoulder (HR 19.4, 95% CI 15.6 to 24.0). After adjusting for other factors such as hyperlipidaemia, hypertension, BMI, thyroid dysfunction, ethnicity, deprivation, sex, and age, the results were approximately similar (aHR 20.0, 95% CI 16.0 to 25.0) (Dyer et al., 2024). The findings of this study suggest people presenting with frozen shoulder should be considered for risk assessment and testing for diabetes. However, it is crucial to state that this study do not support the theory that type 2 diabetes is caused by frozen shoulder (Hernán et al., 2019, Losciale et al., 2023). On the contrary, type 2 diabetes has been proposed as a cause of frozen shoulder (Hsu and Sheu, 2016, Dyer et al., 2023), which may explain why it is more common in people with frozen shoulder.

1.6.3.2 Chronic shoulder pain and respiratory diseases

The association between respiratory function and posture is widely recognised due to their close relationship in anatomy and physiology (Cala et al., 1992, Rasmussen-Barr et al., 2023). Because of these factors, people with respiratory distress adopt positions that help the respiratory muscles work more easily. The diaphragm and other breathing muscles are suggested to play a major role in postural control (Hodges

and Gandevia, 2000). Furthermore, hyperventilation is a problem that affects the breathing muscles and as a result it affects the neck, shoulder, and thoracic region in people suffering from asthma (Lunardi et al., 2011, Shei et al., 2016). The respiratory muscles are used more frequently during an asthma attack to maintain sufficient ventilation in daily activities. An association between the head position and shoulder posture with peak expiratory flow rate has been observed in people with asthma (Robles-Ribeiro et al., 2005). Robles-Ribeiro et al. (2005) reported that people with asthma often presented with forward flexion of the shoulder compared to healthy people, adopting an adaptive posture to overcome respiratory overload.

Shoulder, and neck pain and respiratory distress have been investigated in the literature, with a particular emphasis on neck pain. Recently, a study of a general population cohort in Sweden investigated the relationship between respiratory disorders and neck and shoulder pain (Rasmussen-Barr et al., 2023). Adults who at baseline reported no or only occasional neck/shoulder pain in the last six months were included from two subsamples from the Stockholm Public Health Cohort (SPHC), one subsample (n=15,155) being used to examine if having asthma at baseline was a risk factor, and the other subsample (n=25,273) being used to examine if having chronic obstructive pulmonary disease (COPD) at baseline was a risk factor. Adjusted results showed that those reporting asthma at baseline had a higher risk of neck/shoulder pain at follow-up four years later (RR 1.48, 95% CI 1.10 to 2.01) as did those with COPD at

baseline (RR 2.12 95% CI 1.54 to 2.93) (Rasmussen-Barr et al., 2023). However, the case definition for shoulder pain in this study was not clear.

1.6.3.3 Chronic shoulder pain and psychological status

Psychological stress can increase muscle activity and tension, which can increase shoulder pain (Lundberg et al., 1994, Lundberg et al., 1999). However, the relationship between shoulder pain and psychological status is potentially bidirectional. Psychological factors including depression and anxiety may influence shoulder pain intensity, and conversely, shoulder pain may affect psychological status (Ortego et al., 2016, Martinez-Calderon et al., 2018). A prospective study in Korea examined the relationship between depression and CSP (Roh et al., 2012). 109 people with CSP were evaluated using the disability of arm, shoulder, and hand (DASH) questionnaire, VAS and the Centre for Epidemiologic Studies-Depression (CES-D) Scale. Higher pain scores and greater disability were significantly associated with depressive symptoms in people with CSP (Roh et al., 2012). Although this study highlighted that the severity of depressive symptoms is significantly associated with shoulder pain and disability, the assessment of depression was limited to the CES-D Scale, and more extensive assessment including coping and illness behaviour would have been more valuable. Another study has found that psychological disorders such as depression and anxiety were associated with adhesive capsulitis, and that people with psychological disorders had more self-reported shoulder pain and functional limitations in daily activities (Ding et al., 2014). This is consistent with other research findings

that showed that restricted shoulder movement, CSP or night shoulder pain have a detrimental impact on psychological status (Miranda et al., 2005, Scarlat and Florescu, 2005, Novati et al., 2008).

1.6.3.4 Chronic shoulder pain and thyroid diseases

Evidence for an association between shoulder pain and thyroid disease is inconclusive, and there is a paucity of evidence on the underlying possible mechanisms for such an association. A recent case-control study found that people with thyroid disorders, especially hypothyroidism, are at greater risk of having shoulder complaints and have 2.69 times the risk of developing adhesive capsulitis (Cohen et al., 2020). Chuang et al (2023) conducted a systematic review and meta-analysis to investigate the association of adhesive capsulitis with thyroid disease in comparative studies. They included 10 case-control studies comprising a total of 127,967 participants. The prevalence of thyroid disorders was significantly higher in people with adhesive capsulitis (OR 1.87, 95% CI 1.37 to 2.57) than in those without adhesive capsulitis (Chuang et al., 2023), but no association between thyroid disease and other shoulder problems was identified.

Some authors have proposed that the relationship between adhesive capsulitis and Hashimoto's thyroiditis, which is the most common cause of hypothyroidism, has an autoimmune aetiology (Cakir et al., 2003, Reuters et al., 2009, Wang et al., 2013, Schiefer et al., 2017). Based on several hypothesis, adhesive capsulitis is characterised by inflammation of the synovium with a thickened and stiffened joint capsule (Wiley, 1991).

Histological results in people with adhesive capsulitis have shown increased extracellular matrix and fibroblast proliferation, an increase in the release of cytokines, including platelet-derived growth factor, interleukin, tumour necrosis factor, and transforming growth factor (Rodeo et al., 1997, Jump et al., 2021). Based on this hypothesis, the underlying mechanism of the association between thyroid disease and adhesive capsulitis has been examined in previous studies. Evidence proposed that some comorbidities such as diabetes, Dupuytren contracture, hyperlipidaemia, and thyroid dysfunction may predispose a person to a proinflammatory environment, resulting in an increased inflammatory response with elevated levels of inflammatory cytokines and tendency to fibrosis, and elevated blood lipids (Bunker and Anthony, 1995, Bunker and Esler, 1995, Rizos et al., 2011). Huang et al (2013) suggested that thyroid ophthalmopathy and adhesive capsulitis are caused by cytokine and fibroblast proliferation (Huang et al., 2013). Nevertheless, it is still challenging to identify the underlying mechanism of the association between thyroid disorders and adhesive capsulitis.

1.6.3.5 Chronic shoulder pain and Parkinson's disease

There are several studies in the literature that have explored shoulder problems in people with Parkinson's disease (Stamey et al., 2008, Madden and Hall, 2010, Kim and Jeon, 2013). People with Parkinson's disease frequently presents with rigidity, bradykinesia, and resting tremor (Fukunaga et al., 2014). Additionally, they have severe impairment of posture, characterised by decreased trunk mobility on all planes,

increased thoracic kyphosis and rounded shoulder (Fukunaga et al., 2014). More sever postural changes can occur during advanced phases of the disease progression. As discussed previously in the shoulder biomechanics section, the shoulder's kinematics involves the combined movement of the humerus, scapula, clavicle, thoracic wall and thoracic spine, therefore, decreased trunk mobility can results in impingement syndrome and capsulitis, which can cause inflammation of the bursa shoulder pain and decreased shoulder mobility (Papalia et al., 2019). Recently, Gadgaard et al. (2024) conducted a cohort study to examine the risk of incident Parkinson's disease following a first-time diagnosis of frozen shoulder using nationwide data from Danish population-based healthcare registry. The study identified 37,041 people with frozen shoulder, 370,410 general population comparators, and 111,101 people with back pain comparators. They found that people with frozen shoulder had an increased risk of Parkinson's disease compared with the general population (aHR 1.94, 95% CI 1.20 to 3.13) at 0–1 year and (aHR of 1.45, 95% CI 1.24 to 1.70) at 0–22 years follow-up (Gadgaard et al., 2024). However, the mechanism of this association is not clear. Several hypothesis have been proposed, Parkinson's disease appears to be a plausible cause of severe immobility around the joint due to akinesia and a logical trigger for the onset of frozen shoulder (Riley et al., 1989).

Another hypothesis suggests that that both frozen shoulder and back pain, and some other MSK conditions, are early symptoms of Parkinson's disease and therefore increase the risk of clinical Parkinson's disease diagnosis (Gadgaard et al., 2024). Furthermore, the frozen shoulder

cohort had a higher frequency of comorbidities compared to the general population cohort. Patients seen at the hospital with frozen shoulders or any of their comorbidities may have other early Parkinson's disease-related symptoms (Gadgaard et al., 2024). Therefore, the reported increased risk of Parkinson's disease in patients with frozen shoulder compared with the general population might be explained by a higher chance of early diagnosis rather than a higher risk of developing the disease (Gadgaard et al., 2024). However, this study has some limitations. The study was restricted to inpatient and outpatient hospital diagnoses of Parkinson’s disease, frozen shoulder, and back pain. However, people with mild symptoms of back pain and frozen shoulder might have received diagnoses and treatment in primary care, and therefore not been reported in the Danish medical registries. Additionally, people with mild symptoms of Parkinson’s disease diagnosis might have been misdiagnosed initially, and therefore wrongly classified.

1.6.3.6 Chronic shoulder pain and dementia

Several studies have supported the association between pain, cognitive decline, and dementia (Kao et al., 2021, Rouch et al., 2021, Zhao et al., 2023). Suggested potential mechanisms underlying the association between pain and dementia include inflammation, neuropathological changes (Cao et al., 2019), and changes in the brain function and structures (Tu et al., 2021, Tagliaferri et al., 2022). Tagliaferri et al. (2022) found that people with chronic back pain had higher caudate gray matter volume, lower primary motor and somatosensory grey matter volume

compared with pain-free group. In addition, CWP group had higher caudate gray matter volume, lower amygdala and primary somatosensory cortex gray matter volumes compared to pain-free group (Tagliaferri et al., 2022). These findings demonstrate progressive adaptation of brain structure with increasing pain. However, whether shoulder pain is associated with dementia risk remains unclear, and very few studies have examined this.

A recent cross-sectional study assessed cognitive function and shoulder joint range of motion in 234 participants at 7 memory clinics in Japan (Honjo et al., 2024). The participants were divided into 4 groups based on their diagnosis: Alzheimer's disease dementia, dementia with Lewy bodies (DLB), other dementia and control group (people without dementia). They found that restricted shoulder range of motion was associated with dementia scores, nighttime disturbances scores, hallucinations and irritability (Honjo et al., 2024). Furthermore, dementia groups, particularly DLB, had more restricted shoulder joint range of motion (shoulder range of motion mean and standard deviation (SD) 44±9.3) compared to the control group (shoulder range of motion mean and SD 53.7± 4.5) (Honjo et al., 2024). Hallucinations and sleep disturbance were significantly related to shoulder joint range of motion (parameter estimate −1.71, 95% CI −2.83 to −0.59, p-value= 0.01) (Honjo et al., 2024). One possible explanation for this might be because hallucinations often occur at night, patients may experience drowsiness during the day, which leads to reduced physical activity, and could lead to restricted shoulder movement. However, the mechanism of this relationship is still not clear and more

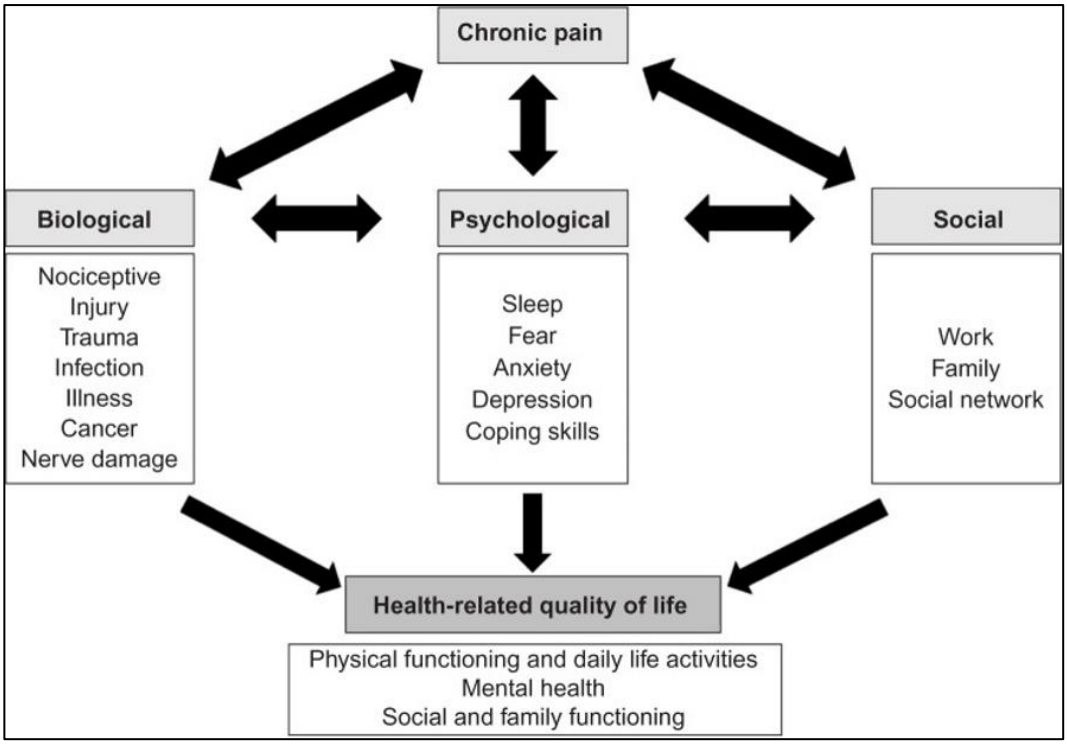
longitudinal research is needed. Similarly, Zheng et al. (2024) investigated the association between MSK pain and dementia risk in 10,759 people aged 45 years old and above in China using cross-sectional and longitudinal analysis. The Rotterdam Study Basic Dementia Risk Model (BDRM) was used to evaluate dementia risk (Zheng et al., 2024). This study revealed that people with persistent shoulder pain had higher risk of dementia during four years of follow-up (β 1.74, 95% CI 0.46 to 3.02, p-value= 0.008) (Zheng et al., 2024). However, this study has some limitations to consider. The BDRM used in this study has been validated in the general population (Licher et al., 2019), however, it was not validated in people with chronic pain. Therefore, it is not clear whether the BDRM can accurately predict dementia in people with chronic pain. Additionally, the BDRM score is a "risk score" and may not accurately assess dementia risk, which requires further investigation.

However, some studies did not find association between pain and dementia and cognitive function, indicating that pain might be an earlier symptom of dementia rather than being a cause of dementia (Ezzati et al., 2019, Kumaradev et al., 2021). Inconsistencies between studies may arise due to differences in study population, study design, definition of dementia, duration and intensity of pain, confounding factors, and outcome measurement. In summary, further exploration is needed to understand the relationship between shoulder pain and the risk of developing dementia.

The previous studies pointed out the importance of taking comorbidities into consideration in the diagnosis and management of CSP. Because most studies available in the literature are cross-sectional, there might be a lack of information available on whether people with shoulder pain are more likely to develop other long-term health conditions. As far as is known, no studies have been carried out in the UK to explore the possible association between CSP and comorbidities other than diabetes.

1.7 The impact of chronic shoulder pain

Chronic pain is considered to be a major health problem and has a detrimental effect on a person's physical health, psychological health, and quality of life. The biopsychosocial model demonstrates the role that social and psychological factors have in the development of biological disease and chronic pain. In the light of this framework, it has been shown that chronic pain is associated with other mechanisms that, in turn, affect pain significantly (Figure 1.13). CSP can negatively affect the patient, their social life and the healthcare system. This section will discuss several aspects of how chronic pain influences the patient's daily activities and quality of life, as well as its impact in the workplace, and on social life. Finally, the financial burden of CSP on the healthcare system is discussed.



The figure was reproduced with permission (Dueñas et al., 2016)

Figure 1.13 Biopsychosocial model of pain and consequences on quality of life.

1.7.1 The effect of chronic shoulder pain on the person

Several studies have investigated how chronic pain affects a person's life and have drawn attention to the substantial association between chronic pain and reduced physical activity (Lerman et al., 2015, Dueñas et al., 2016). CSP can affect individuals in terms of physical activity, quality of life, increased disability, and psychological distress. The severity, duration, and site of the pain have been found to have a detrimental impact on a patient's ability to perform physical activities and even to lead to disability, which in turn has an impact on other aspects of their daily life (Jones et al., 2008).

Badcock et al. (2002) investigated in the general community the impact of CSP on psychological status over time and how restriction of daily

activities affected pain perception and psychological health. Two postal questionnaires were sent to identify a group of people with CSP. The first questionnaire was sent to a random sample of people (n=40026) who were registered with a primary care practice (Badcock et al., 2002). It included a pain manikin, demographic questions, and the Hospital Anxiety and Depression scale (HAD) (Badcock et al., 2002). The second questionnaire was sent two years later to those people who reported unilateral shoulder pain in the first questionnaire and it included a shoulder-specific disability scale, the HAD and pain severity score (Badcock et al., 2002). Follow-up findings showed that shoulder pain was associated with significant disability in 50% of the people with CSP. In addition, both the disability score and psychological distress scores were found to be correlated significantly with pain severity (disability vs pain $r = 0.536$, $p< 0.001$; psychological distress vs pain $r = 0.269$, p-value = 0.002). Disability was significantly correlated with psychological distress on univariate ($r = 0.445$, $p< 0.001$) and multivariate analysis ($r= 0.341$, p-value = 0.002) (Badcock et al., 2002). This study highlights the importance of measuring person-specific disability rather than pain severity alone in people with CSP in order to determine its severity.

Similarly, Hill et al. (2010) measured the impact of shoulder pain on physical function, range of movement and quality of life. Overall, 3,206 participants were included, and were asked to report whether they had pain, or stiffness in their shoulders (Hill et al., 2010). Data were collected on BMI, shoulder range of motion, lifestyle and socioeconomic status. Participants were asked to complete the shoulder pain and disability

index, the short form 36 (SF36), and the centre for epidemiologic studies depression scale. Results showed that 22.3% (776) of participants reported pain, aching or stiffness in either of their shoulders and participants with shoulder symptoms had significantly worse shoulder range of motion, compared to those without symptoms. These differences ranged from 10.4 degrees of flexion, 13.7–16 degrees of abduction and 3 – 4.5 degrees of external rotation. In those with shoulder symptoms, females had more pain and worse shoulder function than males, and older people had worse shoulder function than younger people. Participants with shoulder pain scored lower on all domains of the SF36 (Hill et al., 2010). Moreover, participants with shoulder pain were significantly more likely to report depressive symptoms (OR 2.81, 95% CI 2.23 to 3.55). However, this study was limited by its cross-sectional design, which does not allow determination of causality. Additionally, although they measured range of motion there was a lack of information about the specific shoulder diagnosis in participants.

1.7.2 Impact of chronic shoulder pain on work and social life

Chronic pain can have a major impact on work performance including increased sick leave, inability to perform work, changing occupation, and job loss (Blyth et al., 2003, Breivik et al., 2006, Patel et al., 2012, Azevedo et al., 2012). In Sweden, an 11-year prospective cohort study identified the factors that predict disability among young people on sick leave due to neck or shoulder or back diagnoses. 213 participants were recruited from a large database of all new sick-leave spells > 7 days in the county of

Ostergotland in 1985 (Borg et al., 2001). They found that low back pain and neck–shoulder disorders were considered to be the most common complaint to cause sick leave and early retirement in people aged between 25 to 35 years old (Borg et al., 2001). In addition to sick leave and chronic disability, shoulder complaints also led to reduced productivity at work. Functional limitations led workers to be less productive despite the fact they were present at work (Aronsson et al., 2000).

Van den Heuvel (2007) conducted a cross-sectional study to determine the degree of productivity loss among 654 computer workers with neck/shoulder and arm/hand symptoms in the Netherlands, and to investigate the relationship between pain severity, physical and psychosocial factors and productivity loss in this population (van den Heuvel et al., 2007). Productivity loss had two components: sick leave and decreased performance at work. Decreased performance at work was defined as decreased speed or decrease in working hours. Data were obtained from the baseline measurement of the PROMO-study (Prospective Research On MSK conditions in Office Workers) (Ijmker et al., 2006). In the study by Van den Heuvel et al. (2007), the analyses of associations between several factors such as pain intensity, and psychosocial factors and productivity at work were limited to workers who had reported work-related neck/shoulder and arm/hand symptoms in the previous three months, which included 654 computer workers. They found that of the total population, approximately 10% reported neck/shoulder and arm/hand symptoms. Productivity loss occurred in 26% of workers reporting symptoms, most often in workers reporting both neck/shoulder

and arm/hand symptoms (36%). Approximately, 32% of all workers reported sick leave (van den Heuvel et al., 2007). Productivity loss involved absence from work in 11% of workers with arm/hand symptoms, 32% of workers with neck/shoulder symptoms and 43% of workers reporting both symptoms (van den Heuvel et al., 2007). Productivity loss among computer workers was significantly associated with pain intensity (OR 1.26, 95% CI 1.12 to 1.41), high effort with adequate reward (OR 2.26, 95% CI 1.24 to 4.12), and low job satisfaction (OR 3.10, 95% CI 1.44 to 6.67) (van den Heuvel et al., 2007).

Similarly, Martimo (2009) assessed self-reported productivity loss at work among people with upper limb disorders in Finland. 168 subjects participated in the study from different occupations such as nurses, other healthcare professions, office workers, and warehouse workers (Martimo et al., 2009). The majority of participants were female (87%), and the mean age was 45.3 years. The results showed that 27% of the 168 participants reported high job strain, and 37% reported absence from work due to upper limb disorders in the previous year. The prevalence of specific shoulder disorders was 28%. Approximately 56% reported productivity loss (Martimo et al., 2009). Logistic regression analysis revealed that productivity loss was significantly associated with pain intensity (OR 2.8, 95% CI 1.2 to 6.5), and pain interference with work (OR 5.7, 95% CI 2.2 to14.3) (Martimo et al., 2009). However, both these studies were cross-sectional in design, and the causality between pain severity and productivity loss needs to be examined by longitudinal studies. Additionally, in the study by Van den Huevel et al., the

productivity loss was measured using self-reported measures and it is very hard for workers to estimate the magnitude of their productivity loss, and in the absence of any objective measurement to evaluate employee performance, the validity of findings is open to question.

1.7.3 The consequences of chronic shoulder pain on the healthcare system

The consequences of pain on the healthcare system are considered to be a substantial issue. The total treatment cost of shoulder pain is rising at a rate of 13% annually (Oh et al., 2021). In 1995, MSK conditions accounted for 10 million sick leave days in the UK, of which 4 million (42%) were due to upper limb complaints (Jones, 1998). A study conducted in Sweden reported the cost associated with shoulder pain as €4139 per patient per year, with sick leave accounting for more than 80% of the cost (Virta et al., 2012). Annually, there are approximately 1.5 million shoulder consultations in the UK and the annual total cost of consultations has been estimated to be £100 million (van der Windt et al., 2019).

CSP has a variable prognosis and is predominantly managed in primary care (Artus et al., 2017). In primary care, first-line CSP management usually includes medications and physiotherapy. Shoulder pain conditions account for approximately 2.4 of all consultations in UK primary care (Linsell et al., 2006) and 4.5 million visits to the GPs annually in the USA (Oh et al., 2007). In the UK, from 2000 to 2003 around 22 % of patients with shoulder pain were referred to secondary care, 31% were prescribed NSAIDs and 11% were managed by local injections by their GP (Linsell et al., 2006). The annual cost of shoulder pain management in the USA has

been estimated to be $3 billion (van der Windt et al., 1996). If patients do not improve with these conservative approaches, surgery such as RC repair and shoulder arthroplasty might be considered which could become a significant financial burden for both patients and the healthcare system. Approximately 300,000 RC repairs are performed annually in the United States (US) (Aurora et al., 2007, Wolf et al., 2011). Between 2000 and 2010, a total of 101,254 patients underwent subacromial decompression in the UK (Judge et al., 2014). Of these, 50% (n = 51,177) were females, and 49.5% (n = 50,077) were males. There was a significant increase in RC surgical repair in 2008/2009 (4.7 /100,000 (95% CI 4.5 to 4.8)), which was followed by a considerable decline in 2009/2010 (2.6 / 100,000 (95% CI 2.5 to 2.7)) (Judge et al., 2014). This decline might be explained by the beginning of the UK RC (UKUFF) multicentre randomised controlled trial (Judge et al., 2014). In conclusion, CSP has a major impact including substantial economic costs, increased demands on healthcare resources, and significant effects on an affected individual's health and quality of life.

1.8 Administrative medical databases and research

Medical databases are large repositories that provide substantial information about real-life patient data, hospitalisation, and consultation records. These databases provide a large amount of information for various purposes including epidemiological research (Baron and Weiderpass, 2000, Gavrielov-Yusim and Friger, 2014). The use of administrative medical databases in research has several advantages including the large sample size and inexpensive access to the data (Baron and Weiderpass, 2000). Linkage of several databases such as the Death

Registration Data and Pregnancy Register can enrich the dataset and overcome limitations of data availability (Baron and Weiderpass, 2000, Wolf et al., 2019). Since the data are collected over time, longitudinal follow up of patients is feasible. However, these databases have some limitations, such as information bias, coding inaccuracies and limitations in external validity, which should be considered in the planning stage and when interpreting the research results (Gavrielov-Yusim and Friger, 2014). Additionally, there are methodological concerns in database research including chance associations, confounding, and selection bias (Baron and Weiderpass, 2000). Appropriate training in epidemiological and statistical methodology, along with knowledge of each specific database and their coding systems, is vital to enhance the advantages of databases and reduce potential problems.

1.8.1 The Clinical Practice Research Datalink

The CPRD is a routinely collected nation-wide primary care database in the UK (Herrett et al., 2015, Wolf et al., 2019). CPRD was established in London in 1987 and was named as the small Value-Added Medical Products (VAMP) dataset based on general practices with VISION clinical system. Later in 1993, it grew to become the General Practice Research Database (GPRD), and in 2012 was renamed as the CPRD. The CPRD routinely collects anonymised electronic health record data from general practices to provide data monthly (Herrett et al., 2015). In 2018, CPRD launched a new data resource called CPRD Aurum (Wolf et al., 2019, Persson et al., 2020) which contains data contributed by general practices

that use EMIS health (previously Egton Medical information system) software systems. The CPRD contains data including demographics, symptoms, diagnoses, referrals, immunisations, tests and results (Herrett et al., 2015). Approximately 20 million patients from 738 practices were included in the CPRD database at the year 2018 (Herrett et al., 2015, Wolf et al., 2019, Persson et al., 2020). In 2023, around 67 million patients from 1,720 practices were included (Clinical Practice Research Datalink, 2023).

1.8.1.1 Structure of the CPRD Aurum

The CPRD Aurum collects data broadly including two categories, namely practice data and patient data. In practice data, the geographical regions are recorded according to the 10 regions in the UK from England and Northern Ireland (Wolf et al., 2019).The contents of the CPRD are divided into *registration data*, which records demographics of patients, staff and practices, and *clinical data*, which records clinical information on consultations, observations (medical history, and diagnosis), referrals, problems, and drugs (Wolf et al., 2019). Descriptions of the CPRD Aurum structure are provided in Table 1-3

Table 1-3 Contents of data files in the CPRD

Data files	Contents
Registration files	
Patient	Patient demographics and patient registration details.
Practice	The practice identifier, practice region, and the last collection date.
Staff	Practice staff details for each staff member, job category.
Clinical data files	
Consultation	Information relating to the type of consultation as entered by the GP (e.g., telephone, home visit, practice visit).
Observation	The medical history data entered on the GP system including symptoms, clinical measurements such as blood pressure, height, and weight, laboratory test results, and diagnoses.
Referral	Referral details recorded on the GP system
Problems	Details of the patient's medical history that have been defined by the GP as a 'problem'
Drugs	Details of all prescriptions on the GP system

Abbreviations: GP, general practitioners

1.8.1.2 External linkages

The CPRD provides linkages to other databases including the Hospital Episode Statistics (HES), Cancer Registry, mother-baby link, socioeconomic status data and Office for National Statistics (ONS) mortality data, which greatly extends the scope for research (Wolf et al., 2019). However, ONS mortality data and HES are only available for practices within England. The CPRD also includes small area-level linkages on practice or patients. These linkages contains residence postcodes, and several measures of area-level deprivation (Index of Multiple Deprivation (IMD), Townsend Index) (Wheeler, 2022), and practice-level rural–urban classification (Office for National Statistics, 2016). If needed, researchers should request these external linkages with appropriate justification, in their Independent Scientific Advisory Committee (ISAC) application.

1.8.1.3 Diagnostic codes and validation

The CPRD provides data dictionaries to identify codes in the CPRD Aurum database. The Medical Dictionary lists CPRD medical codes related to information about medical history and diagnosis and corresponds to Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT)(UK edition), Read Version 2 and local EMIS Web® codes (Wolf et al., 2019, Persson et al., 2020). Observations in CPRD Aurum are coded using medical codes (Wolf et al., 2019). CPRD undertakes various levels of validation process, through frequent checks of the integrity of the data, that maintain the data quality. The accuracy may differ across diagnoses, and ongoing validations have shown good agreement between GP and linked data (Jick et al., 2023). However, further assessment of other data elements is needed to provide additional insight into this recent data resource, and its utility for epidemiological research.

1.8.1.4 Strengths and limitations of the CPRD

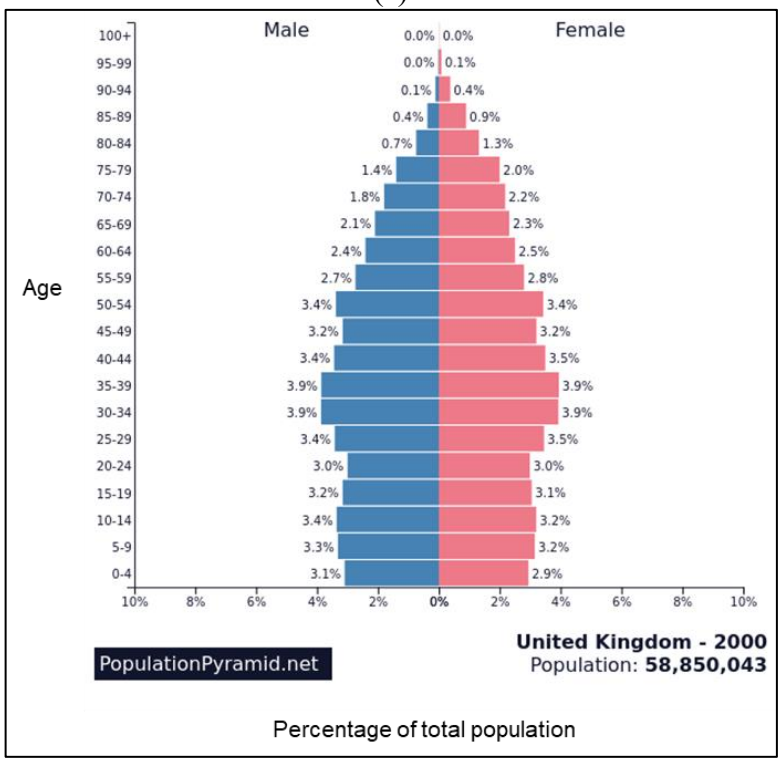
The CPRD is one of the largest healthcare datasets, It provides a large amount of patient data and its representative of the UK population, thus giving an excellent opportunity for clinical research and epidemiological studies (Herrett et al., 2015, Wolf et al., 2019). The CPRD do not provide patient identifiers such as name, full date of birth, or postcode to external researchers (Wolf et al., 2019, Jick et al., 2020). These identifiers are removed prior to transfer of data to CPRD in order to protect patient confidentiality. A major strength of CPRD is that the quality of the data is maintained by the Quality and Outcomes Framework (QOF), which was

introduced in 2004 (Roland, 2004, Kontopantelis et al., 2014). QOF has certain criteria for measuring the quality of services provided by general practices (Roland, 2004, Kontopantelis et al., 2014). CPRD data underwent various levels of validation and quality assurance covering the integrity, structure and format of the data. CPRD also provides a patient-level data quality check in the form of an 'acceptability' flag (Wolf et al., 2019, Persson et al., 2020). A patient is considered acceptable if they have completed data entered about the key variables including date of birth, date of registration in the practice and transfer out date. Other strengths include the availability of examination, and laboratory results data, and multiple external linkages (Persson et al., 2020). However, CPRD has several limitations. For example, occupation and employment data are generally limited in this database, though recent external linkage to patient-level data for social deprivation (Townsend score, Index of Multiple Deprivation) helps to compensate for that (Wolf et al., 2019). Also some records within general practice may not be electronically coded and therefore available to researchers, but the addition of linkage to the Hospital Episode Statistic (HES) may fill these gaps (Wolf et al., 2019). The size and complexity of the CPRD requires comprehensive experience and statistical training. The cost of accessing the database is also a burden for some researchers (Strom and Kimmel, 2006).

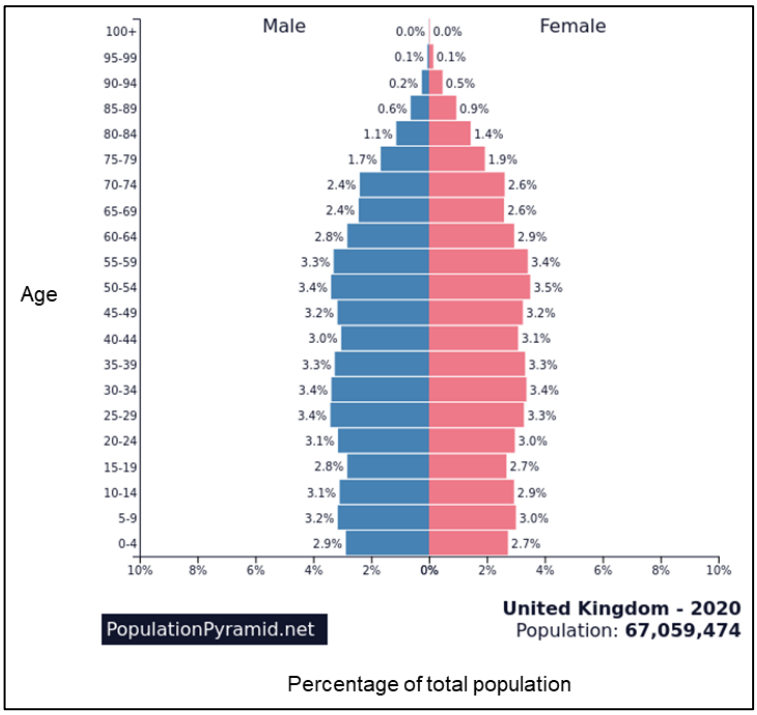
1.9 Population structure of the UK (2000 - 2020)

It is important to understand the population structure in the UK since 2000, and to recognise that general practice delivery in the year 2020 was significantly affected by the coronavirus (COVID-19) pandemic. The UK population has continued to increase from 2000 to 2020 (Figure 1.14) (Office for National Statistics, 2020). In 2020, the percentage of the population aged 60-79 years and above was higher than in 2000 and continues to increase since 2020 (Population pyramids of the world from 1950 to 2000, 2020). In mid-2020 there were 12.5 million people aged 65 years and above in the UK, compared to 10.3 million a decade earlier (Office for National Statistics, 2020). However, the number of deaths in the UK in 2020 exceeded the number of live births (689,629) and was higher in the older population due to the pandemic (Office for National Statistics, 2020).

(a)



(b)



Source: Office For National Statistics, National Records of Scotland and Northern Ireland Statistics and Research Agency,2020

Figure 1.14 Population structure of the UK in the year 2000 (a), and 2020 (b).

1.10 Rationale of the thesis

Current UK data exploring the prevalence and incidence of shoulder pain at different time points, and the geographical variations of CSP are lacking in the literature. As far as is known, only one prospective cohort study in 2006 has assessed the incidence and prevalence of consultations for shoulder complaints in UK primary healthcare (Linsell et al., 2006). They used the Mediplus database that contains anonymised medical records of approximately 1,700,000 patients from 211 general practices in the UK. The overall prevalence and incidence of patients consulting GPs for shoulder pain was 2.36% and 1.47%, respectively. Prevalence was found to be increased in older people and was higher in females compared to males (Linsell et al., 2006). Additionally, they found that GPs used only a limited number of codes when reporting diagnosis, specifically five out of 426 Read codes related to shoulder conditions and accounted for 74.6% of the diagnosis recorded by GPs. However, this study has several limitations. The Mediplus database used in this study has limited regional assessment compared to other databases such as the CPRD, which represents wider regional assessment and has a large number of patients. They examined only two risk factors, specifically, sex and age, and omitted other possible risk factors associated with shoulder pain such as smoking, BMI, alcohol consumption and occupation. Also, they did not explore the outcomes of shoulder pain in the UK such as number of hospitalisations per year, number of consultations, comorbidities and mortality rate. Additionally, this study was published in 2006, which may

not capture the current prevalence of shoulder pain in the UK. Therefore, current data about shoulder pain and the risk factors associated with this condition in the UK are required to investigate the epidemiology and the determinants of shoulder pain using an available good quality resource. In the UK, there are less data available on whether people with CSP are more likely to have other long-term health conditions and based on existing evidence no study has been carried out in the UK to explore comorbidities that associate with CSP disorders apart from diabetes.

1.11 Aim and study objectives

1.11.1 Aims

This study aimed to investigate the epidemiology of CSP from 2000 to 2020, specifically (1) prevalence and incidence, and the trend of prevalence and incidence; and (2) the risk factors, and comorbidities associated with CSP. The study was conducted using the large UK CPRD which is representative of the general population in the UK.

1.11.2 Objectives and general methods

1- To undertake a systematic review and meta-analysis of observational studies on the prevalence and incidence of CSP and its related risk factors, and comorbidities.

2- To determine the current prevalence and incidence of CSP in the UK in the year 2019 using CPRD.

3- To determine the trends of prevalence and incidence of CSP in the past 20 years (2000–2020).

4- To examine potential risk factors, and comorbidities associated with CSP using a nested matched case-control study within the CPRD.

5- To explore the outcomes of CSP using a cohort study within the CPRD.

1.12 Structure of this thesis

This thesis examines and discusses the epidemiology of CSP in the UK. The contents of each chapter are briefly summarised as follows:

Chapter 2 presents the systematic review and meta-analysis of the prevalence, incidence, risk factors and comorbidities associated with CSP.

Chapter 3 reports the prevalence and incidence of CSP in primary care in the UK.

Chapter 4 explores the risk factors, and comorbidities associated with CSP.

Chapter 5 presents the outcomes of CSP.

Chapter 6 presents the Patient and Public Involvement (PPI) that I have been involved with during my research studies.

Chapter 7 is the general discussion that summarises this thesis and presents the implications of the findings and future research questions.

Chapter 2. Epidemiology of chronic shoulder pain in people aged 40 or older – a systematic review and meta-analysis of observational studies

2.1 Methods

2.1.1 Protocol

A systematic review was performed using a predetermined protocol, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The review was registered with the PROSPERO database in September 2021 (registration number CRD42021283902).

2.1.2 Data sources and search strategy

Electronic searches were undertaken using Medline (OVID), Scopus and CINAHL (EBSCO), EMBASE and the first 100 records Google Scholar, from their inception to September 2022. A systematic search was conducted using different search terms according to three domains, specifically shoulder pain and its subtypes, outcomes of interest, and type of study, as shown below.

- **Shoulder pain**: [(Shoulder) OR (glenohumeral) OR (acromioclavicular) AND (chronic pain) OR (chronic shoulder pain) OR (pain$) OR (osteoarthritis) OR (periarthritis) OR (frozen shoulder) OR (adhesive capsulitis) OR (rotator cuff tear) OR (subacromial pain) OR (shoulder impingement syndrome) OR (shoulder impingement) OR

(subacromial impingement syndrome) OR (tendinopathy) OR (tendinosis) OR (tendinitis) OR (bursitis).

- **Outcomes**: incidence, prevalence, risk factors, epidemiology
- **Type of study**: observational studies such as case control or cohort studies

The three domains of searches were combined using the Boolean operator 'AND'. The references of the included articles and relevant systematic reviews were also searched to maximise the findings. The search strategy is outlined below, and the detailed search strategy is presented in Appendix 2 (Table 9-1 and Table 9-2, pages 321-323). The search was conducted independently by a single reviewer, Nouf Alotaibi (NA). The search strategy was piloted initially and refined by the research team to mitigate the potential bias with a single independent search. Potentially relevant articles were selected initially through title and abstract screening, followed by full text screening for those articles which meet the inclusion criteria. The articles identified were managed by the Endnote web database. All identified references were gathered and the duplicates removed using a software platform (Rayyan) (Ouzzani et al., 2016). All articles meeting the inclusion criteria were retained for data extraction and quality assessment.

2.1.3 Study selection (Inclusion and Exclusion criteria)

All types of observational studies that documented prevalence or incidence of CSP were included. CSP was defined as pain in the shoulder

for more than three months and included specific CSP conditions such as adhesive capsulitis and RC disease as listed above. For risk factors and comorbidities, the PECO approach (Participants, Exposure, Comparator, Outcomes) was used to determine the inclusion criteria. There were no restrictions with respect to the language or publication date of papers. Studies were excluded if they were reviews, case reports, or conference abstracts (Table 2-1).

Table 2-1 Study selection criteria

	Inclusion	**Exclusion**
Participants	All adults aged 40 or more	Postoperative shoulder pain, patients with severe acute trauma, fracture, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, metastasis, Paget's disease of bone, avascular necrosis and co-existent neck pain.
Exposure	Exposure to any of the potential risk factors, e.g., occupation, smoking, alcohol etc.	-
Comparator	people without chronic shoulder pain	
Outcomes	Prevalence, incidence and risk factors and comorbidities associated with chronic shoulder pain	-

2.1.4 Data extraction

During the initial review of the studies, the data were extracted using a standardised data extraction form which included the following information: authors, date, country, study design, participants, population age, case definition of shoulder pain, prevalence, incidence, risk factors,

diagnosis of shoulder pain and outcome measurements. Data extraction was managed using covidence software (Babineau, 2014).

2.1.5 Validation of study data

Each stage of screening and data extraction was conducted by a single reviewer (NA). This was independently validated by a second reviewer (Monirah Shuaib (MS)) who screened a random 10% sample using the same software platform (Rayyan) (Hartling et al., 2012). Agreement between the two reviewers of above 80% was considered acceptable (Furlan et al., 2011, Belur et al., 2021). Discrepancies in the screening were recorded and resolved by discussion with a third reviewer (MH). If the overall level of agreement was less than 80%, reasons for the disagreements would be explored thoroughly, and a further screening of 10% of full text articles would be undertaken. The quality assessment was independently validated by a second reviewer (MS). Again, a level of agreement between the two reviewers of above 80% was considered acceptable (Furlan et al., 2011, Belur et al., 2021). If the level of agreement was less than 80%, disagreement between the two researchers (NA and MS) was resolved by discussion with a third reviewer (MH), if required.

2.1.6 Quality assessment

All included studies were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS) for observational studies (Wells et al., 2000). The NOS assessment includes three broad perspectives, specifically selection, comparability, and outcome (exposure in case

control studies). The scale has three different forms for each study design. For the case control and cohort studies, NOS has eight questions, while for cross-sectional studies NOS has seven questions (the NOS for cross sectional studies was adapted from the NOS for cohort studies) (Lo et al., 2014, Luchini et al., 2017). The risk of the following bias categories were allocated according to the NOS score for each study: low bias risk (7–9 points); moderate risk bias (4–6 points); and high bias risk (< 4 points) (Sun et al., 2019).

For cross-sectional studies, the maximum score is ten and stars were awarded according to the representativeness of the sample (maximum one star), sample size (maximum one star), non-respondents (maximum one star), ascertainment of the exposure (risk factor) (maximum two star), assessment of the outcome (maximum two star), statistical test (maximum one star), and comparability of the subjects in different outcome groups on the basis of the design or analysis (maximum two stars).

For case-control studies, the maximum score for the NOS is 9 and stars were awarded according to selection of cases (maximum one star), representativeness of the cases (maximum one star), selection of the control (maximum one star), ascertainment of exposure (maximum one star), ascertainment for cases and controls (maximum one star), non-response rate (maximum one star), and comparability of cases and controls on the basis of the design or analysis (maximum two stars).

For cohort studies, the maximum score for the NOS is nine and stars were awarded according to representativeness of the exposed cohort

(maximum one star), selection of non-exposed cohort (maximum one star), ascertainment of exposure (maximum one star), assessment of outcome adequacy of follow-up for cohorts (maximum one star), demonstration that the outcome of interest was not present at the start of the study (maximum one star), follow-up being long enough for outcomes to occur (maximum one star), selection of the non- exposed (maximum one star), and comparability of cohorts on the basis of the design or analysis (maximum two stars). The stars serve as an indicator of the quality of the specific studies.

2.1.7 Data synthesis and meta-analysis

The statistical analysis was conducted using the R package (meta, metafor) (Schwarzer, 2007). All the equations and R codes used in this analysis are provided in Appendix 3, pages 324-325. Heterogeneity between the studies was measured using I^2 test (Morris, 2008), the thresholds used being "low" (I^2=25%–49%), "moderate" (I^2 = 50%–74%), and "high" ($I^2 \geq 75\%$) (Higgins et al., 2003). If the test of heterogeneity was significant, a random effect model was applied for pooling the results, and if the studies were homogenous and the test of heterogeneity was zero, a fixed effect model was applied (Morris, 2008, Borenstein et al., 2010, Higgins et al., 2024).

Publication bias was assessed using funnel plots and Egger test when there were at least ten studies, but if there were less than ten studies Begg's test and Harbord test were used instead (van Enst et al., 2014).

The characteristics of the included studies were summarised. The prevalence and incidence rate of CSP were calculated where possible. To perform meta-analysis for prevalence, the cross-sectional studies were used to pool prevalence. For prevalence estimation, subgroup analysis was undertaken according to the population studied (e.g., general population, people with physically demanding jobs, people with diabetes). Physically demanding jobs were defined as those that require a high level and/or duration of physical exertion to perform occupational tasks (Smith et al., 2009). This included occupations such as painters, dental hygienists, plane pilots and crewmembers, physical therapists, kitchen workers, and motor vehicle manufacturing workers.

The 'inverse variance weighted' method was used in the analysis (Barendregt et al., 2013). This method uses untransformed proportions to perform meta-analysis for prevalence. Standard error (SE) of prevalence was calculated from the following formula, where p is the prevalence or incidence, and n is the total population for prevalence or the population at risk of CSP for incidence.

$$SE=\sqrt{\frac{p(1-p)}{n}}$$

Incidence was reported narratively as it was not possible to group the studies in a meta-analysis because the selected studies did not measure the occurrence of CSP in a uniform way. Identified risk/associated factors were grouped into three domains (personal, work-related, comorbidities). A p value of 0.05 were used for a statistically significant inference. When

data from at least two studies could be combined, a meta-analysis was performed to obtain a pooled estimate of the odds ratio (OR) with corresponding 95% CI. All relative risk estimates (e.g., OR, risk ratio (RR)) were transformed into a natural logarithm. The log-transformed OR (logOR) and its standard error (SE) were used for the meta-analysis. The SE for the logOR was calculated based on the 95% CI for the risk estimate. The LogOR and its SE were entered to R package and a random effects model meta-analysis was used to generate the forest plots and the pooled OR and its 95% CI.

2.2 Results

2.2.1 Selection of studies

The systematic search identified a total of 5,208 titles. Nine more studies were collected and added through manual searching of the references. After removing duplicates, 3,382 were screened by title and abstract. Subsequently, 200 studies were screened for full texts. The final number of studies that met the eligibility criteria was 29. The PRISMA flow diagram presents the process of study selection and reasons for exclusion (Figure 2.1).

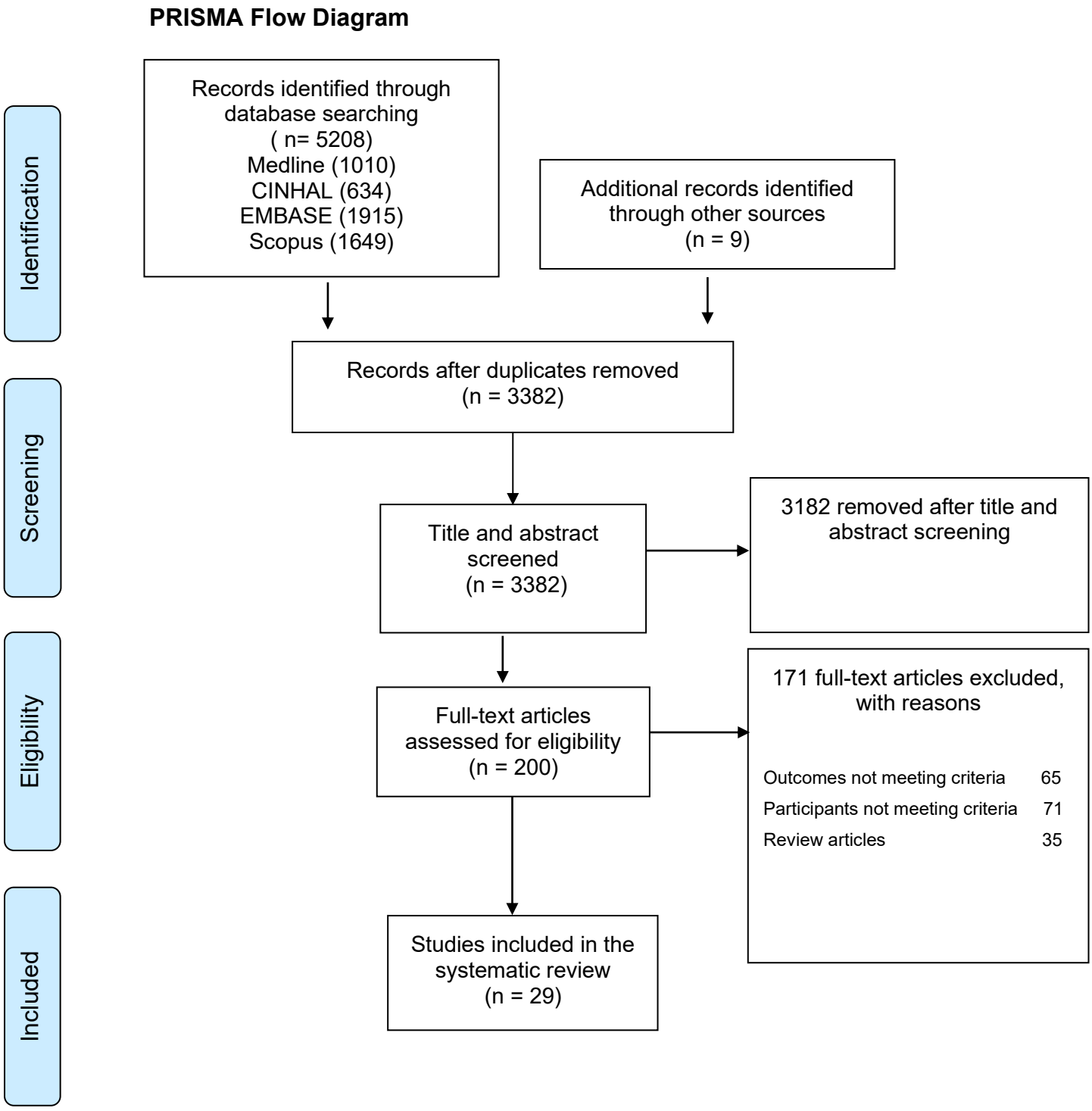


Figure 2.1 PRISMA flow diagram for the study selection process

2.2.2 Study Characteristics

The 29 included studies were published between 1998 and 2022. The characteristics of the included studies are shown in Table 2-2. The studies comprised 21 cross-sectional, four case-control, and four cohort studies (two retrospective and two prospective cohort studies). Most of the included studies examined shoulder pain in the general population (n=10) (Vogt et al., 2003, Hill et al., 2010, Burner et al., 2014, Kobayashi et al., 2014, Otoshi et al., 2014, Wright et al., 2015, Cho et al., 2015, Ahmad et al., 2020, Wu et al., 2021, Hinsley et al., 2022), eight studies examined workers in specific occupations (Niedhammer et al., 1998, Haukka et al., 2006, Morse et al., 2007, Janwantanakul et al., 2008, Alrowayeh et al., 2010, Kaliniene et al., 2016, Loew et al., 2019, Posch et al., 2019), and three studies examined the prevalence of shoulder pain in people with diabetes (Thomas et al., 2007, Kiani et al., 2014, Ahmed et al., 2021). Four studies examined the incidence of shoulder pain (Leclerc et al., 2004, Östergren et al., 2005, White et al., 2011, Tekavec et al., 2012). The sample size ranged from 93 to 2,188,958 and the age ranged from 40 to 87 years. Two studies did not report the mean age (Leclerc et al., 2004, Hill et al., 2010), and one study just reported the median age (71 years) (Hinsley et al., 2022).

The definitions of shoulder pain varied across the studies. Some studies reported specific criteria for shoulder pain, for example, in the Kobayashi et al. (2014) study, glenohumeral OA was defined and classified according to the Samilson-Prieto classification14 (S-P classification) (Elsharkawi et al., 2013). In other studies, definitions were more general, for example in the study by Burner et al (2014) shoulder pain was defined as pain in the shoulder region for more than three months in the last year (Table 9-3, Appendix 4, pages 326-337). In 14 studies shoulder pain was defined using a combination of validated questionnaire, clinical assessment, and imaging. Two studies defined shoulder pain using clinical assessment alone, while eight studies focused on self-reported shoulder pain. The other studies used imaging alone or electronic medical record databases (Table 2-2). The characteristics of the individual studies are presented in Table 9-3 (Appendix 4, pages 326-337).

Table 2-2 Summary of study characteristics

Study characteristics	Number of studies	N
Total	29	3,382,099
Age range, years	40-87	
Study design		
Cross-sectional	21	
Case-control	4	
Retrospective cohort study	2	
Prospective cohort study	2	
Country of the study		
Europe	11	
North America	7	
Asia	10	
Oceania	1	
Study setting		
Community	21	
Hospital	8	
Outcomes examined		
Prevalence	20	
Incidence	4	
Risk factors	13	
Comorbidities	9	

Definition of shoulder pain	
Self-reported	8
Clinical assessment	2
Radiographs*	1
Medical record database	2
Mixed	14

* Radiographs were used to define glenohumeral osteoarthritis according to Kellgren Lawrence grades and the presence of osteophytes plus narrowing of the glenohumeral articulation. N = number

2.2.3 Methodological quality and risk of bias

For the quality analysis, there was some disagreement between the two reviewers regarding seven items (Appendix 5, Table 9-4, page 338), which was resolved by discussion with the third reviewer (MH). The quality analysis scores of the included studies are reported in Tables 2-3, 2-4 and 2-5.

Of the 29 studies, 20 had a high quality, and nine had moderate quality. The most common issues across the 21 cross-sectional studies were the lack of description of the tool used to determine the outcome, whether it was validated or not, and whether it relied on self-report alone. The most common risk of bias aspect across the case-control studies was that the definition of shoulder pain was based on medical records. For cohort studies, the most common risk of bias aspects was the lack of information concerning the adequacy of follow-up and the fact that assessment of shoulder pain was based on self-report alone. Details about individual study risk of bias aspects are reported in Appendix 6 (pages 340- 342).

Table 2-3 Quality analysis scores for cross-sectional studies

Author, year	Selection				Comparability	Outcome		Total stars	Standardised quality score (% of the maximum score)
Question number	1	2	3	4	5	6	7		
Maximum number of stars per question (10)	1	1	1	2	2	2	1		
Ahmad, 2020	★	★	★	★★		★★	★	8	80
Burner, 2014	★	★	★	★★		★★	★	8	80
Ding, 2014	★			★★		★★	★	6	60
Kiani, 2014	★			★★	★	★★	★	7	70
Kobayashi, 2014	★	★	★	★★		★★	★	8	80
Loew, 2019	★	★		★★		★★	★	7	70
Morse, 2007	★			★★	★	★★	★	7	70
Otoshi, 2014	★			★★	★	★★	★	7	70
Posch, 2019	★		★	★★		★★	★	7	70
Wright, 2015	★		★	★★	★★	★	★	8	80
Wu, 2015	★	★		★★		★★	★	7	70
Cho, 2015	★			★★	★★	★★	★	8	80
Vogt, 2003	★			★	★★	★	★	6	60
Hill, 2010	★		★	★★	★★	★★	★	9	90
Alrowayeh, 2010	★		★	★★		★	★	6	60
Haukka, 2006	★		★	★★	★★	★	★	8	80
Kaliniene, 2016	★	★	★	★★	★★	★★	★	9	90
Janwantanakul, 2008	★		★	★★		★	★	6	60
Hinsley, 2022	★		★	★★	★★	★★	★	9	90
Fehringer, 2008	★	★		★	★★	★★	★	8	80
Niedhammer ,1998	★		★	★★	★★	★★	★	9	90

Table 2-4 Quality analysis scores for case-control studies

Author, year	Selection				Comparability	Exposure			Total stars	Standardised quality score (% of the maximum score)
Question number	1	2	3	4	5	6	7	8		
Maximum number of stars per question (10)	1	1	1	1	2	1	1	1		
Milogram 2008	★	★		★		★	★	★	6	60
Rodriguez Diez-Caballero 2020		★	★	★	★	★	★	★	7	70
Thomas 2007	★	★		★		★	★	★	6	60
Baumgarten 2010	★	★		★	★		★		5	50

Table 2-5 Quality analysis scores for cohort studies

Author, year	Selection				Comparability	Exposure			Total stars	Standardised quality score (% of the maximum score)
Question number	1	2	3	4	5	6	7	8		
Maximum number of stars per question (10)	1	1	1	1	2	1	1	1		
Tekavec, 2012	★		★	★		★	★	★	6	60
White, 2011	★	★	★	★	★★	★	★		8	80
Ostergren, 2005	★			★	★		★	★	5	50
Lecrac, 2004	★	★		★	★	★	★	★	7	70

2.2.4 Prevalence of chronic shoulder pain

20 cross-sectional studies examined the prevalence of CSP. The prevalence of CSP in these studies ranged from 4% to 61% (Figure 2.2). The pooled prevalence in the included cross-sectional studies was 29% (95% CI 20 to 37). The funnel plot was asymmetric (Figure 2.3), and the results of Egger's test were significant p-value = 0.0009, indicating that there was publication bias.

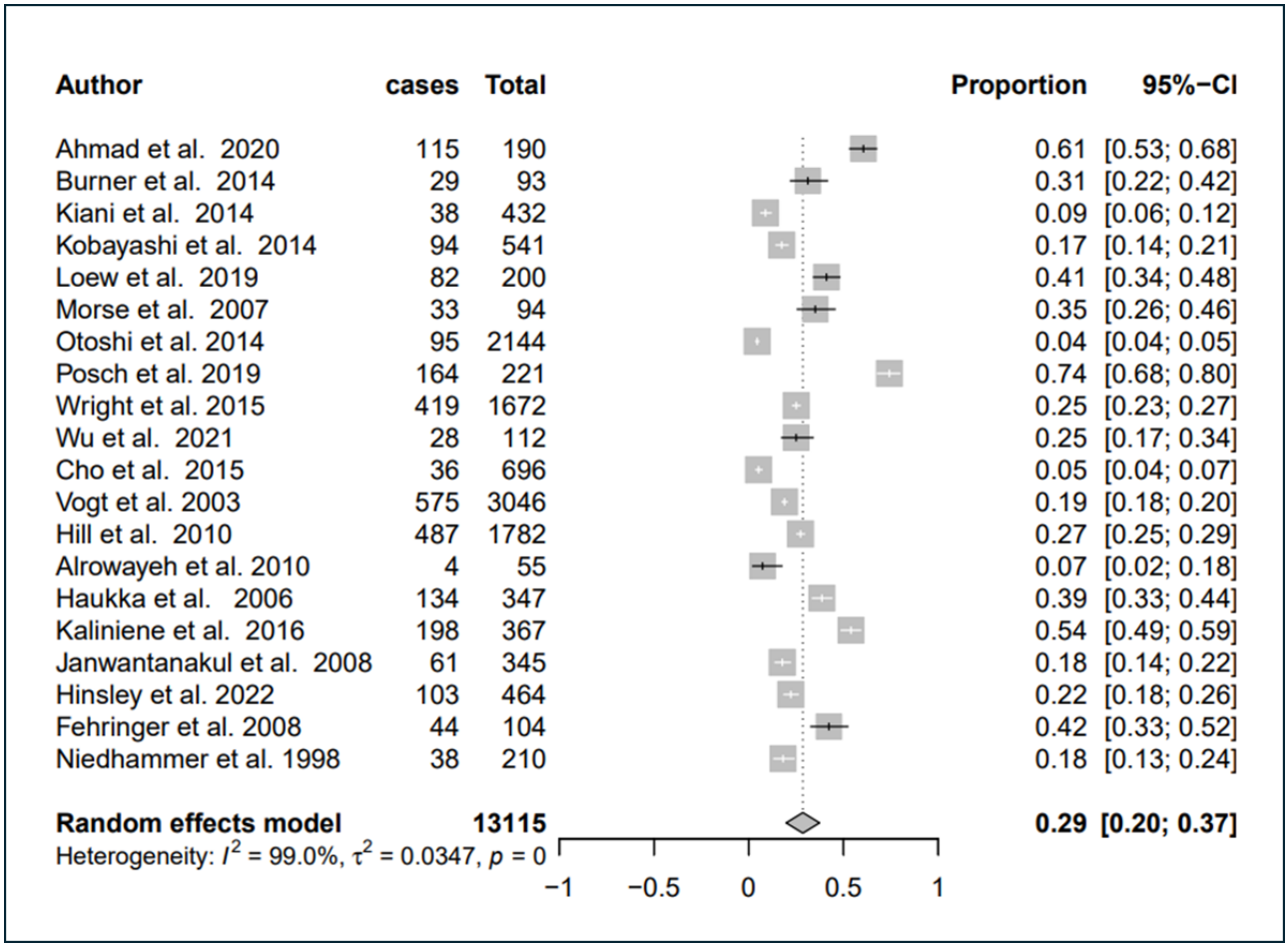


Figure 2.2 Forest plot showing the prevalence of chronic shoulder pain in the twenty included cross-sectional studies

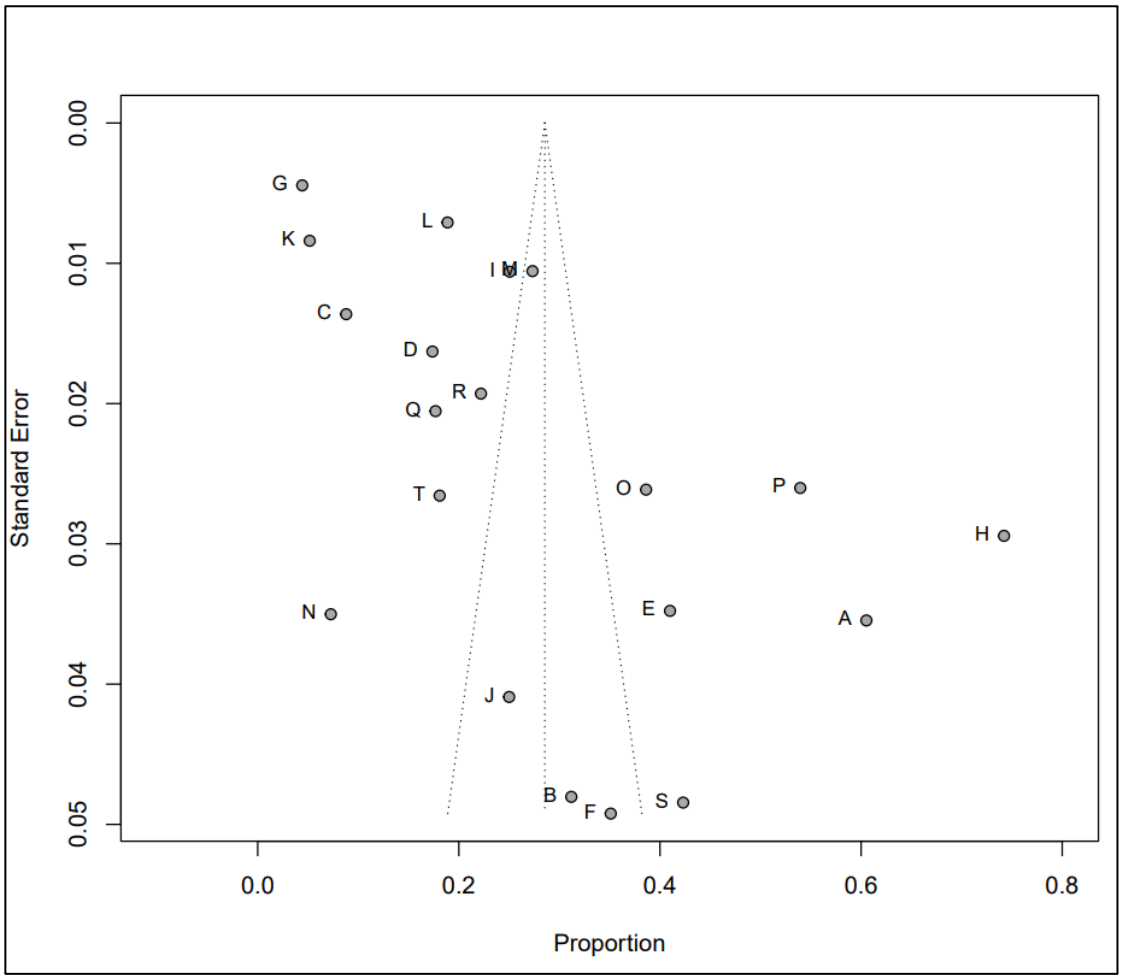


Figure 2.3 Funnel plot showing the prevalence of chronic shoulder pain in the twenty included cross-sectional studies

A, Ahmed et al., 2020, B, Burner et al., 2014, C, Kiani et al. 2014, D, Kobayashi et al. 2014, E, Loew et al. 2019, F, Morse et al. 2007, G, Otoshi et al. 2014, H, Posch et al. 2019, I, Wright et al. 2015, J, Wu et al. 2021, K, Cho et al. 2015, L, Vogt et al. 2003, M, Hill et al. 2010, N, Alrowayeh et al. 2010, O, Haukka et al. 2006
P, Kaliniene et al. 2016, Q, Janwantanakul et al. 2008, R, Hinsley et al. 2022, S, Fehringer et al. 2008, T, Niedhammer et al. 1998

2.2.5 Subgroup analysis

2.2.5.1 Prevalence of chronic shoulder pain in the general population

The prevalence of CSP in the general population ranged from 4% to 42% (Figure 2.4). There was very high heterogeneity between the included studies (I^2 = 99%), so the random effects model was selected. The pooled prevalence of CSP in 10,654 participants was 21% (95% CI 13 to 29). The funnel plot was asymmetric (Figure 2.5), and the results of Egger's test were not significant (p = 0.058), which may suggest no publication bias. The larger studies (i.e., smaller SE) tended to have a smaller prevalence, whereas the smaller studies (i.e., larger SE) tended to have a larger prevalence (Figure 2.5).

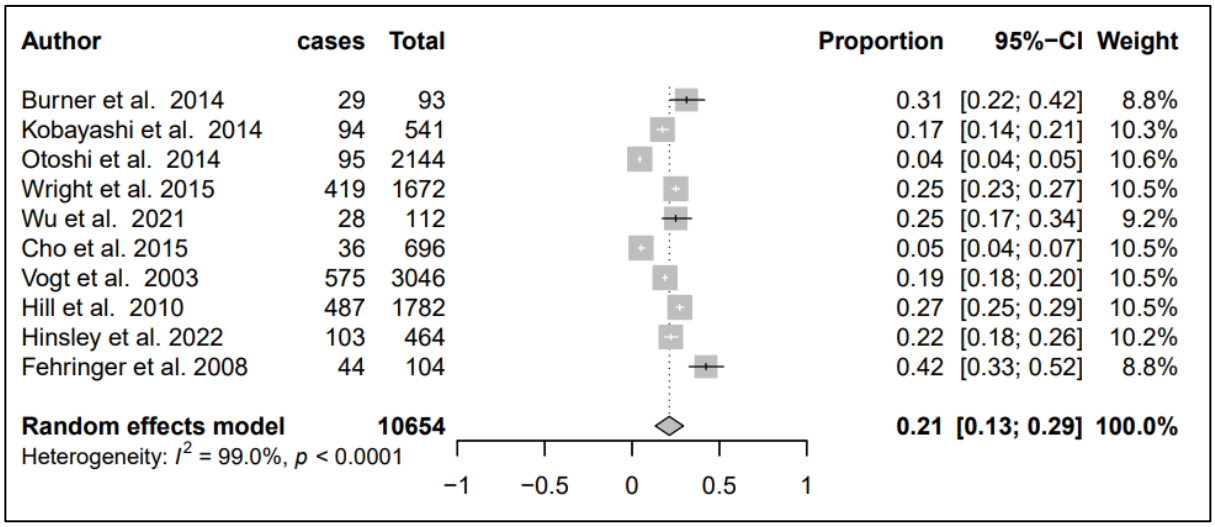


Figure 2.4 Forest plot showing the prevalence of chronic shoulder pain in the general population

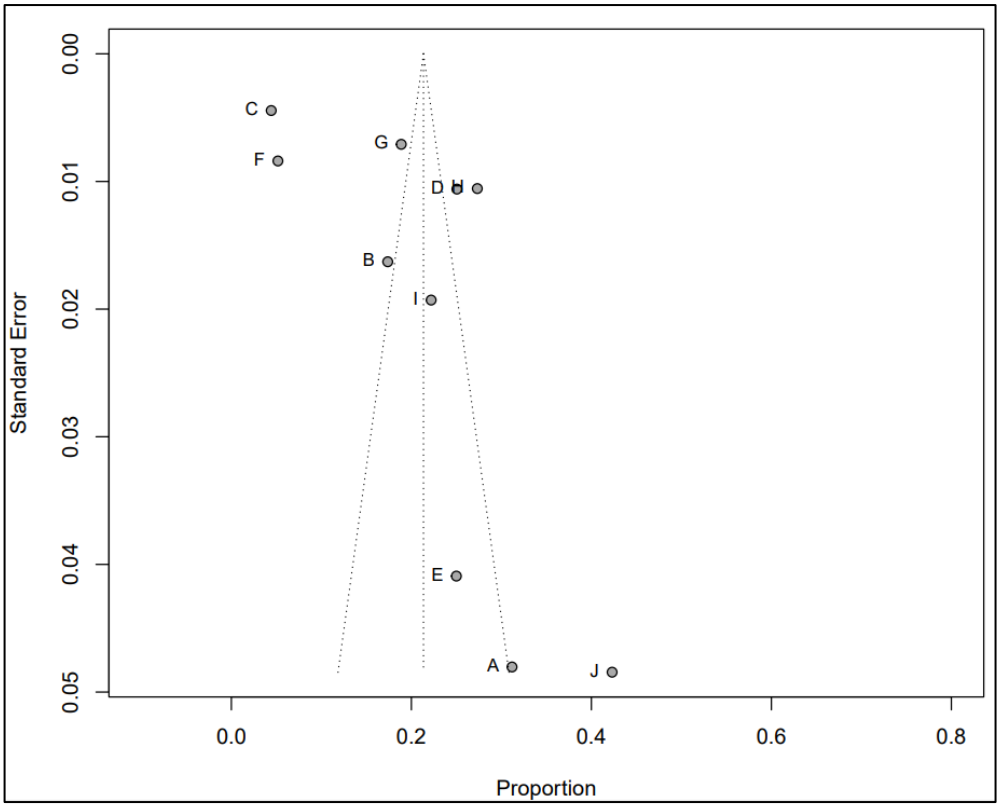


Figure 2.5 Funnel plot showing the prevalence of chronic shoulder pain in the general population

A, Burner et al., 2014, B, Kobayashi et al. 2014, C, Otoshi et al. 2014, D, Wright et al. 2015, E, Wu et al., 2021, F, Cho et al. 2015, G, Vogt et al. 2003, H, Hill et al. 2010, I, Hinsley et al. 2022 J, Fehringer et al.2008

2.2.5.2 Prevalence of chronic shoulder pain in people with diabetes

Two cross-sectional studies assessed the prevalence of shoulder pain, specifically adhesive capsulitis, in people with diabetes (Appendix 7, Figure 9.1, page 343). The prevalence ranged from 9% to 61%. There was a significant heterogeneity between included studies (I^2 = 99%). The prevalence of CSP in 622 people with diabetes was 35% (95% CI 0 to 85). The statistical test for publication bias could not be performed because the number of studies were too small to test for small study effects.

2.2.5.3 Prevalence of chronic shoulder pain in physically demanding occupations

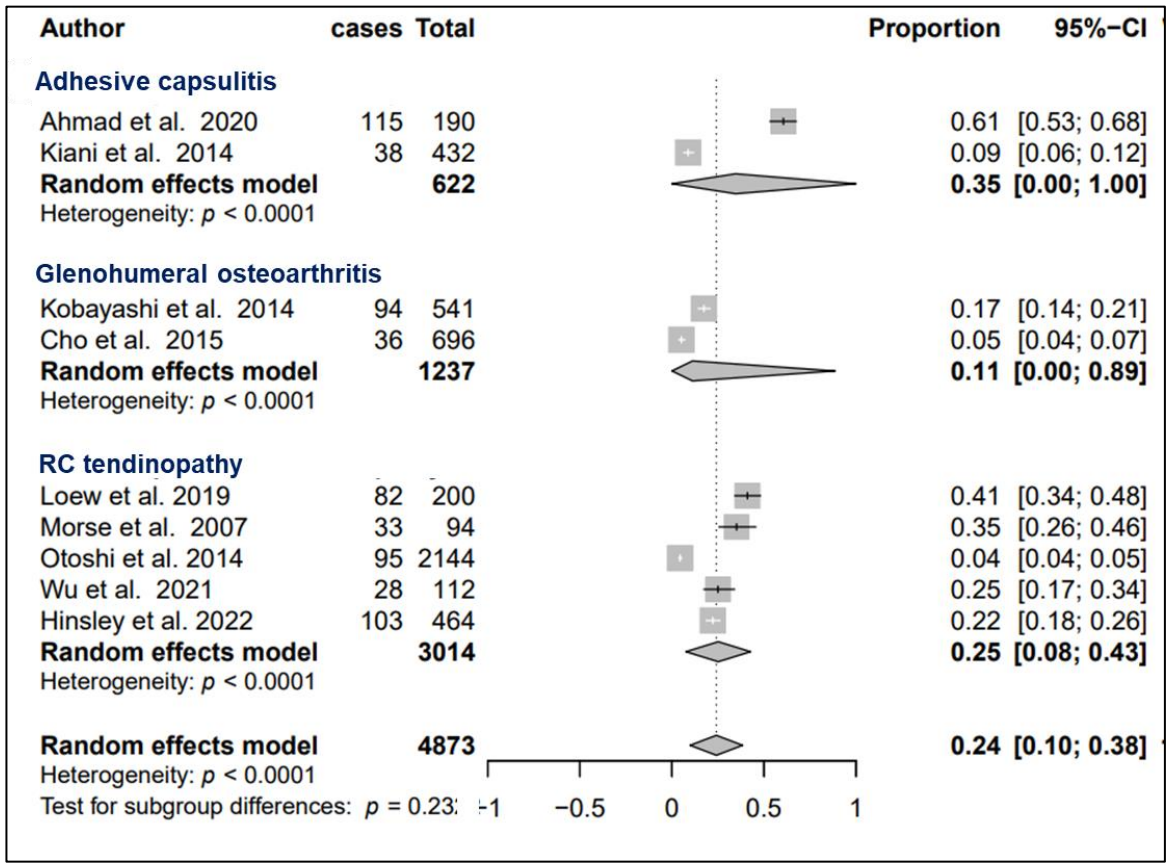
A total of eight cross-sectional studies examined the prevalence of CSP in people employed in physically demanding occupations. The overall prevalence in these population ranged from 7% to 53%. There was a significant heterogeneity between included studies (I^2 = 97%). The pooled prevalence of CSP in 1839 workers was 36% (95% CI 18 to 54) (Appendix 7, Figure 9.2, page 343). The funnel plot was approximately symmetrical (Appendix 7, Figure 9.3, page 344). The results of the Begg test P = 0.69 were not significant, indicating that there was no publication bias. The prevalence of CSP in different subgroups are summarised in Table 2-6.

Table 2-6 Prevalence of chronic shoulder pain in different subgroups

Population	Number of studies (participants)	Prevalence (95% CI)	Heterogeneity I^2	Publication bias, p
All cross-sectional studies	20(13,115)	29% (20- 37)	99%	p = 0.0009
General	10 (10,654)	21% (14- 28)	99%	p = 0.058
Diabetes	2 (622)	35% (0 - 85)	99%	-
Physically demanding occupations	8 (1839)	36% (18- 54)	97%	p = 0.69

2.2.6 Type of chronic shoulder pain

While a number of specific CSP conditions were identified in the included studies (adhesive capsulitis, glenohumeral OA, shoulder impingement, bursitis, acromioclavicular joint disorders, biceps tendon injury, RC tear, RC tendinopathy), only three specific conditions could be pooled statistically. Only nine studies reported a specific diagnosis for CSP conditions (Appendix 7, Figure 2.6, Figure 9.4, page 345). Meta-analysis for the prevalence of CSP based on different types of shoulder disorders was performed (Figure 2.6). The pooled prevalence of shoulder pain according to different specific diagnoses was 24%. The test for subgroup difference (random effect model) was p-value = 0.23, which means that there was no statistical difference between different types of shoulder pain prevalence.



RC, rotator cuff

Figure 2.6 Prevalence showing chronic shoulder pain based on different types of shoulder disorders

2.2.7 Incidence of chronic shoulder pain

Four cohort studies examined the incidence of CSP with follow-up periods ranging from one year to 13 years, two of which were conducted in the general population (White et al., 2011, Tekavec et al., 2012), and two focused specifically on workers (Leclerc et al., 2004, Östergren et al., 2005) (Table 2-7). Risk of bias varied across the studies, six had low risk of bias and two had moderate risk of bias. The incidence was higher in females compared to males in three studies (Östergren et al., 2005, White et al., 2011, Tekavec et al., 2012), except in the study by Leclerc et al. (2004) in which the incidence was higher in males than in females.

Table 2-7 Incidence of chronic shoulder pain in the four included studies

Author	Incidence measures	Female	Male
White et al., (2011)	Incidence rate per 1,000 person-years	3.38	2.36
Tekavec et al. (2012)	Incidence rate per 10,000 person-years	80 129 (50 to 59 years)	74 116 (60 to 69 years)
Ostergren et al. (2005)	One-year cumulative incidence	8.9% 45-49 years (10.3%)	5.9% 55-59 years (6.8%)
Leclerc et al. (2004)	Three- years cumulative Incidence	21 %	29%

2.2.8 Person-specific risk factors for chronic shoulder pain

A total of 15 studies (11 cross-sectional, two case-control, and two cohort) reported risk factors. A total of eight person-specific risk factors were identified in this review (Table 2-8). Risk of bias varied across the studies, 12 had low risk of bias and three had moderate risk of bias. Risk factors that were found to be significantly associated with CSP were: age above 40 years (Appendix 7, Figures 9.5 and 9.6, pages 346-347); female sex (Appendix 7, Figures 9.7- 9.10, pages 348-350); and lower educational level. Table 2-8 presents the identified risk factors with pooled odds ratio, heterogeneity and publication bias. Forest plots and funnel plots for the identified risk factors are presented in Appendix 7 (pages 346-351).

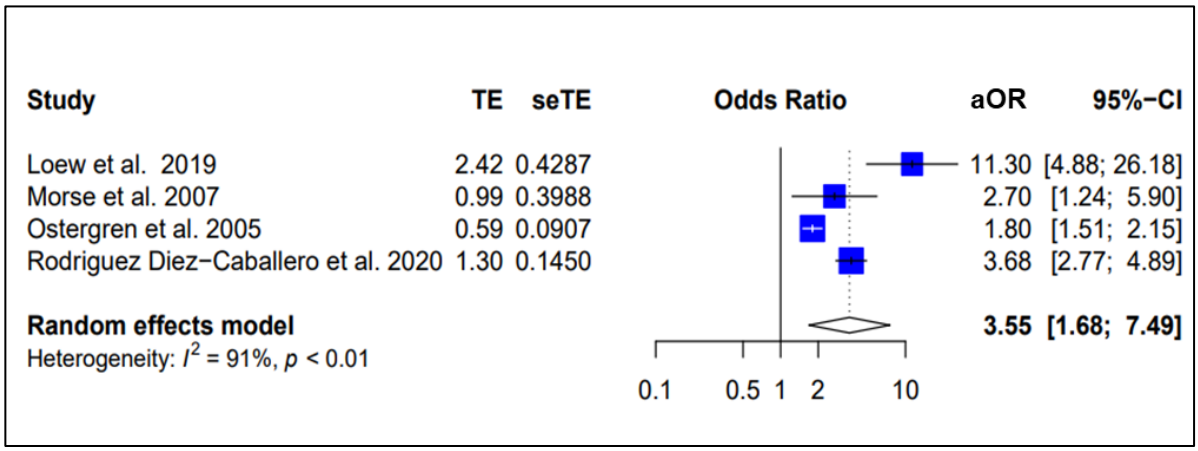
Table 2-8 Risk factors associated with chronic shoulder pain

Risk factors	No. of studies (participants)	OR (95% CI)	Heterogeneity I^2	Publication bias *p*
Age >40 years	4 (3408)	2.44 (2.14, 2.78)	18.2%	p = 0.29
50-69	3 (3198)	1.98 (1.08 , 3.64)	10%	p = 0.60
70-79	2 (2685)	2.44 (2.13, 2.80)	31.5%	-
>80	2 (2685)	2.56 (0.70, 9.31)	65%	-
Sex (F/M)	4 (3364)	2.05 (1.54, 2.72)	38%	p = 0.49
BMI, kg/m²*	1 (696)	1.70 (0.80, 3.80)	-	-
Smoking (Yes/No)	3 (1216)	1.72 (0.92, 3.24)	67%	p = 0.68
Educational level**	1(4919)	1.80 (1.35, 2.38)	-	-
Dominant arm	1 (200)	1.88 (0.70, 5.01)	-	-
Kyphosis	1 (2144)		-	-
Thoracic		1.65 (1.02, 2.64)		
Lumbar		1.06 (0.68,1.67)		
Manual work	4 (5380)	3.55 (1.68, 7.49)	91%	p= 0.174

F, female, M, male, BMI, body mass index , OR , odds ratio, CI=confidence interval, * BMI of 25Kg/m2 or greater vs. BMI below 25Kg/m2, **education level (< 9 years Vs. >10-12 years). No.= number of

2.2.9 Work-related risk factors

Four studies (two cross-sectional, one case-control and one cohort) examined manual work versus non-manual work as a risk factor for CSP in working populations. Risk of bias varied across the studies, three had low risk of bias and one had moderate risk of bias. The results showed that people who undertook manual work were more likely to have CSP compared to non-manual workers, with an adjusted OR of 3.55 (95% CI 1.68 to 7.49, z= 3.33, p-value = 0.0009) (Figure 2.7). There was high heterogeneity between the included studies (I^2 = 91%, p-value = 0.01). The funnel plot was approximately symmetrical (Appendix 7, Figure 9.15, page 352), and there was no indication of publication bias (Begg test: p = 0.174).



TE= log odds ratio, seTE=standard error of odds ratio, CI= confidence interval, aOR=adjusted odds ratio

Figure 2.7 Forest plot showing the association between manual work and shoulder pain (adjusted odds ratio for age and occupation)

2.2.10 Comorbidities associated with chronic shoulder pain

A total of 13 comorbidities were identified from eight studies (five cross-sectional, two case-control, and one cohort). Risk of bias varied across the studies, three had low risk of bias and five had moderate risk of bias. Several comorbidities were found to be significantly associated with CSP including: angina (Vogt et al., 2003, Östergren et al., 2005, Wright et al., 2015); pain in other joints (Vogt et al., 2003, Milgrom et al., 2008, Kobayashi et al., 2014, Wright et al., 2015) (Appendix 7, Figures 9.16 and 9.17, page 353); diabetes (Thomas et al., 2007, Milgrom et al., 2008, Kobayashi et al., 2014, Wright et al., 2015) (Appendix 7, Figures 9.18-9.20, pages 354-355); and arthritis (Vogt et al., 2003) (Table 2-9). In another study with 190 participants, family history of diabetes was found to be associated with adhesive capsulitis (Ahmad et al., 2020). There were some other potential comorbidities found from just single studies that might be associated with CSP including anxiety, sarcopenia, and hypothyroidism (Milgrom et al., 2008, Ding et al., 2014, Wu et al., 2021). Also, there were some comorbidities found in this review that were not associated with CSP including depression, cardiovascular diseases, hyperlipidaemia, and hypertension. The study outcomes are presented in Table 9-5 (Appendix 8, pages 357-362).

Table 2-9 Comorbidities associated with chronic shoulder pain

Comorbidities	No. of studies (participants)	OR (95% CI)
Arthritis	1 (3046)	5.1 (3.2, 8.2) *
Diabetes	4 (3506)	2.97 (1.29, 6.80) 1.73(1.37, 2.19)* RR 5.42 (4.15, 7.08)*
Pain in other joints	3 (9637)	2.73(1.73, 4.30) *
Angina	1 (3046)	1.63 (1.23, 2.15) *
Hypothyroidism	1 (224)	F** RR 7.3 (4.8, 11) M** RR 2.6 (0.4,17)
Sarcopenia	1 (122)	2.7 (1.33, 5.79)
Anxiety	1 (254)	1.9 (1.0, 3.7)
Depression	2 (4718)	2.39 (0.99, 5.76) *
Hypertension	2 (3587)	1.69 (1.03, 2.77) 1.39 (0.91, 2.11)*
Hyperlipidaemia	1(541)	0.95 (0.59,1.5)
Myocardial infarction	1(3046)	1.35 (0.94,1.92) *
Cardiovascular diseases	1 (1672)	1.99 (1.58, 2.49) *
Lung conditions (bronchitis and emphysema)	1(1672)	1.97 (0.9, 4.32) *

Abbreviations: * adjusted odds ratio, Pain in other joints: defined as musculoskeletal pain at other musculoskeletal regional sites includes the neck, knee, hip, back, hand, and foot,
, **F female, M male, ***RR risk ratio

2.3 Discussion

This systematic review and meta-analysis have summarised the current evidence on the prevalence and incidence of CSP, risk factors and associated comorbidities. A total of 29 studies from 19 countries, were included. The following were the key findings. (1) The pooled prevalence of CSP in the included studies was 29% and was higher in specific populations such as those with physically demanding jobs (36%) and people with diabetes (35%). (2) The incidence of CSP was higher in

female and increased over the age of 40 years. (3) CSP was associated with age, female sex, lower educational level, and manual work. (4) Several comorbidities were found to be associated with CSP, specifically, angina, other MSK pain, diabetes and arthritis. (5) The pooled prevalence of shoulder pain according to different specific diagnoses was 26%. Although the pooled prevalence was estimated, this needs careful interpretation owing to the large heterogeneity between the included studies. There were large differences in age range studied, for example, Vogt et al. (2003), Burner et al. (2014) and Cho et al. (2015) focused on shoulder pain in people aged over 60 years old only, while for most of the other studies the mean age was 45. Differences in prevalence estimates across these studies could be due to the diversity of shoulder pain conditions, the definitions used, the population studied (e.g., workers in different work sectors, people with diabetes), the research method used, and sampling method. For example, Kobayashi et al. (2014) examined glenohumeral OA, which was more common in the older population (17%), while Otoshi et al. (2014) defined shoulder pain as subacromial pain syndrome (4%) and the prevalence of glenohumeral OA was higher than subacromial pain syndrome. Another potential explanation for the variations in prevalence estimates across studies was the reference periods used. Some studies focused on participants experiencing shoulder pain in the last three months, while others used reference periods of up to 12 months. Where the reference period was specified clearly, a longer duration of the reference period was associated with increasing prevalence estimates. For example, Posch et al. (2019)

focused on any reported pain experience in the previous 12 months giving a prevalence of 74%, while Haukka et al. 2006 used a reference period of three months which gave a prevalence of 39%.

The incidence of CSP was consistently higher in females than in males (3.38 and 2.36 per 1000 person-years respectively). Furthermore, females born between 1920 and 1929 were 8% less likely to develop adhesive capsulitis than females born between 1930 and 1939. Females born between 1940-1949, 1950-1959, and 1960-1969 were 1%, 11%, and 14% more likely to develop adhesive capsulitis respectively (White et al., 2011). According to the 2002 Labour Force Survey, the number of working females in the UK between the ages of 50 and 64 has increased, with increases in jobs with low physical activity (Duffield, 2002). Since adhesive capsulitis is more common in sedentary jobs compared to active jobs, these shifts toward more recently born females taking more sedentary jobs might explain the increase in adhesive capsulitis incidence (Neviaser and Neviaser, 1987). The cumulative incidence in males seemed to peak in the age group 55-59, which might be due to the nature of the work at this age group, which includes manual work, and occupations that required high force transmission through the shoulder (Östergren et al., 2005). The incidence was found to decline with further increase in age, which might be explained by the retirement stage.

The current results are consistent with other systematic reviews in terms of variations of prevalence, and incidence estimates. Lumie et al (2004) conducted a systematic review to investigate the incidence and

prevalence of shoulder complaints in the general population. A total of 17 studies met their inclusion criteria for prevalence, and one study met the inclusion criteria for both prevalence and incidence (Luime et al., 2004). The prevalence of shoulder pain ranged from 6.9 to 26% for point prevalence, 18.6 to 31% for one month prevalence, 4.7 to 46.7% for one year prevalence and 6.7 to 66.7% for lifetime prevalence (Luime et al., 2004). The incidence ranged between 0.9 and 2.5% for different age groups (Luime et al., 2004). The prevalence estimate decreased, when the case definition was restricted, and increased when the shoulder pain was defined more broadly. Although it is evident that studies with larger sample size could estimate the prevalence more precisely, this did not influence the prevalence estimates. In two studies with a large sample size, but different case definition, the prevalence varied significantly (11.8% and 27% respectively) (Allander, 1974, Badley and Tennant, 1992). On the other hand, Pope et al. (1997), with a small sample size but comparable case definition, found prevalence results similar to Makela et al. (1999) with large sample size (31% and 28% respectively) (Pope et al., 1997, Mäkelä et al., 1999). The previous studies supported the claim that the broad range of prevalence estimates reported in epidemiological studies is mostly due to different definitions of shoulder pain.

This review identified several person-specific risk factors that could have a major role in the development of CSP. Increasing age and female sex were the most common risk factors associated with shoulder pain, as they are for many other common MSK regional pain syndromes (e.g. chronic knee pain)(Bunt et al., 2018, Takahashi et al., 2018).

Shoulder pain would be expected to increase with age because of degenerative changes of the shoulder joint and tendons of the RC which both associate with the ageing process (Linsell et al., 2006, Pribicevic, 2012). Many studies have reported the highest prevalence of shoulder pain in middle age (40-64 years), which could relate to occupational activities, with a subsequent decline in older people that may result from reduced biomechanical stress following retirement (Chard and Hazleman, 1987, Picavet and Schouten, 2003, Parsons et al., 2007, Pribicevic, 2012). Also, several previous hypotheses have explained why shoulder symptoms are more prevalent in females than males. For example, hormonal changes and physiological differences in females can contribute to higher pain sensitivity (Vincent and Tracey, 2008). According to one large prospective cohort study, sex was identified as a major risk factor for the development of shoulder pain, with females being particularly at risk—showing a prevalence of 15% compared to 8% in males (Cassou et al., 2002).

The current review found that smoking was not associated with CSP, which differs from the results of a previous systematic review (Bishop et al., 2015). 13 studies were included in that review, comprising a total of 16,172 patients, of whom 6,081 were smokers. Four of those studies examined the association between smoking and patient-reported shoulder dysfunction (i.e., poor scores on shoulder rating scales) and symptoms. Another four studies examined the correlation between smoking and provider-reported RC disorder. The other studies investigated the relationship between smoking and degree of RC pathology (three clinical,

one cadaveric, and one basic science study). Bishop et al. (2015) found that smoking was associated with shoulder dysfunction, RC tears, poor shoulder function and higher pain scores. Also, it can accelerate RC muscle degeneration (Bishop et al., 2015). However, one study in the current review had examined time-dependent and dose-dependent relationship between tobacco use and RC tears (Baumgarten et al., 2010). The odds ratio for risk of RC tear in people who smoked > two packs per day was 3.35 (p-value = 0.0007) compared to 1.08 (p-value = 0.79) for people who smoked < one pack per day. Possible explanations for the different results might be due to the population studied in the current review (painters vs. diabetic vs. general population), the definition of shoulder pain (adhesive capsulitis vs. RC pathology), or smoking measurement.

Further study would potentially clarify the causative components of tobacco smoke and the biochemical and pathophysiologic mechanisms in RC pathology, which is essential for understanding whether nicotine replacement therapy is appropriate option for people at risk of RC pathology.

In the current review, low educational level was considered as a risk factor with an aOR of 1.80 (95% CI 1.35 to 2.38). This is consistent with the results of other studies of chronic MSK conditions where the prevalence has been reported to be associated with lower educational level (Cimmino et al., 2011, Farioli et al., 2014, Oha et al., 2014, Madadizadeh et al., 2017). Less educated people have been reported to experience

more upper limb pain (OR = 2.99, 95% CI 1.89 to 4.71), lower limb pain (OR = 2.26, 95% CI 1.38 to 3.70), and low back pain (OR = 4.09, 95% CI 2.71 to 6.16), compared to more highly educated people (Baek et al., 2010). A possible explanation for this is that low education might increase psychological distress and financial burden, which might lead to aggravation MSK pain. Additionally, less well-educated people are more likely to have manual work.

This review also confirmed that people working in occupations that require manual work and higher physical demands on the shoulder are likely to report more shoulder pain compared to other occupations and non-manual work. The current results align with the results of some previous studies. Highly demanding jobs were found to be a major risk factor for neck and shoulder pain in two prospective cohort studies (OR 1.50, 95% CI 1.20 to 1.90; and OR 2.00, 95% CI 1.20 to 3.30, respectively) (Andersen et al., 2003, Rasmussen-Barr et al., 2014).

Regarding comorbidities associated with CSP, one study in the current review reported that angina was associated with shoulder pain. However, that was a cross-sectional study, so was unable to confirm a temporal or causal relationship. There is thus very limited evidence regarding the relationship between angina and shoulder pain. A previous cross-sectional study conducted in the UK examined the prevalence and association between chronic MSK pain and cardiovascular diseases (Ryan et al., 2014). Older adults with chronic MSK pain were significantly more likely to have cardiovascular diseases with an OR of 1.82 (95% CI 1.45 to 2.30; p-

value < 0.001) (Ryan et al., 2014). However, the primary limitations of this study were its cross-sectional design and the grouping together of any chronic MSK pain. Further prospective cohort studies are needed to explore the temporal and causal association between cardiovascular diseases and CSP.

CSP was found to be significantly associated with other painful MSK conditions including arthritis and pain in other MSK regions. However, research about such relationships with CSP are limited. One cross-sectional study conducted in Finland found that chronic neck pain was associated with chronic pain at other joint sites, specifically, low back pain (OR 5.82, 95% CI 4.98 to 6.81), and shoulder joint disorders (OR 6.43, 95% CI 5.19 to 7.96) (Mäkela et al., 1991). Another prospective cohort study reported that back and foot pain each were significantly associated with incident shoulder pain with odds ratios of 2.46 (95% CI 1.72 to 3.51) and 1.68 (95% CI 1.08 to 2.61), respectively (Gill et al., 2013). However, in that study, there was a lack of specific diagnosis for shoulder pain.

The identification of diabetes as a risk factor for CSP was not unexpected. MSK conditions are recognised to be the most common complications in people with diabetes (Sözen et al., 2018). Shoulder disorders, such as adhesive capsulitis and RC tendinopathy are commonly seen in people with diabetes (Cole et al., 2009, Sözen et al., 2018). Although the causes of adhesive capsulitis are still underexplored and have not been identified, it is generally believed that it develops because of perivascular inflammation and fibroblastic proliferation, followed by capsular fibrosis

and contractures. Hyperglycaemia is the key factor in the progression of fibrosis in people with diabetes. Hyperglycaemia can cause subsequent formation of non-enzymatic glycosylation products and produce advanced glycosylation end-products (AGEs) (Goldin et al., 2006). These AGEs increase cross-linking in collagen, tendons, and ligaments, making these structures stiffer and weaker (Goldin et al., 2006). This unfavourable microvascular environment occurs around the shoulder joint as well (Goldin et al., 2006). The impaired circulation leads to tissue hypoxia and overproduction of free radicals, which can lead to joint tissue damage and enhancement of degenerative changes (Goldin et al., 2006).

Other potential comorbidities found in this review that might be associated with CSP including thyroid diseases, anxiety and sarcopenia. However, the evidence for these is from single cross-sectional studies, so further longitudinal studies that examine these possible associations are required to draw a conclusion.

Strengths and weakness

This review has some limitations. Firstly, there was no standard definition for CSP, and a wide range of shoulder pain definitions was used which had a major impact on the heterogeneity across the studies. Some studies had a general definition for shoulder pain, for example “any shoulder pain in the past 3 months” (Haukka et al., 2006, Burner et al., 2014), while others had specific criteria for shoulder pain (for example RC tendinopathy: shoulder pain during shoulder elevation and a positive Neer

or Hawkins impingement test result) (Morse et al., 2007, Loew et al., 2019). Also, there was marked variability between the studies as they examined different populations (e.g., general population, people with diabetes, and specific working populations). Another reason that might contribute to the significant heterogeneity in this review was the large differences in age range studied, for example, some studies focused on shoulder pain only in people aged over 60 years, while for most of the studies the mean age was 45 years. Secondly, 20 of the included studies were cross-sectional in design, which does not allow determination of the temporal and causal relationship between associations and shoulder pain. Thirdly, publication bias was difficult to assess because of the small number of studies included in the meta-analysis. However, this systematic review and meta-analysis has several strengths, including inclusion of all observational study designs. A major strength of this review was the inclusion criteria of the meta-analysis which identified several risk factors and comorbidities. Furthermore, the current review highlights the variations of shoulder pain definition and the need for a standard protocol to diagnose and define CSP in future studies. This will facilitate interpretation of the results and comparisons with other data.

2.4 Conclusion

The prevalence of CSP in the included studies ranged from 4% to 61%. One in four people aged 40 years old or more has CSP. Major risk factors

and comorbidities associated with CSP include age, female sex, lower education, manual work, arthritis, diabetes, and MSK pain elsewhere. The results need cautious interpretation owing to the heterogeneity between the included studies, and the relatively limited number of studies. Knowledge of evidence-based related risk factors and associated comorbidities can inform strategies for primary and secondary prevention of CSP. There is a significant need for specific policy and workplace interventions to address the quality of work and the intensity of work to reduce work-related CSP. Some comorbidities such as cancer, cardiovascular and lung disorders need further exploration in longitudinal studies, because the cross-sectional design of existing studies in the literature cannot explain the temporal and potentially causal relationships between shoulder pain and associated comorbidities. As CSP is considered to be a common MSK problem, and can have a detrimental effect on patients' lives, it would be interesting to understand the burden of shoulder pain. Thus, in the next chapter (Chapter 3), the trend of CSP in the UK will be explored.

Chapter 3. The prevalence and incidence of chronic shoulder pain in the UK from 2000 to 2020: a temporal trend analysis

3.1 Introduction

As far as is known, no study has been conducted on the trends of CSP in the UK. The lack of up-to-date information makes it challenging to estimate the burden of CSP. Based on existing evidence, only two countries have explored the trends of shoulder pain.

In Sweden, the trends of the prevalence of neck, shoulder-arm pain and concurrent low back pain were examined in the general population aged between 21 and 64 from 1996 to 2006. They used questionnaire data collected every 4 years from 1996 to 2006. Over this 16-year period, the prevalence of self-reported neck-shoulder-arm pain rose slightly, from 22.8% to 25.0% among females (prevalence rate ratio 1.10) and from 12.8% to 15.4% among males (prevalence rate ratio: 1.21) (Leijon et al., 2009). In Norway, Engebretsen et al. (2015) explored the prevalence of shoulder pain in the general population over the period 1990 to 2004. A questionnaire was sent to participants belonging to the six birth cohorts of 1918–20, 1928–30,1938–40, 1948–50, 1958–60 and 1968–70 in 1990 and1994 (Engebretsen et al., 2015). The case definition of shoulder pain in this study was categorized into localized shoulder pain, and regional shoulder pain. Localised shoulder pain was defined as pain in the shoulder site only, without neck or upper arm pain, while regional shoulder pain was defined as the occurrence of shoulder pain with neck or upper back pain or both. The prevalence of shoulder pain only, increased from 7.7% in 1990 to 8.6% in 2004 (Engebretsen et al., 2015). However, it might have been difficult to clearly identify shoulder and neck complaints. Pain in these body regions is considered to have multifactorial origins, and this might involve shared pathology. However, in most of the available

studies, the case definition of shoulder pain was not limited to the shoulder region only and incorporated other areas including neck and upper limb. Not all of them were conducted in the general population, and none of these studies focused on the epidemiology of CSP conditions. Furthermore, none of these studies explored the trends of incidence of shoulder pain. Therefore, the current study aimed to explore the prevalence and incidence of CSP in the year 2019 by age, sex and UK regions, and the trends in both incidence and prevalence of CSP in the UK during the period from 2000 to 2020 using the CPRD which is a large national representative primary care database.

3.2 Methods

3.2.1 Ethical approval

The study was approved by the Independent Scientific Advisory Committee (ISAC) for conducting research using the UK CPRD (protocol number: 21_000633) (Appendix 9, pages 363-382). The approval grants the legitimacy to conduct research using the CPRD to determine the prevalence, incidence, and associated risk factors of CSP in the UK.

3.2.2 Funding

This study was jointly funded by the University of Nottingham and the PhD studentship from the Kuwait Cultural Office and the Ministry of Health in Kuwait.

3.2.3 Data source

For this study, CPRD Aurum data was used for people registered from 1st January 2000 until 31st December 2020.

3.2.4 Case definition of chronic shoulder pain

The case definition of CSP used in this study was having at least two consultations for shoulder pain in primary care within a six-month period and with no history of severe acute shoulder trauma or fracture in the six months prior to the first consultation for shoulder pain. The sample size calculation presented in Appendix 9, page 383. Medical codes were extracted to identify people with a diagnosis of CSP within the CPRD between 1st January 2000 to 31st December 2020 (Appendix 10, Table 9-6, pages 384-387). The list of CSP used in this study was derived from the Read codes of CSP from Keele university (https://www.keele.ac.uk/mrr/), and an extensive search was undertaken using an open safely code lists platform, which allows creating and sharing of code lists (https://www.opencodelists.org) to include other CSP conditions. The list of CSP codes included 120 codes for chronic shoulder conditions. The code list was initially generated by one of the researchers (Nouf Alotaibi (NA), physiotherapist and PhD student) and independently validated by two others, specifically Professor Michael Doherty (MD), Emeritus Professor of Rheumatology at the University of Nottingham and internationally recognised expert in MSK conditions, and Dr. Barbara Iyen (BI), Clinical Associate Professor in Primary Care at the University of

Nottingham, with expertise in public health and epidemiology. This multidisciplinary validation process ensured both clinical relevance and coding accuracy of the final list.

3.2.5 Rational for the definition of CSP

Chronic pain is typically defined as pain lasting for three months or more. While direct symptom duration data may not always be available in primary care settings, repeated consultations can serve as a practical proxy to identify patients with pain persisting beyond an acute phase (Mills et al., 2016). The IASP (International Association for the Study of Pain) defines chronic pain as pain that persists for three months or longer (Treede et al., 2019). The definition used was specifically designed for this study to capture chronic cases of shoulder pain within the large database. It has not been reported directly from previous studies but aligns with approaches used in previous research on MSK conditions (Coates et al., 2023), where repeated consultations within a specific time frame serve as proxies for chronicity in the absence of direct symptom duration data (Coates et al., 2023). Coats et al.,(2023) defined a chronic pain episode as a series of pain-related GP consultations relating to pain symptoms associated with chronic low back pain (CLBP) or OA and/or a pain-related specialist consultation (rheumatology, orthopaedics, or pain management) in the secondary care setting, where gaps between visits were ≤12 months.

The reason for choosing more than one consultation was to include people with CSP and to exclude acute self-limiting cases. The rationale is

that people experiencing short-term or self-limiting pain episodes are less likely to return for repeated consultations. By adopting this definition, it was intended to avoid transient conditions and identify people with persistent shoulder pain while excluding cases related to acute injuries, thereby focusing on non-traumatic or degenerative causes of CSP. People having shoulder surgery in the three months before the first consultation were excluded to ensure that only people with chronic non-surgical shoulder pain are included, and not those recovering from recent procedures. People with cervical root entrapment/neuralgia three months before or after incident CSP were excluded because people with cervical disorders often experience referred pain to the shoulder, which could confound the results of the study. People with a previous diagnosis of rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis were excluded because these conditions could lead to secondary shoulder pain due to joint involvement. By excluding people with these conditions, the study was more focused on primary CSP.

3.2.6 Selection of study population

3.2.6.1 Inclusion criteria

Inclusion criteria were: 1) age 18 and above; 2) registered for at least one year after the earliest date that the practice started contributing quality-assured (the up-to-standard) data to CPRD; 3) a minimum of two GP consultations within a six months period for the same problem/complaint (the reason for choosing more than one consultation was to include patients with CSP and to exclude acute self-limiting cases; the first

consultation date was used as the index date); and 4) data quality flagged as ‘acceptable’ in the database.

3.2.6.2 Exclusion criteria:

1. Severe acute trauma, including fracture, in the past 6 months prior to the first consultation
2. Shoulder surgery within the previous 3 months.
3. A diagnosis of cervical root entrapment and neuralgia 3 months before or after incident shoulder pain (to exclude patients with referred pain to the shoulder)
4. Previous diagnosis of rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis.

The methodological process for inclusion and exclusion criteria is presented In Appendix 11 (pages 388-390) .

3.2.7 Study design

A cross-sectional study and a cohort study were conducted to examine the prevalence and incidence, respectively, of CSP each year from 2000 to 2020 in the UK, according to age, sex and geographic distribution. The trend of prevalence and incidence of CSP in the UK over the past 20 years (2000-2020) was determined. Additionally, the prevalence of different diagnostic codes for CSP in the year 2019 was examined.

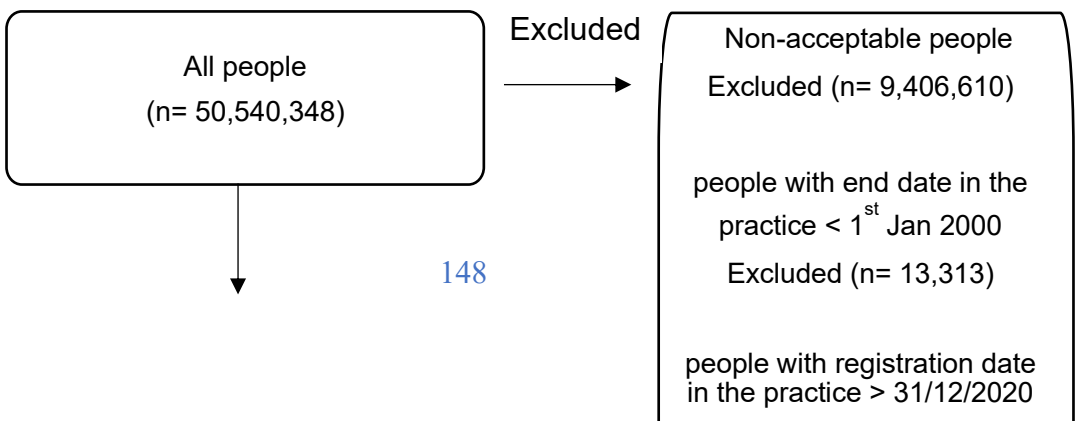
3.2.8 Outcomes

- Primary outcomes:
    1- Current prevalence and incidence of CSP in the UK. To avoid the influence due to the COVID-19 pandemic and lockdown, the prevalence and incidence in 2019 were used to present the current prevalence and incidence.
    2- The prevalence and incidence for the year 2019 according to age, sex and UK region
    3- Trends of CSP prevalence and incidence over the past 20 years (2000 – 2020).

- Secondary outcomes:
    1- Prevalence of different types of CSP diagnosis in 2019

3.2.9 Data management

All data management was conducted using R statistical software (3.4.2) and STATA SE v 15 software. Data were extracted by YV and then downloaded and saved on OneDrive and R Drive. Data management is explained in Figure 3.1.



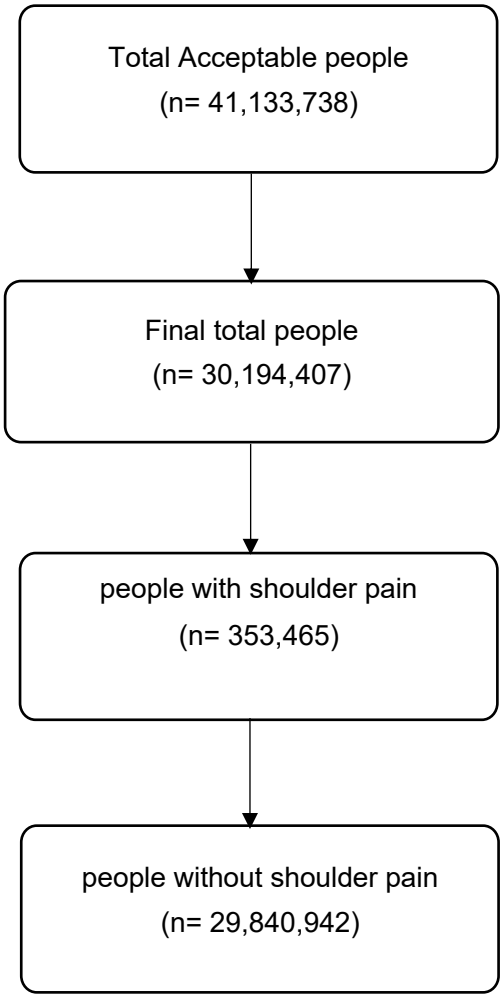


Figure 3.1. CPRD study flow chart

3.2.10 Data analysis

All data analysis was conducted using R (3.4.1) and STATA SE v 15 software. Cross-sectional studies were conducted to examine the prevalence of shoulder pain each year from 2000 to 2020. The current

prevalence of shoulder pain in the year 2019 was calculated by dividing the number of people diagnosed with shoulder pain at 1st July 2019 by the total number of people in the sample at that time point in the calendar year.

For incidence rate calculations, the eligible population for incidence rate calculations were those with their first time recording of shoulder pain during the study period. People at risk (i.e., no previous diagnosis of shoulder pain) were identified at 1st January of 2019 and followed them until 31st December 2019 to identify incident cases of shoulder pain (i.e. the first diagnosis of shoulder pain during that year). Total person-years of follow up were calculated by summing the individual follow-up times for all participants. The prevalence and incidence for the year 2019 was reported overall and by age, sex, and UK regions and the prevalence of different types of shoulder pain in 2019 was also examined. The 95% confidence interval (CI) was calculated for the prevalence and incidence.

The trend of prevalence and incidence of shoulder pain in the UK over the past 20 years (2000-2020) was calculated. A similar approach as mentioned above for 2019 was followed for each year starting from 2000 to 2020. The 95% confidence interval (CI) was calculated for the prevalence and incidence for the 20 years (2000-2020). Prevalence and incidence for each year from 2000 until 2020 was standardised according to the age and sex structure of the 2019 CPRD population.

The Joinpoint Regression Program (V.4.0.4) was used to estimate trends of prevalence and incidence of CSP. The program uses Bayesian

Information Criterion to generate different numbers of 'joinpoints' in time when the trend of prevalence and incidence of CSP changed significantly and to determine the best-fit data series. Initially models contained zero joinpoints (i.e., a straight line fitted to the data) with joinpoints added whenever a change in trend over time was statistically significant, with the user specifying the maximum number of allowable joinpoints (Kim et al., 2000, Ghafoor et al., 2003). Using a Bayesian information criterion approach, a maximum of three joinpoints were selected (Kim et al., 2000, Ghafoor et al., 2003). Annual percentage changes (APC) for each segment and average APC for the entire study period of prevalence and incidence of CSP were calculated. The significance level was set at 0.05.

3.3 Results

People aged 18 and above with a diagnosis of CSP were identified from the CPRD Aurum between January 2000 to December 2020 (Figure 3.1). Patients with at least 2 consultations for shoulder pain within 6 months were selected (n= 353,465). The total number of patients who met the inclusion criteria for calculating the prevalence and incidence of CSP was 30,194,407.

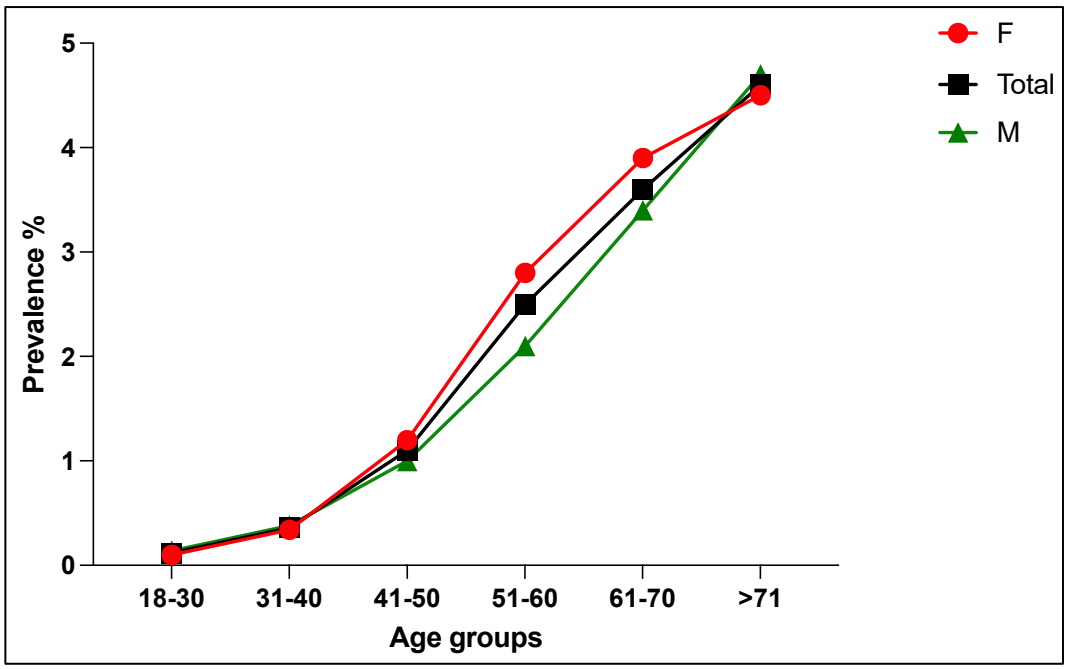
3.3.1 Current prevalence and Incidence of chronic shoulder pain in the UK.

Of 11,092,332 eligible individuals in 2019, there was 202,876 prevalent cases of CSP, giving a prevalence of 1.91% (95% CI 1.91% to 1.92%).

Females had a higher prevalence of CSP (2.04 %, 95% CI 2.03% to 2.05%) than males (1.68 %, 95% CI 1.67% to 1.69%). CSP prevalence was increased in both females and males aged 40 years and above, peaking at 4.5% in those aged >70 years (Figure 3.2a). In people aged 40 to 70 years, the prevalence was higher in females (2.85%, 95% CI 2.83% to 2.86%) than in males (2.6 %, 95% CI 2.59% to 2.62%) (Figure 3.2a).

There was a total of 11,164,066 person years of follow-up in 2019 during which 13514 incident cases of CSP were identified, giving an overall incidence of 1.2 (95% CI 1.19 to1.23) per 1,000 person years. The incidence per 1,000 person years of CSP was higher in females (1.35, 95% CI 1.32 to1.38) than in males (1.06, 95% CI 1.04 to1.09). As shown in Figure 3.2b, the incidence of CSP increased in people aged 40 years and above in both males and females, then it decreased slightly in males aged 70 years and above. Females had a higher incidence of CSP (2.12, 95% CI 2.07 to 2.17, per 1,000 person years), than males (1.63, 95% CI 1.59 to1.68 per 1,000 person years) in people aged 40 years and above.

(A)



(B)

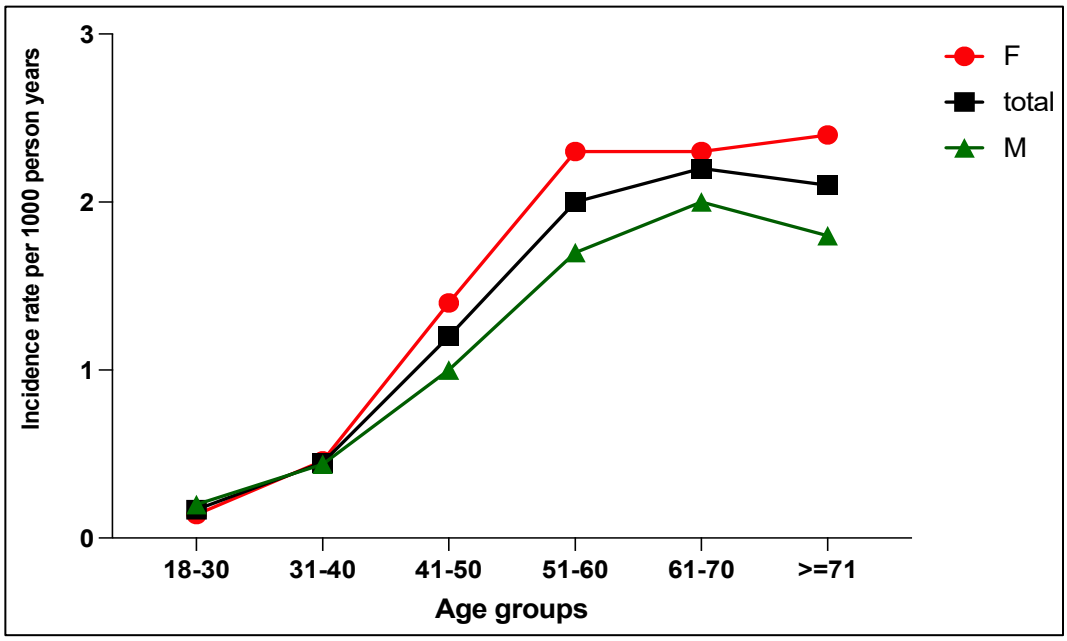


Figure 3.2 Age-specific prevalence (A) and incidence (B) of chronic shoulder pain in 2019 (red-females; green-males; back-total).

3.3.2 The prevalence of different types of chronic shoulder pain diagnosis in the year 2019

The most common eight diagnostic codes for CSP identified in the CPRD database in 2019 were: shoulder bursitis, acromioclavicular joint arthralgia, painful arc syndrome, glenohumeral OA, RC syndrome, RC tear, frozen shoulder, RC syndrome and shoulder pain (Figure 3.3). Shoulder pain and RC syndrome codes were those most commonly used by GPs giving an individual prevalence of 0.75% (95% CI 0.75 to 0.76) and 0.49% (95% CI 0.49 to 0.50), respectively.

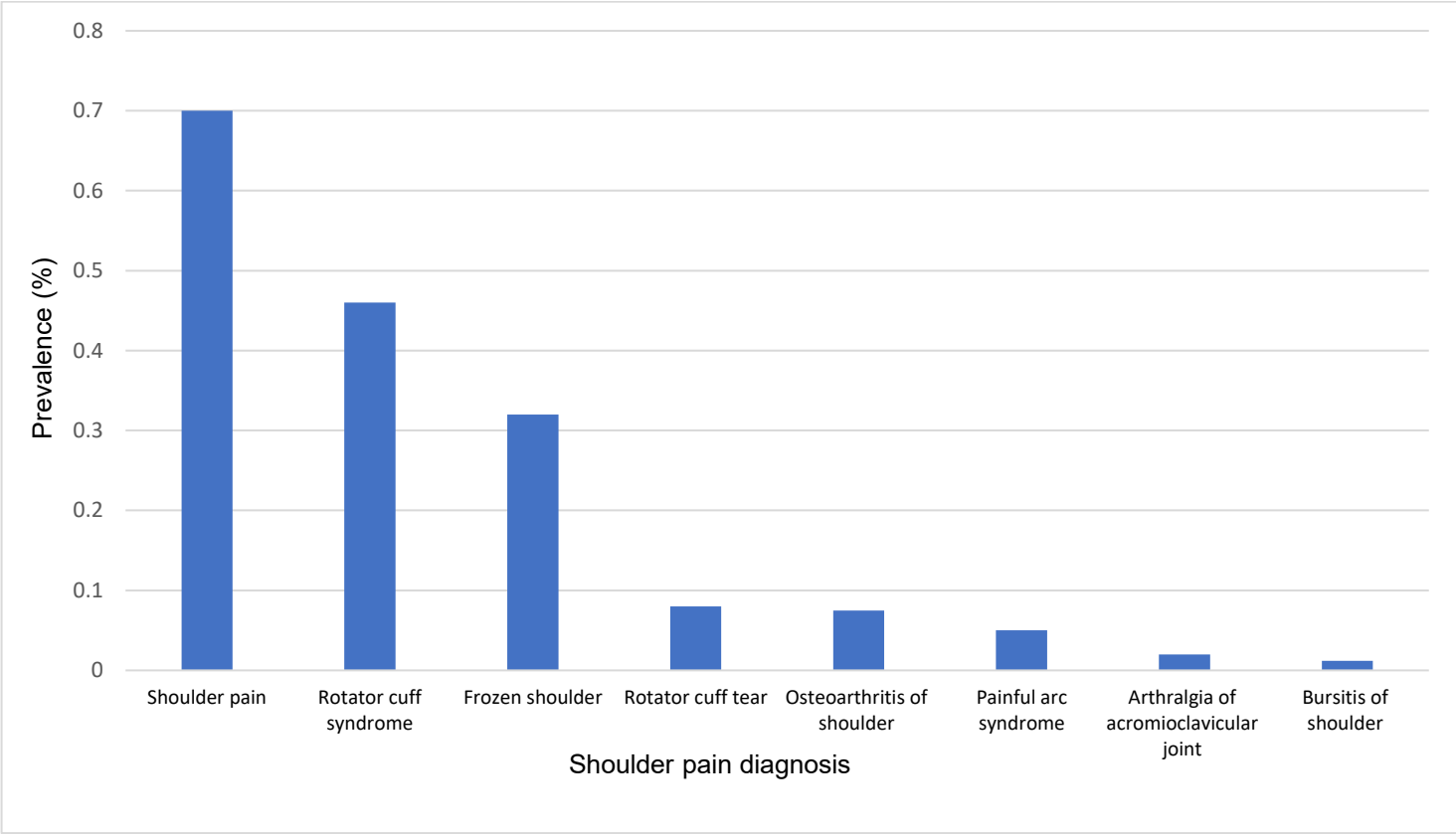


Figure 3.3 Prevalence of different chronic shoulder pain diagnoses in the year 2019.

3.3.3 Trend of prevalence and incidence of chronic shoulder pain between 2000 and 2020

Table 3-1 shows the trends in prevalence and incidence of CSP from 2000 to 2020. In general, both crude and standardised overall prevalence estimates increased over time during this period. However, both crude and standardised incidence estimates increased from 2000 to 2011, then decreased back to the 2000 level. The standardised estimates were slightly higher than the crude ones, accounting for the fact that the population structure was different in the year 2019 and 2000.

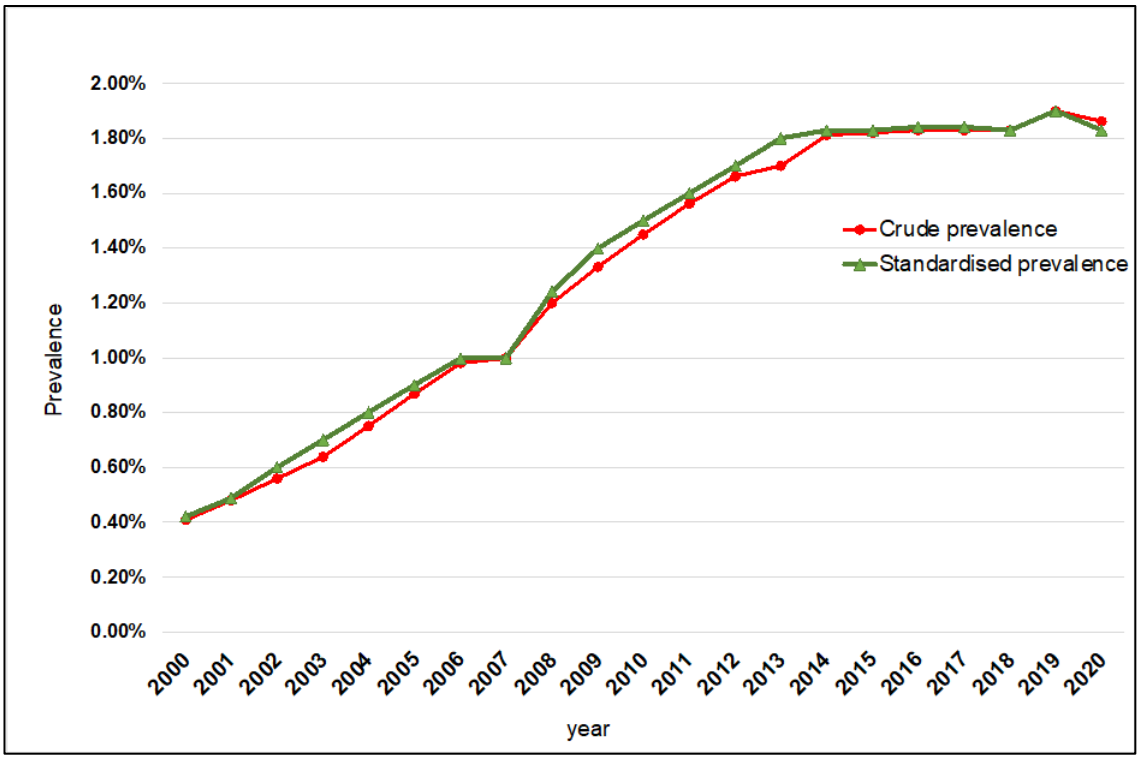
The age and sex standardised prevalence of CSP increased over the study period from 0.42% (95% CI 0.42 to 0.43) in 2000 to 1.83 (95% CI 1.83 to 1.84) in 2020 (Figure 3.4a). Furthermore, there were two joinpoints at 2004 and 2012 with respective APCs of 17.81% (12.2 to 23.7), 10.29% (8.8 to 11.7) and 0.63% (-0.2 to 1.5) for segment 2000–2004, 2004–2012 and 2012–2020, respectively (Figure 3.5).

The age and sex-standardised incidence also increased significantly from 0.88 (95% CI 0.86 to 0.9) in 2000 to 2.00 (95% CI 1.96 to 2.00) per 1000-person years in 2011, then decreased back to the 2000 level (Figure 3.4b). The significant decline in 2020 coincided with the pandemic (COVID 19). There were two joinpoints at 2004 and 2011 with respective APCs of 18.7 (7.6 to 29.6), 2.8 (-2.2 to 8) and -8.2 (-10.7 to -5.7) for segment 2000–2004, 2004–2011 and 2011–2020, respectively (Figure 3.6).

Table 3-1 Crude and age and sex standardised prevalence and incidence of chronic shoulder pain from 2000 to 2020

Year	Eligible population	Crude prevalence % (95% CI)	Age and sex standardised prevalence % (95% CI)	New cases	Person years	Incidence rate (95% CI) per 1000 person-years	Age and sex standardised incidence rate (95% CI)
2000	8,290,526	0.41(0.40,0.41)	0.42 (0.42,0.43)	7289	8486862	0.80 (0.83 0.87)	0.88 (0.86,0.90)
2001	8,507,293	0.48 (0.47,0.48)	0.49 (0.49,0.50)	8971	8797974	0.96 (0.99,1.04)	0.97 (0.94,0.98)
2002	8,666,178	0.56 (0.55,0.56)	0.60 (0.58,0.60)	10333	8994771	1.14 (1.12,1.17)	1.20 (1.15,1.20)
2003	8,903,632	0.64 (0.64,0.65)	0.70 (0.66,0.70)	12519	9041854	1.38 (1.36,1.41)	1.40 (1.38,1.40)
2004	9,060,695	0.75 (0.75,0.76)	0.80 (0.77,0.80)	14617	9223488	1.58 (1.5,1.61)	1.63 (1.60,1.65)
2005	9,183,707	0.87 (0.86,0.87)	0.90 (0.89,0.90)	15724	9443151	1.66 (1.63,1.70)	1.68 (1.66,1.70)
2006	9,338,158	0.98 (0.98,0.99)	1.00 (1.0,1.10)	16645	9600071	1.73 (1.70,1.76)	1.80 (1.75,1.80)
2007	9,497,766	1.00 (1.0,1.10)	1.00 (1.0,1.10)	17507	9606080	1.82 (1.79,1.84)	1.84 (1.82,1.88)
2008	9,641,986	1.20 (1.2,1.22)	1.24 (1.23,1.25)	18222	9735029	1.87 (1.84,1.9)	1.90 (1.88,1.90)
2009	9,739,329	1.33 (1.33,1.34)	1.40 (1.37,1.40)	19108	9964209	1.90 (1.89,1.94)	1.94 (1.91,1.96)
2010	9,862,577	1.45 (1.44,1.46)	1.50 (1.47,1.50)	19627	10083636	1.94 (1.91,1.97)	1.98 (1.95,2.00)
2011	9,951,774	1.56 (1.5,1.60)	1.60 (1.58,1.60)	19848	10033362	2.00 (1.95, 2.00)	2.00 (1.96,2.00)
2012	10,089,619	1.66 (1.65,1.67)	1.70 (1.67,1.70)	19173	10170891	1.88 (1.85,1.91)	1.90 (1.89,1.94)
2013	9,986,825	1.75 (1.65,1.75)	1.80 (1.78,1.80)	16627	10234206	1.62 (1.60,1.64)	1.63 (1.59,1.64)
2014	10,063,864	1.81 (1.80,1.82)	1.83 (1.80,1.83)	14090	10304359	1.36 (1.34,1.39)	1.40 (1.35,1.40)
2015	10,236,584	1.82 (1.82,1.83)	1.83 (1.82,1.84)	14011	10313375	1.35 (1.33,1.40)	1.35 (1.33,1.37)
2016	10,433,313	1.83 (1.82,1.84)	1.84(1.83,1.85)	13798	10527742	1.31 (1.28,1.33)	1.32 (1.3,1.34)
2017	10,648,742	1.83 (1.82,1.84)	1.84 (1.83,1.85)	13888	10862196	1.27 (1.25,1.30)	1.27 (1.25,1.30)
2018	10,859,453	1.83 (1.82,1.84)	1.83 (1.83,1.84)	13806	11072909	1.24 (1.22,1.26)	1.26 (1.23,1.30)
2019	11,092,332	1.91 (1.91,1.92)	1.91 (1.91,1.92)	13514	11164066	1.20 (1.19 ,1.23)	1.20 (1.19 ,1.23)
2020	10,912,158	1.86 (1.86, 2.00)	1.83(1.83,1.84)	8063	10686985	0.75 (0.73, 0.77)	0.74 (0.73,0.76)

(A)



(B)

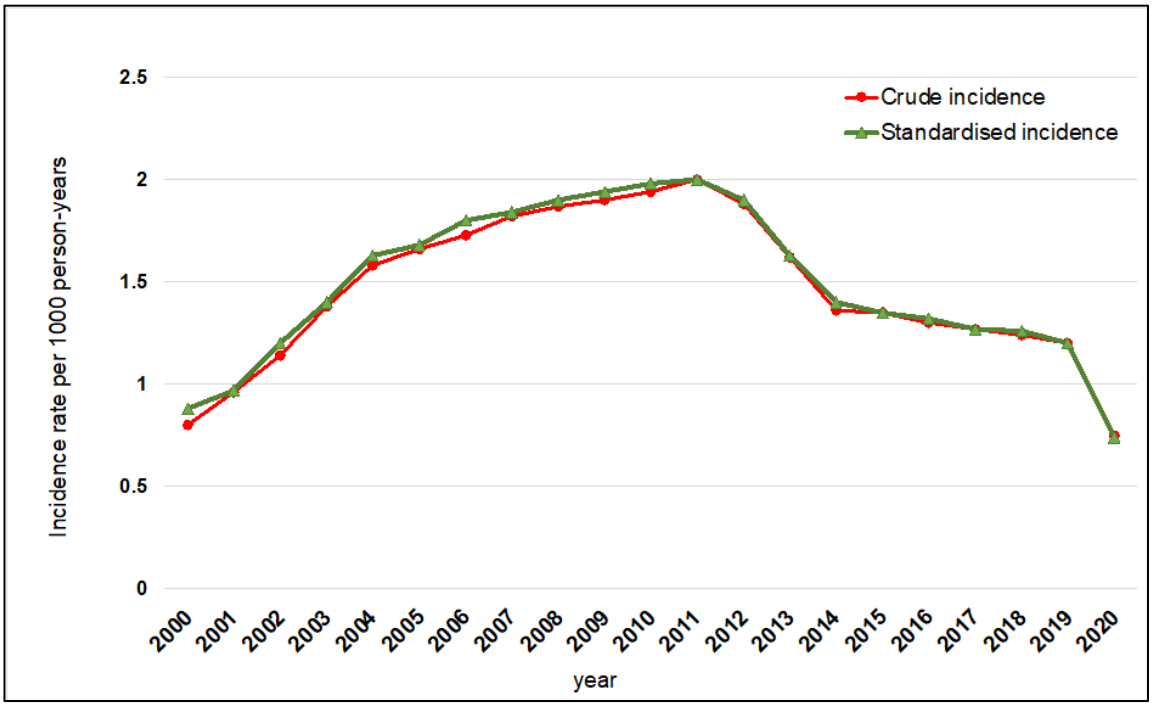


Figure 3.4 Crude and age and sex standardised prevalence (A) and incidence (B) of chronic shoulder pain from 2000 to 2020.

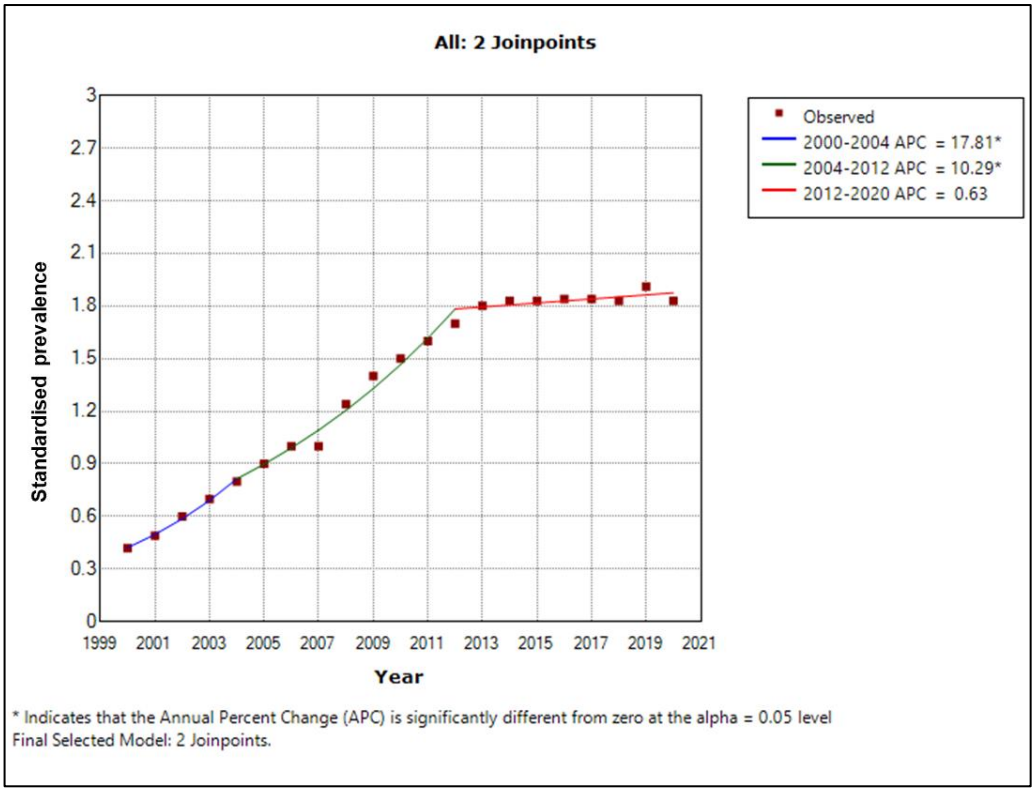


Figure 3.5 Trends of prevalence of chronic shoulder pain

Two joinpoints at 2004 and 2012 with respective APCs of 17.81% (12.2 to 23.7), 10.29% (8.8 to 11.7) and 0.63% (-0.2 to 1.5) for segment 2000–2004, 2004–2012 and 2012–2020, respectively

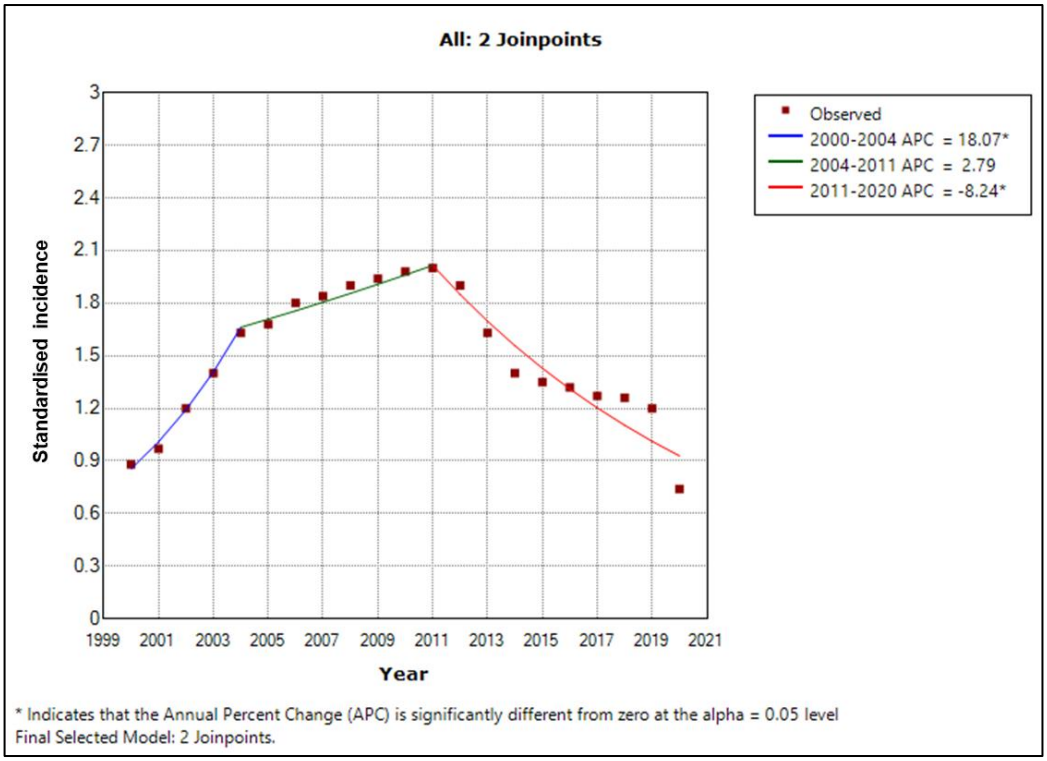


Figure 3.6 Trends of incidence of chronic shoulder pain

Two joinpoints at 2004 and 2011 with respective APCs of 18.7(7.6 to 29.6), 2.8 (-2.2 to 8) and -8.2 (-10.7 to -5.7) for segment 2000–2004, 2004–2011 and 2011–2020, respectively

3.3.4 Specific and non-specific chronic shoulder pain

The prevalence of specific CSP, that is those with a specified cause, increased from 2000 to 2020. After the year 2012, specific CSP diagnoses continued to increase, and the use of non-specific CSP terms declined (Figure 3.7).

With respect to incidence, after the year 2005 rates for specific CSP diagnoses decreased. However, in 2013 a sharp decline was found in the incidence of non-specific CSP whereas the incidence of specific CSP diagnoses increased (Figure 3.8).

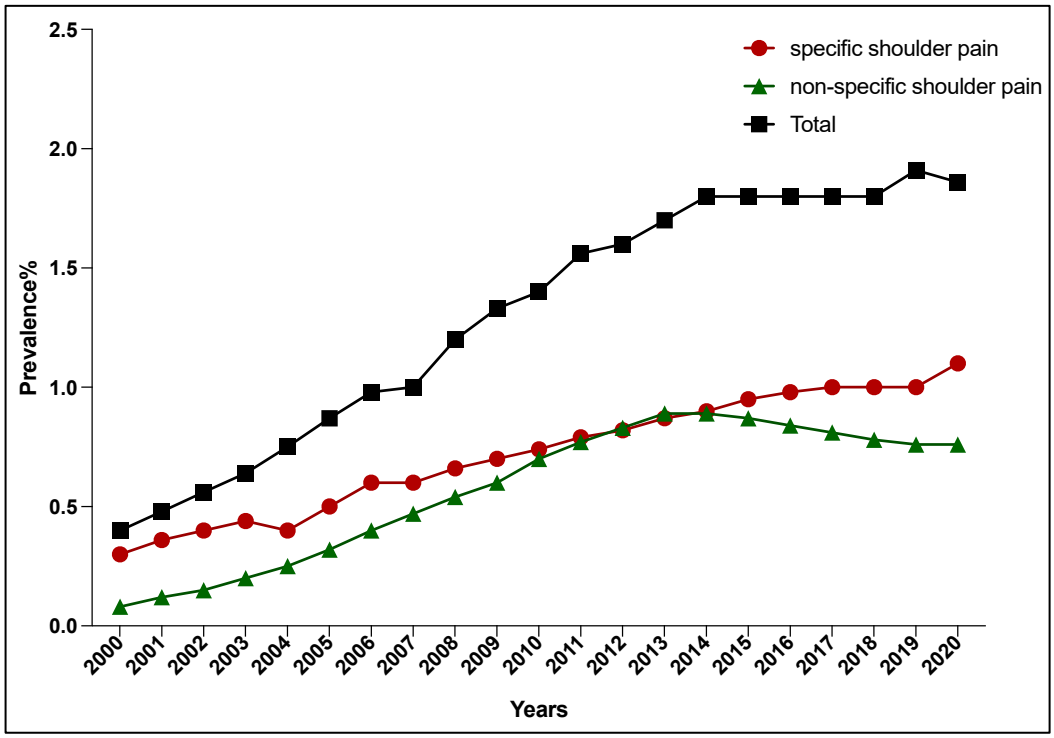


Figure 3.7 Prevalence of specific and non-specific chronic shoulder pain

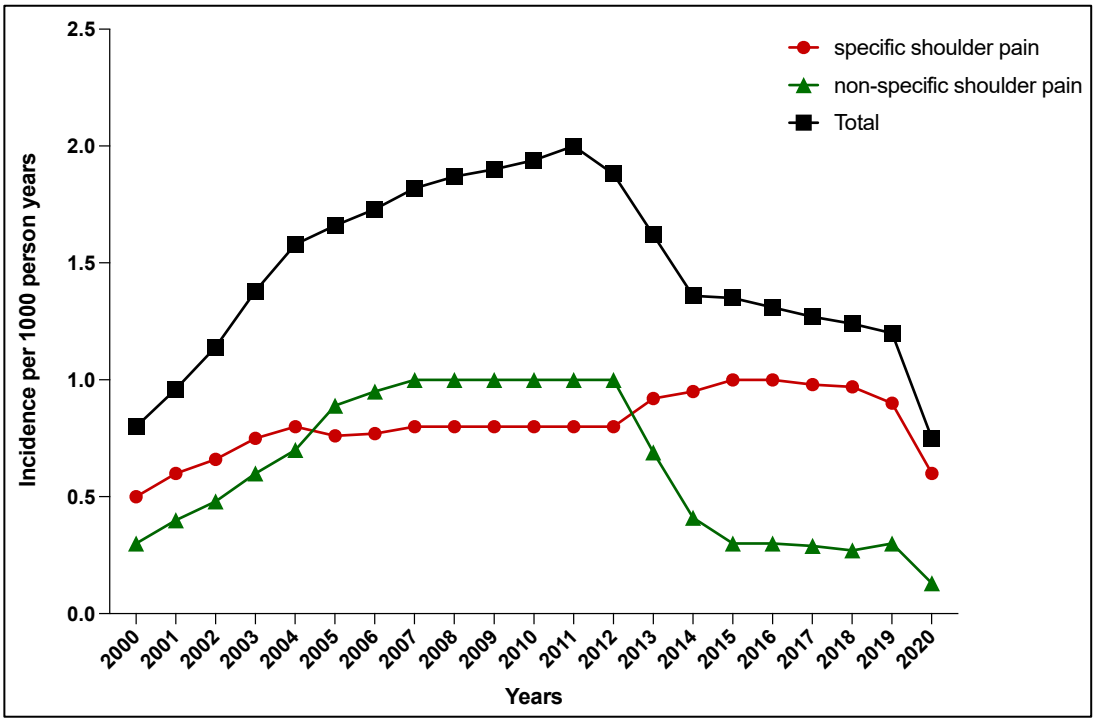


Figure 3.8 Incidence of specific and non-specific chronic shoulder pain

3.3.5 Geographic variation of chronic shoulder pain in 2019

Both the prevalence and incidence of CSP were not uniform throughout the UK. As shown in Figure 3-9a, the age and sex standardised prevalence (95% CI) of CSP was highest in Yorkshire and the Humber (2.4%, 95% CI 2.3% to 2.4%) and the East of England (2.2%, 95% CI 2.2 to 2.3). Regions with the lowest prevalence of CSP were London (1.4%, 95% CI 1.4% to 1.4%) and Northern Ireland (1.2%, 95% CI 1.1% to 1.3%).Yorkshire and the Humber and the North West had the highest incidence (2.2, 95% CI 2.0 to 2.4 and 2.0, 95% CI 2.0 to 2.2 per 1,000 person-years, respectively). The North East and Northern Ireland were the regions with the lowest standardised incidence of CSP (1.5, 95% CI 1.3 to 1.7), and 0.32, 95% CI 0 to 0.3 per 1000 person-years, respectively) (Figure 3.9b)

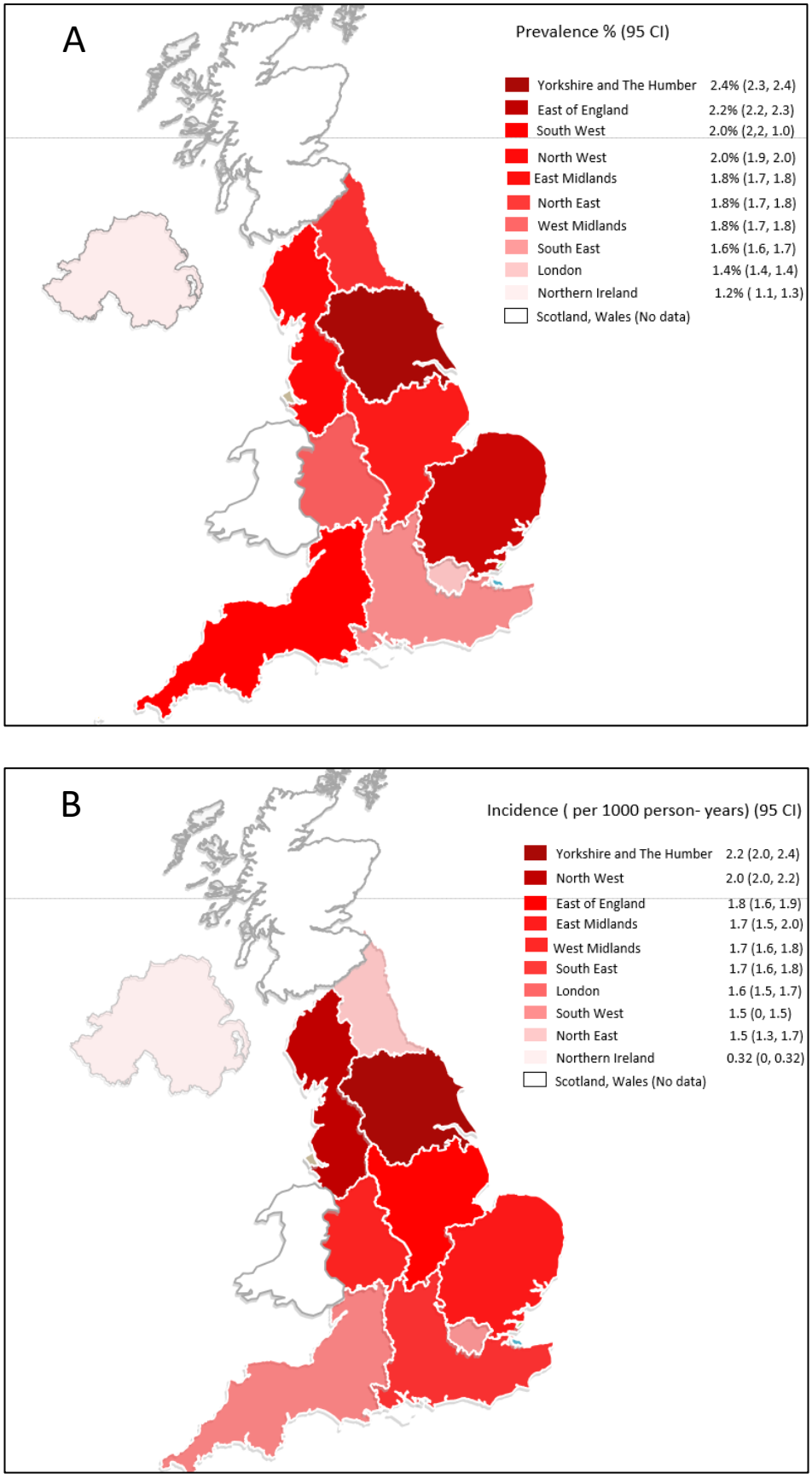


Figure 3.9 Geographic variations in the prevalence (A) and incidence (B) of chronic shoulder pain in the UK in 2019

3.4 Discussion

This study demonstrates that the burden of CSP in the UK during the study period was higher than previously thought, with a current (year 2019) prevalence of 1.9% and an incidence of 1.2 per 1000 person-years in people aged 18 years and over. The prevalence of CSP continued to increase from 2000 to 2019, while the incidence of CSP showed an increase from 2000 to 2011 but then a decline after 2011. Females had a higher prevalence of CSP than males in those aged 40 years and above, peaking in those aged >70 years (4.5%). Females had a higher incidence of CSP (2.12, 95% CI 2.07 to 2.17 per 1,000 person years), than males (1.63, 95% CI 1.59 to 1.68 per 1,000 person years) in those aged 40 years and above. Both prevalence and incidence of CSP declined in 2020 which might be due to fewer consultations during the COVID-19 pandemic and lockdown. Shoulder pain and RC syndrome were the most common codes used by GPs in the year 2019. Geographically, CSP was not distributed uniformly within the UK, the highest prevalence and incidence of CSP being found in Yorkshire and the Humber region.

Very few studies have addressed the prevalence and incidence of CSP in the UK. The current estimates of prevalence and incidence in general fall within the previous reported ranges. Previous studies showed an increase in shoulder pain prevalence in the UK up until 2000, when a prospective cohort study by Linsell et al (2006) assessed the incidence and prevalence of shoulder complaints in UK in 2000 using the IMS Disease Analyzer-Mediplus UK. In that study, the overall annual prevalence and

incidence of adult patients consulting GPs for shoulder pain was 2.4% and 1.47%, respectively. There was a significant increase in prevalence from 1% in the population aged 18–29 years old to 4% in those aged > 80 years old and the prevalence was higher in females aged ≥ 40 years than in males aged ≥ 40 years old (X^2; P< 0.001). Additionally, they reported that a limited number of codes were used for recording shoulder pain diagnosis, with just five out of 426 Read codes related to shoulder conditions accounting for 75% of the diagnoses recorded by GPs. These five codes were sprained shoulder, shoulder joint pain, dislocated shoulder, RC shoulder syndrome and shoulder syndrome. Shoulder syndrome was the most common diagnostic code used by GPs, which aligns with the current results. However, the study by Linsell et al. (2006) included the use of the Mediplus database which has limited regional coverage of general practices in Scotland and Northern Ireland, whereas the CPRD data includes more regions in the UK. Recently, Hinsley et al. (2022) explored the prevalence of RC tears in a large general practice in North London. The study participants were part of the Chingford Females cohort, which included 464 females aged between 64 and 87. Full-thickness tear was defined as having at least one unilateral full-thickness tear using MSK ultrasound assessment on bilateral shoulders (Hinsley et al., 2022). The prevalence of full-thickness tears was 22% and showed to be increase with age (Hinsley et al., 2022). That study demonstrated a higher prevalence figure compared to the current study, which can be due to different case definition of shoulder pain, and the sample size. Additionally, the clinical presentation of RC tears varies across

populations and sometimes may not be associated with symptoms that require medical help, which might underestimate the true prevalence of shoulder pain in general practices.

3.4.1 Trends of incidence and prevalence

Surprisingly, there was an overall slow decline in incidence rates of CSP since 2011. In the current study, Joinpoint analysis revealed a sharp decline in incidence from 2011 to 2020. Swain et al. (2020) found a similar overall decline in incidence rates for OA from 1998 to 2017. An increase in incidence rate of specific CSP was found this century, whereas the incidence rate for 'unspecified' CSP declined, indicating a possible improvement in clinical coding. Although the incidence rate declined over the second part of the study period, prevalence continued to increase. There was an increase in standardised prevalence of CSP from 2000 to 2019, with an annual percentage increase of 7.7%. The increased prevalence trend could be due to the cumulative nature of the longitudinal database. CPRD is a dynamic electronic health records database with people moving in and out of the database at any time point, which might affect the eligible population for every year. Also, the prevalence trend has become more stable since 2007/2008, which might explain the effect of declining incidence.

Another case definition, which requires specific shoulder pain diagnosis and non-specific CSP diagnosis, was used to identify if the coding toward specific diagnosis has been improved in the past 20 years. The prevalence and incidence of specific shoulder pain from 2000 to 2020

suggests that the GP coding might have changed in 2004/2005 and 2012/2013. Similar findings were found in previous studies on gout by Kuo et al. (2015) and OA by Swain et al. (2020). Furthermore, a cross-sectional study by Rockenschaub et al. (2020) identified changes in cardiovascular disease recording in two English electronic health records databases (CPRD Gold and secondary care (HES data) between 2001 and 2015. They found an improvement in primary care coding in 2004/2005, which might be linked to the introduction of the Quality and Outcomes Framework (QOF), a financial incentive scheme introduced in 2004 aimed to improve the management and recording of chronic disease in primary care (Gillam and Siriwardena, 2011). Also, they detected notable changes in primary care coding after 2011, and this potentially was due to the introduction of new practice management software that was incompatible with CPRD Gold.

Another possibility is that ultrasound imaging, which in recent years has become much more widely available outside of a hospital setting might be used more as an investigation by GPs and this will often give a specific diagnosis for CSP. Therefore it may be that improvements in coding by GPs may have led to the apparent decline of the incidence of gout (Kuo et al., 2015), OA (Swain et al., 2020) and CSP in the UK. There is a paucity of evidence regarding the experience of GPs in diagnosing shoulder MSK conditions in primary care. Artus et al. (2017) explored the diagnosis of shoulder pain by GPs in the UK between April and July in the year 2015. Binley's database was used to select 5000 UK GPs randomly. A random sample of 2500 GPs received a postal questionnaire, and an email with a

link to an online survey was sent to the remaining 2500 (Artus et al., 2017). The questionnaire included three main sections, GP characteristics (e.g. sex, duration of clinical experience), scenario-based questions, and general questions. For scenario-based questions GPs were asked to choose the clinical diagnosis from a list of options: acute RC tear, glenohumeral OA, acromioclavicular joint disorders, RC tendinopathy, referred neck pain, and adhesive capsulitis (Artus et al., 2017). For each diagnosis selected GPS were asked to rate their confidence in the diagnosis on a 7-point scale (‘definitely yes’, ‘most likely’, ‘likely’, ‘not sure’, ‘unlikely’, ‘most unlikely’ and ‘definitely not’). GPs were asked whether they would request investigations for each patient. If yes, they were asked to select from several options such as blood tests, plain radiograph, MRI and ultrasound and state the reason for choosing this investigation whether to confirm or to exclude the diagnosis (Artus et al., 2017). The general questions were not related to specific diagnoses and aimed to assess GP decision making in terms of requesting MRI scans and ultrasound and management decisions. The findings demonstrated that 56% of the GPs who selected the correct diagnosis of RC tendinopathy indicated they were confident of this diagnosis, 10% were not sure, and 26% stated the diagnosis was likely. The majority of GPs (83%) indicated that they were confident about adhesive capsulitis diagnosis, 4% were not sure, and 9% stated that the diagnosis was likely. Plain shoulder radiographs were the most common investigation for RC tendinopathy (60%), followed by blood tests (42%) and ultrasound scans (38%). For adhesive capsulitis, the most common investigations were

blood tests (60%), plain shoulder radiographs (58%), and ultrasound scans (31%). A theme of GPs' apparent reluctance to base their diagnosis only on clinical assessment appears to be reinforced by the fact that, even when they were confident in the diagnosis, they requested investigations to confirm it. The results of this survey might represent low confidence among GPs in the UK in making a specific diagnosis on clinical assessment alone and the frequent use of investigations, particularly blood tests and plain radiographs. However, in this study the coding of shoulder disorders by GPs was not discussed. Furthermore, the low response indicates that the results should be interpreted with caution.

In light of the challenges related to diagnostic accuracy and data quality, there has been growing emphasis on incorporating patient-reported outcomes into electronic health records (EHRs) to more effectively reflect the burden of MSK conditions. Yu et al. (2021) conducted a population-based study to explore the feasibility of using routinely collected primary care electronic health records (EHRs) to estimate the population health burden of non-inflammatory MSK conditions in England. They collected patient-reported data through a local survey of adults aged >35 years presenting to English general practices over 12 months for low back pain, shoulder pain, osteoarthritis and other regional MSK disorders. Then, they combined patient-reported data with linked EHRs to develop and validate models for estimating five key health indicators, specifically high-impact chronic pain, MSK-specific health status (MSK-HQ), quality of life (EQ-5D), and moderate-to-severe low back and shoulder pain. The authors applied their models, utilising code lists, to an independent national

primary care electronic health record database (CPRD) to generate national and regional estimates for each health indicator across three consecutive years (2014/15, 2015/16, and 2016/17). After applying models to national EHR, the study estimated that 31.9% of adults aged 35 years and over who had consulted for any non-inflammatory MSK condition in 2016–2017 experienced high impact chronic pain. Approximately, 26.0% had moderate-to-severe chronic LBP, and 27.8% had moderate-to-severe CSP. Yu et al. (2021) concluded that routinely collected EHR data can be effectively used to generate national and subnational estimates of MSK health burden. However, this study also emphasised the limitations of using coded data, especially the under-representation of subjective factors like impact and severity of pain. In the absence of direct patient-reported outcomes, their techniques set a useful guideline for the secondary use of EHRs to estimate the burden of MSK conditions. The prevalence of CSP identified in the present study was 1.9% using CPRD Aurum data and a strict case definition of chronicity. This is considerably lower than the prevalence estimate of moderate-to-severe shoulder pain (27.8%) reported by Yu et al. (2021) using CPRD Gold data and predictive modelling applied to a consulting MSK population. This discrepancy likely reflects differences in study populations, case definitions, and methodological approaches, with the present study focusing exclusively on chronic cases identified through coded consultation data, while Yu et al. (2021) estimated the burden of moderate-to-severe pain using a model incorporating proxy measures for symptom severity.

3.4.2 Geographical distribution of chronic shoulder pain

There appeared to be regional variations in CSP. However, such variation in CSP needs careful interpretation because of the non-uniform practices involved in the CPRD database. The patterns for prevalence and incidence were similar, with the Yorkshire and Humber regions having the highest estimates for both prevalence and incidence. Regional variation in MSK conditions within the UK has been examined previously in two studies. In 2015, Kuo et al. reported a higher prevalence and incidence of gout in the North East and Wales, with a prevalence of 3.11% (95% CI 3.00% to 3.23%) and 2.98% (95% CI 2.93 to 3.02), respectively, and an incidence of 2.28 (95% CI 2.13 to 2.43) and 2.17 (95% CI 1.85 to 2.54) per 1000 patient-years, respectively (Kuo et al., 2015).

More recently, Swain et al. (2020) reported that the prevalence of OA was highest in Scotland and Northern Ireland ranging from 7% (95% CI 6 to 7) to 9% (95% CI 7 to 9), but the incidence was highest in the East Midlands and the North East (12.6, 95% CI 12 to 13 per 1000 person-years and 11.7, 95% CI 11 to 12 per 1000 person-years, respectively) (Swain et al., 2020). However, only one previous study, using the THIN database, has examined the geographical variation for incidence of RC tendinopathy from 1987 to 2006 (White et al., 2014). The regional distribution of incidence demonstrated an even spread across 13 UK health authorities apart from Wales, where the incidence was significantly higher (122 per 100 000 person-years; $p < 0.001$) (White et al., 2014). The results from this study could not be compared with the current results because of the

area coverage of Wales and Scotland in THIN database compared to CPRD Aurum. However, the high incidence in North West and East of England were comparable with the current results. Based on the current evidence, there are no previous reports of geographical variation in prevalence of CSP in the UK. The reasons for current geographic variation in CSP most likely may relate to differences in lifestyle, educational level, prevalent occupations, and socioeconomic status, though further studies are required to explore these. East Anglia and East Yorkshire were found to have a higher proportion of agricultural industry compared to other regions, which might contribute to the higher burden of shoulder pain (Alderton, 2017). In the UK, there is a well-established "North–South divide", which suggest that the North generally has poorer health compared to the South including higher premature mortality (Whitehead et al., 2014, Buchan et al., 2017). A recent study in the UK found a strong association between physical inactivity and higher prevalence of back pain in coastal areas and the South West (Smalley and Edwards, 2023). This was explained by the proportion of residents that were over age 60 years, in low-skilled jobs, smokers, disabled, female, obese, and pregnant (Smalley and Edwards, 2023).

3.4.3 Limitations of this study

There are some limitations to this study. Firstly, the case definition was based on diagnosis by the GPs, rather than a specific diagnosis or to a 'gold standard' obtained by a physician with MSK expertise and use of imaging such as ultrasound, and this may lead to misclassification bias. The coding of MSK conditions in healthcare database might be

controversial. However, A narrow definition of CSP with a specific inclusion criterion was used in this study to identify patients with chronic shoulder conditions. Secondly, because the current estimates were based on GP consultations for symptomatic CSP, and not all people with symptomatic shoulder pain will consult their GP, these data may underestimate the true population prevalence and incidence of symptomatic CSP. Furthermore, the prevalence and incidence of CSP might have been underestimated because CSP was not included in the QOF by the NHS in 2004. Additionally, the exclusion criteria used in this study might have led to underestimation of the burden of CSP. Finally, it is important to acknowledge that the underlying data are predominantly derived from sources based in England and North Ireland. As such, these estimates may not fully capture the epidemiological patterns in Scotland, and Wales, where demographic characteristics, healthcare systems, and disease recording practices can differ. This limitation affects the extent to which the findings can be generalised to the entire UK population and should be carefully considered when interpreting the results.

3.5 Conclusion

In conclusion, both the prevalence and incidence of CSP have risen in the UK in the past 20 years despite the decline in incidence after 2011. The prevalence and incidence of CSP were higher in females compared to males and increased in those aged over 40 years. Geographically, the highest prevalence and incidence of CSP were found in the Yorkshire and the Humber regions. The results of this study suggest that there might

have been a recent improvement in the coding of CSP by GPs toward a more specific shoulder pain diagnosis, however, validation studies are needed to confirm this. Having insight into the burden of CSP might help to inform strategies to reduce the occurrence of CSP in the UK and to understand the impact of CSP on primary healthcare utilisation. Future research is needed to explore the outcomes of CSP and its associated comorbidities.

Chapter 4. Risk factors associated with chronic shoulder pain: a nested case-control study in the UK primary care setting.

4.1 Introduction

There are several risk factors of shoulder pain reported in the literature such as older age, female sex, heavy manual work, and smoking. However, current UK data exploring risk factors and comorbidities associated with CSP is limited. As far as is known, only one case-control study in the UK has explored the comorbidities associated with RC tendinopathy using the THIN database. That study identified a number of comorbidities that associated with RC tendinopathy including lateral epicondylitis, diabetes, carpal tunnel syndrome, trigger finger, and Achilles tendinitis (Titchener et al., 2014). However, the list of comorbidities examined in this study might be limited. Therefore, this study aimed to explore the risk factors and comorbidities associated with CSP using the CPRD.

4.2 Methods

A nested case-control study was conducted to examine the risk factors associated with CSP. Incident cases of shoulder pain were identified between 2000 and 2020 (first diagnosis date as index date). Each case was matched with a control without shoulder pain by age, sex, and practice and was assigned the same index date. The potential exposures

such as alcohol consumption, smoking, BMI, ethnicity IMD and a list of comorbidities were compared between cases and controls retrospectively at the index date.

4.2.1 Ethical approval

The study was approved by the Independent Scientific Advisory Committee (ISAC) (protocol number: 21_000633). The protocol approved is provided in Appendix 1.

4.2.2 Data source

CPRD Aurum data for registered people from 1st January 2000 until 31st December 2020 were used for this study (details of CPRD Aurum were presented in the Introduction).

4.2.3 Selection of the study population

4.2.3.1 Case definition of chronic shoulder pain

The case definition of CSP used in this study, the list of CSP codes included in this study and inclusion and exclusion criteria were the same as in the prevalence and incidence study and are explained in Chapter 3. Sample size calculation for the case-control study is provided in Appendix 12 (page 391).

4.2.4 Selection of controls

Controls were people registered for at least 12 months of registration and with no record of diagnosed CSP. One control was selected per CSP case

(i.e. 1:1 matching), matched by year of birth, sex, and practice. The same index as their matched date (i.e. date of first CSP diagnosis) was used. The controls were selected using incidence density sampling. Each patient was utilised only once. Cases without controls were also removed, using a similar approach to that employed in a previous study (Swain et al., 2021). Selection of cases and controls is explained in Figure 4.1.

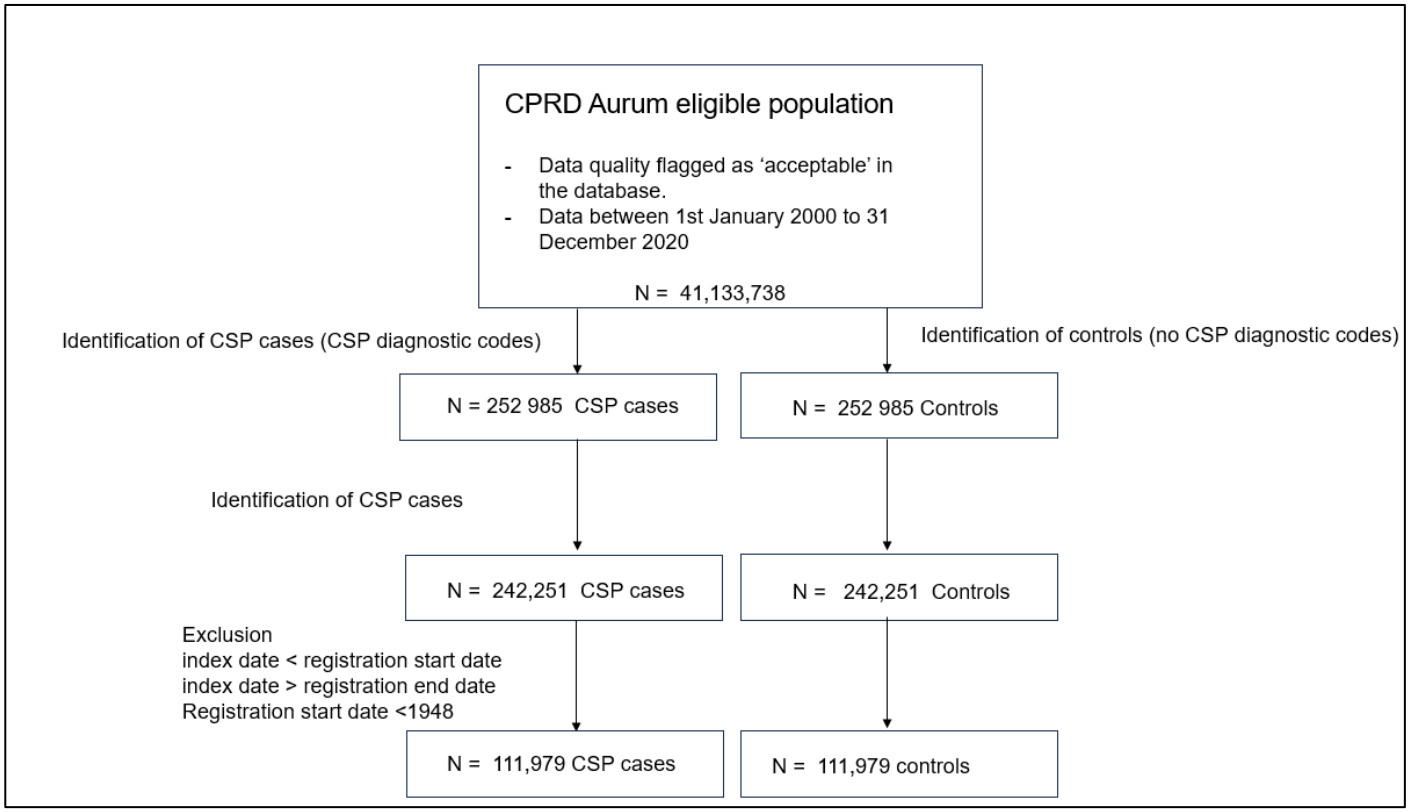


Figure 4.1 Selection of study population

4.2.5 External linkages

The 2019 English patient IMD was used to determine socio-economic status (Wolf et al., 2019). HES linkage data were used to determine ethnicity.

4.2.6 Definition of key epidemiological variables

In this study, key epidemiological variables are defined to establish a clear conceptual and analytical framework. A risk factor is defined as any characteristic or exposure that increases the likelihood of developing the outcome of interest (CSP). For example, smoking may be a risk factor for the development of CSP. Comorbidities refer to the presence of additional diseases or conditions in a person that occur alongside the primary condition being studied. For instance, cardiovascular disease, and diabetes are present in someone with CSP. Covariates are variables that are included in statistical models to control for their potential influence on the relationship between exposure and outcome. These can include demographic variables such as age, and sex, which may independently affect the outcome. Confounders are defined as a specific subset of covariates that are associated with both exposure and the outcome. For example, socioeconomic status was considered a confounder because it may be associated with lifestyle factors such as occupation, smoking, or alcohol use which may influence the risk of CSP.

In the case-control study, the outcome is the presence of CSP, with exposures including risk factors such as smoking, BMI, alcohol consumption, socioeconomic status, and comorbidities. Comorbidities, such as diabetes or depression, are existing medical conditions that may influence both the exposure and the outcome. Covariates, including demographic factors like age and sex, are controlled for in the analysis to account for their potential influence. In this context, confounders refer to variables such as age or comorbidities that are associated with both the exposure (e.g., BMI or smoking) and the outcome (CSP), potentially biasing observed associations if not adjusted for. To address this, the model adjusts risk factors and comorbidities for each other, and also for relevant demographic covariates.

In the cohort study, the exposure is CSP, and the outcomes are the development of comorbidities. Again, covariates such as age and sex are adjusted for, as well as risk factors and baseline comorbidities, some of which acted as confounders depending on their associations. All relevant variables were selected based on existing literature, theoretical relevance, and statistical significance in the univariate model. There were no moderating variables examined in this study.

4.2.7 Exposures and Outcome

The outcome in this study was a record of CSP. The exposures were risk factors and comorbidities prior to the record of CSP.

4.2.7.1 Risk factors

The list of risk factors examined were alcohol consumption, smoking BMI, IMD, and ethnicity. Risk factors were defined as previous recording any of these prior to the index date (date of CSP diagnosis). Values recorded at the closest date before the index date were captured and used in the analysis.

Recorded risk factors were identified using primary care coding (SNOMED codes). SNOMED codes were extracted and transferred to medical codes to extract risk factors data. Risk factors were categorised as follows:

1. For smoking status, the following categories were used: current smoker; ex-smoker; and non-smoker (Marston et al., 2014, Matharu et al., 2019, Swain et al., 2022).
2. Records of alcohol consumption included codes quantifying alcohol drinking, specifically non-drinker (never), ex-drinker, current drinker 1-9 units/week, current drinker >=10 units/week, and current drinker (unknown amount) (Swain et al., 2021, Swain et al., 2022).
3. For BMI, height and weight were extracted and BMI was calculated. Then, BMI was categorised as normal, underweight, overweight, and obese using extensive code lists (NHS, 2018, Jan and Weir, 2021).
4. Ethnicity and socioeconomic data were extracted from Linkage data (HES patient, and IMD, respectively). Ethnicity was categorised as white, black, Asian, mixed, other, and unknown (UK Government, 2021, Chen et al., 2023, Somathilake et al., 2025). The practice/patient level IMD (the 2019 English IMD, using composite and individual domains), was used as a marker for the socioeconomic status. The IMD was ranked from 1 to

5, where 1 represents least deprived and 5 represents most deprived (Ministry of Housing/Communities & Local Government, 2019, Heward et al., 2024).

The code lists for risk factors were developed using the CPRD code browser, which is a tool that was created to support the development of code lists (CPRD Code Browser quick user guide September 2022). The Wildcare search method using (*) (e.g. *smoking*) was carried out to develop the code lists (CPRD Code Browser quick user guide September 2022). Additionally, an extensive search was undertaken using an open safely code lists platform, which allows creation and sharing of code lists (https://www.opencodelists.org) to include other risk factor codes. The code lists of the risk factors were extracted by NA, and validated by three reviewers (BA, SS, and TA).

4.2.7.2 Comorbidities

The comorbidities identified in the systematic review were examined. Comorbidities were defined as previous recording of chronic conditions prior to the index date. Comorbidities identified in the systematic review were other MSK pain, anxiety, depression, sarcopenia, hypothyroidism, diabetes, hyperlipidaemia, OA, hypertension, cardiovascular conditions (angina, heart failure, ischemic heart disease, myocardial infarction), and lung conditions (emphysema, bronchitis, COPD). In addition to comorbidities identified in the systematic review, sleep problems, fatigue and fibromyalgia were examined since these had been associated with

shoulder pathologies, and also MSK pain and lower physical function (Mannerkorpi et al., 1994, Macfarlane, 1999, Tekeoglu et al., 2013, Côté, 2014, Daneshmandi et al., 2017, Longo et al., 2019, Hammad et al., 2022). Some other comorbidities were examined as negative controls such as tinnitus, urinary incontinence, benign prostatic hyperplasia, diaphragmatic hernia, and diverticular disease, as they could not be linked logically with shoulder pain so were considered to be very unlikely to associate with shoulder pain. Recorded comorbidities were identified using primary care coding (SNOMED codes). The comorbidities code lists were developed using the CPRD code browser. Additional codes were obtained from clinical code repositories, in the Primary Care Unit of the University of Cambridge, University of Nottingham, University of Manchester and Keele University (Table 4-1). The comorbidities codes were validated by clinicians (BI, TA). The code lists for comorbidities are provided in Appendix 13 (pages 392-456).

Table 4-1 Comorbidities examined in the study

Comorbidities	Source
Insomnia	Developed using CPRD code browser (*insomnia*, *sleep problems*), and additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
Anxiety	Developed using CPRD code browser (*anxiety*)
Depression	The codes were obtained from the Primary Care Unit, University of Cambridge (https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/v11/)
Fatigue	Developed using CPRD code browser (*fatigue*), and additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
hyperlipidaemia	Developed using CPRD code browser (*hyperlipidaemia*, *high cholesterol*), and additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
hypertension	Developed using CPRD code browser (*hypertension*), and additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
Other MSK pain	Developed using CPRD code browser (*neck pain*, *knee pain*, *elbow pain*, * wrist pain*, *hip pain*, *ankle pain*, *spine pain*, *lumbar pain*, *thoracic pain*, *cervical pain*), and additional codes were obtained from Keele university (https://www.keele.ac.uk/mrr/codelists/musculoskeletalcodelists/)

Fibromyalgia (chronic widespread pain)	Developed using CPRD code browser (*fibromyalgia*, * chronic widespread pain*), and additional codes were obtained from Keele university (https://www.keele.ac.uk/mrr/codelists/musculoskeletalcodelists/), and from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
Sarcopenia	Developed using CPRD code browser (* muscle atrophy *, * muscle wasting*, * Sarcopenia*)
Hypothyroidism	Developed using CPRD code browser (*hypothyroidism*), and additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
OA	Developed using CPRD code browser (*osteoarthritis*), additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk), and Keele university (https://www.keele.ac.uk/mrr/codelists/musculoskeletalcodelists/)
Diabetes	Developed using CPRD code browser (*diabetes*), additional codes were obtained from the Primary Care Unit, University of Cambridge (https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/v11/)
Myocardial infarction	Developed using CPRD code browser (*myocardial infarction*, *heart attack*), additional codes were obtained from the code list developed by a clinician in the in the primary care unit, University of Nottingham.
Heart failure	Developed using CPRD code browser (*heart failure*, *congestive Heart Failure*), additional codes were obtained from the code list developed by a clinician in the in the primary care unit, University of Nottingham.

Ischemic heart diseases	For angina, the code list was developed using CPRD code browser (*angina*). Additional codes for other ischemic heart diseases were obtained from the code list developed by a clinician in the primary care unit, University of Nottingham.
COPD	Developed using CPRD code browser (*chronic obstructive pulmonary disease*, * chronic obstructive disease*, *COPD*), and additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
Tinnitus	Developed using CPRD code browser (*tinnitus *), and additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
Scleroderma	Developed using CPRD code browser (*scleroderma *), and additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
Urinary incontinence	Developed using CPRD code browser (*urinary incontinence * incontinence of urine*), additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)
Diverticular disease	Developed using CPRD code browser (*diverticular disease *, *diverticulitis* diverticulosis*), additional codes were obtained from the Primary Care Unit, University of Cambridge (https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/v11/)
Diaphragmatic hernia	Developed using CPRD code browser (*diaphragmatic hernia*, *hiatus hernia*), additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)

Benign Prostatic Hyperplasia	Developed using CPRD code browser (*benign prostatic hyperplasia*), additional codes were obtained from clinical codes repository (https://clinicalcodes.rss.mhs.man.ac.uk)

4.2.8 Statistical analysis

All data management and analysis were conducted using R (3.4.1) and STATA SE v 15 software (Appendix 14, pages 457- 458). For the retrospective analysis, a nested matched (please see above concerning matching) case-control design was undertaken. Number and percentage were used to present categorical variables. All continuous data were checked for the assumption of normality. For normally distributed variables measures were presented as the mean and the SD. Although some variables (such as BMI, age) were moderately skewed, descriptive characteristics were presented as mean and SD according to the central limit theorem, that is, when sample size increases, the data for these measures tend to be normally distributed (McDonald, 2009, McDonald, 2014).

Attempts were made to transform (log-transformation, square and square-root transformation) skewed data (for example, BMI) and after transformation data were tested for normality. If transformation was successful, parametric tests were used. If transformation was not successful, non-parametric tests were used. If a continuous variable was normally distributed and the comparison was between two dependent groups (for example, matched sets), then, paired t-test was used

(Armitage et al., 1971, Conway et al., 2013). McNemar test was used to estimate the association between categorical variables (Lachenbruch, 2014). ORs and 95% CI were used to estimate the associations between CSP and each risk factor and comorbidity using conditional logistic regression. All included risk factors were adjusted for each other in the multivariable conditional logistic regression model and adjusted p-values were calculated. All examined comorbidities were adjusted for each other in conjunction with demographic variables (for example, BMI, alcohol status, ethnicity, smoking status, and IMD) in multivariable conditional logistic regression model, and adjusted p-values were calculated. All variables that were significantly ($p < 0.05$) associated with shoulder pain in the univariate model were included as potential confounders in the multivariable model.

Multiple imputation was used to replace missing values for BMI, smoking status, IMD and alcohol consumption. Multiple imputation with chained equations was used to generate five imputations using the MICE package in R software (R Foundation for Statistical Computing, Vienna, Austria) (Van Buuren and Oudshoorn, 2005, Van Buuren and Groothuis-Oudshoorn, 2011). In the imputation model all predictor variables, along with age, sex, index year and the outcome variable were included. Results were combined across the imputed datasets using Rubin's rules (Rubin, 2004, Nguyen et al., 2017, Rubin, 2018).

To address the risk of a higher false discovery rate (FDR) due to 'multiple significance testing" (Greenland, 2008), the FDR method proposed by Benjamini-Hochberg was used to calculate adjusted p-values (Benjamini

and Hochberg, 1995, Benjamini and Yekutieli, 2001). The steps for calculating adjusted p-values are presented in Appendix 15 (page 459). The results were re-checked using the R built in function for calculating adjusted p-values (Appendix 15, page 459). The results were deemed to be statistically significant when the p-value was less than the adjusted significance level of 0.05. Multicollinearity was checked using the Variance Inflation Factor (VIF) function in R (Shrestha, 2020). A value of VIF =1 indicates that there is no correlation between a predictor variable and any other predictor variables in the model. A value between 1 and 5 indicates moderate correlation between a predictor variable and other predictor variables in the model. A value > 5 indicates potentially severe correlation between a predictor variable and other predictor variables in the model. No multicollinearity was found between predictors (Appendix 16, pages 460- 461).

4.3 Results

4.3.1 Participant characteristics

Table 4-2 summaries the demographic data of the people with shoulder pain and controls. During the period 1st January 2000 to 31st December 2020, 111,979 incident CSP cases were identified and matched to 111,979 controls. The mean age of the cases at diagnosis was 50.08 years (S.D 10.2) with 54.23% being females. The same mean age (SD) and proportion of females were obtained in the control group. The majority of participants were white, and the ethnic distribution was approximately similar between cases and controls for both males and females. People

who developed CSP were more likely to live in more deprived areas ($p < 0.0001$). Cases were more overweight and obese compared to controls (Table 4-2). Also, there were more former and current smokers and more current alcohol consumers in cases than in controls ($p < 0.0001$).

Table 4-2 Characteristics of the study population

Characteristics	Cases (n = 111,979)	Controls (n = 111,979)	p-value
Age, mean (S.D.), years	50.08 (10.2)	50.08 (10.2)	NA[a]
Age (male) mean (S.D.), years	49.82 (10.7)	49.82 (10.7)	
Age (Female) mean (S.D.), years	50.29 (9.7)	50.29 (9.7)	
Age (years)			NA[a]
18-30	5990 (5.35)	5990 (5.35)	
31-40	13393 (11.96)	13393 (11.96)	
41-50	35497 (31.70)	35497 (31.70)	
51-60	42256 (37.74)	42256 (37.74)	
61-70	14536 (12.98)	14536 (12.98)	
≥ 71	307 (0.27)	307 (0.27)	
Sex, n (%)			NA[a]
Male	51257 (45.77)	51257 (45.77)	
Female	60722 (54.23)	60722 (54.23)	
Ethnicity			p*<0.0001
White	82167 (73.38)	69666 (62.21)	
Black	3038 (2.71)	2305 (2.06)	
Asian	6151 (5.49)	3897 (3.48)	
Mixed	676 (0.61)	466 (0.42)	
Other	1410 (1.26)	1067 (0.95)	
Unknown	3376 (3.01)	5146 (4.60)	
Missing	15161 (13.54)	29432 (26.28)	
Practice			NA[a]
England	110200 (98.42)	110200 (98.42)	
North Ireland	320 (0.29)	320 (0.29)	
IMD			p*<0.0001
1(Least deprived)	22806 (20.37)	23991 (21.42)	
2	23132 (20.66)	23589 (21.07)	
3	20926 (18.69)	20866 (18.63)	
4	21315 (19.03)	20422 (18.24)	
5 (Most deprived)	21683 (19.36)	20226 (18.06)	
Missing	2117 (1.89)	2885 (2.58)	
BMI (kg/m^2), n (%)			p*<0.0001
BMI, mean (S.D.)	28.06 (6.0)	27.37 (5.8)	0.69 (0.64,0.74)
<18.5 (underweight)	1600 (1.43)	1844 (1.65)	
18.5–24.9 (normal)	33171 (29.62)	35115 (31.36)	

25.0–29.9 (overweight)	32839 (29.33)	29740 (26.56)	
≥ 30 (obese)	26820 (23.95)	20886 (18.65)	
Missing	17549 (15.67)	24394 (21.78)	-
Smoking status, n (%)			p*<0.0001
Non-smoker	57562 (51.40)	58093 (51.88	
Current smoker	24775 (22.12)	22579 (20.16)	
Ex-smoker	24880 (22.22)	20931 (18.69)	
Missing	4762 (4.25)	10376 (9.27)	
Alcohol consumption (units/week), n (%)			p*<0.0001
Non- drinker (Never)	27015 (24.13)	22267 (19.88)	
Ex-drinker	536 (0.48)	371 (0.33)	
Current drinker 1-9	38688 (34.55)	37920 (33.86)	
Current drinker ≥10	20484 (18.29)	21043 (18.79)	
Current drinker (amount unknown)	5903 (5.27)	5182 (4.63)	
Missing	19353 (17.28)	25196 (22.50)	

[a]Matched by age, sex, practice, and index date, BMI- Body mass index, NA-not applicable. SD-standard deviation.

4.3.2 Risk factors for chronic shoulder pain

Risk factors for CSP prior to the index date are shown in Table 4-3. Of the five risk factors studied, significant associations were seen with four, specifically smoking, IMD, ethnicity and BMI. All results, both crude OR and adjusted (aOR) models are presented in Table 4-3.

Alcohol consumption was found to be negatively associated with CSP in cases compared to controls in both crude and adjusted models (Table 4-3). participants with records of alcohol drinking were less likely to have records of CSP (crude OR 0.82, 95% CI 0.80 to 0.85; p-value <0.0001), and this association remained significant after adjusting for all other demographic variables (aOR 0.87, 95% CI 0.84 to 0.90; p-value <0.0001). However, being a former alcohol drinker was associated with CSP with a crude OR of 1.17 (95% CI 1.03 to 1.32, p-value = 0.01) and an aOR of 1.15 (95% CI 1.01 to 1.30, p-value = 0.02). Being a current smoker was found to be significantly associated with CSP in crude and adjusted analyses (crude OR 1.11, 95% CI 1.08 to 1.13 and aOR 1.14, 95% CI 1.19 to 1.24, respectively; both p-value <0.0001). Compared with non-smokers, former smokers were at higher risk of having CSP in the crude and adjusted analysis (crude OR 1.21, 95% CI 1.18,1.23 and aOR 1.21, 95% CI 1.19 to1.24 respectively; both p < 0.0001) (Table 4-3). People in more deprived areas were found to be at higher risk of having CSP compared to those in the least deprived areas (crude OR 1.23, 95% CI 1.19 to 1.27, and aOR 1.13, 95% CI 1.09 to 1.17 respectively; both p-value < 0.0001). People of Asian ethnicity and mixed ethnicity were at greater risk of having CSP compared to those of white ethnicity (aOR

1.43, 95% CI 1.36 to 1.50 and aOR 1.26, 95% CI 1.12 to 1.41, respectively; both p-value <0.0001). People who were underweight showed lower odds of CSP compared to people in the normal weight category (aOR 0.86, 95% CI 0.78 to 0.94; p-value <0.0001) and those who were overweight and obese were more likely to develop CSP (aOR 1.16, 95% CI 1.13 to 1.19, and aOR 1.32, 95% CI 1.29 to1.35, respectively, both p-value < 0.0001).

Table 4-3 Risk factors associated with chronic shoulder pain during a maximum period of 20 years prior to the index date

Characteristics	Crude OR (95% CI), p-value	aOR* (95% CI), p-value**
Alcohol consumption (units/week)		
Non- drinker (never)	(Reference)	(Reference)
Current drinker 1-9	0.82 (0.80, 0.85), p < 0.0001	0.87 (0.84, 0.90), p < 0.0001
Current drinker ≥10	0.78 (0.76, 0.80), p < 0.0001	0.81 (0.79, 0.84), p < 0.0001
Current drinker (amount unknown)	0.92 (0.88, 0.97), p =0.002	0.96 (0.91, 1.01), p = 0.1
Ex-drinker	1.17 (1.03, 1.32), p = 0.01	1.15 (1.01, 1.30), p = 0.02
Smoking status		
Non-smoker	Reference	Reference
Current smoker	1.11(1.08,1.13), p <0.0001	1.14 (1.11, 1.16), p < 0.0001
Ex-smoker	1.21(1.18,1.23), p < 0.0001	1.21 (1.19, 1.24), p < 0.0001
Index of multiple deprivation (IMD)		
1(Least deprived)	Reference	Reference
2	1.05 (1.02, 1.08), p = 0.0001	1.03 (1.00, 1.06), p = 0.01
3	1.09 (1.06,1.13), p < 0.0001	1.05 (1.02,1.08), p =0.0006
4	1.17 (1.13, 1.20), p < 0.0001	1.10 (1.06, 1.13), p < 0.0001
5 (Most deprived)	1.23 (1.19, 1.27), p < 0.0001	1.13 (1.09, 1.17), p < 0.0001
Ethnicity		
White	(Reference)	(Reference)
Black	1.18 (1.12, 1.25), p < 0.0001	1.14 (1.08, 1.21), p <0.0001
Mixed	1.26 (1.12, 1.41), p = 0.0001	1.24 (1.10, 1.40), p = 0.0003
Asian	1.44 (1.37,1.52), p < 0.0001	1.43 (1.36,1.50), p < 0.0001
Other	1.15 (1.06,1.25), p = 0.0005	1.14 (1.05,1.24), p = 0.001
Unknown	0.54 (0.51,0.57), p < 0.0001	0.56 (0.53, 0.58), p < 0.0001
BMI (kg/m^2)		
18.5–24.9 (normal)	(Reference)	(Reference)
<18.5 (underweight)	0.89 (0.81, 0.98), p = 0.02	0.86 (0.78, 0.94), p < 0.0001
25.0–29.9 (overweight)	1.17 (1.14, 1.20), p < 0.0001	1.16 (1.13,1.19), p < 0.0001
≥ 30 (obese)	1.36 (1.33, 1.39), p < 0.0001	1.32 (1.29, 1.35), p < 0.0001

*aOR, odds ratio adjusted for ethnicity, BMI, smoking, alcohol, and IMD. ** p- value adjusted for multiple testing using 'False discovery rate'

4.3.3 Comorbidities associated with chronic shoulder pain

Comorbidities prior to the index date within the maximum 20-year observational period in the CSP case and control groups are shown in Table 4-4. Of the 22 comorbidities studied, significant associations were seen with 16 comorbidities (Table 4-5). The strongest associations were seen with OA (aOR 1.76, 95% CI 1.70 to 1.82), other MSK conditions (aOR 1.71, 95% CI 1.68 to 1.75), diabetes (aOR 1.48, 95% CI 1.43 to 1.53) and fibromyalgia (aOR 1.40, 95% CI 1.32 to 1.48). Other comorbidities found to be associated with CSP were depression, insomnia, COPD, hypothyroidism, diverticular disease, and diaphragmatic hernia (Table 4-5).

Table 4-4 Comorbidities identified retrospectively in the case-control study

Comorbidities	Cases (111,979)	Controls (111,979)	p-value
Metabolic/endocrine			
Diabetes	19005 (16.79%)	11974 (10.69%)	<0.001
Hypothyroidism	6184 (5.52%)	4502 (4.02%)	<0.001
Hyperlipidaemia	12845 (11.47%)	9201 (8.22%)	<0.0001
Cardiovascular/Circulatory			
Congestive heart failure	7042 (6.29%)	4502 (4.02%)	<0.0001
Hypertension	23386 (20.88%)	19458 (17.38%)	<0.0001
Ischemic heart diseases	4922 (4.40%)	3293 (2.94%)	<0.0001
Myocardial Infarction	1725 (1.54%)	1137 (1.02%)	<0.0001
Respiratory			
COPD	16017 (14.30%)	11757 (10.50%)	<0.0001
Psychological			
Depression	42560 (38.01%)	30391 (27.14%)	<0.0001
Anxiety	17950 (16.03%)	13437 (12.0%)	<0.0001
Musculoskeletal			
OA	16851 (15.05%)	8834 (7.89%)	<0.0001
Other MSK conditions	54224 (48.42%)	36945 (32.99%)	<0.0001
Fibromyalgia	5207 (4.65%)	2588 (2.31%)	<0.0001
Fatigue	4202 (3.75%)	2757 (2.46%)	<0.0001
Sarcopenia	90 (0.08%)	56 (0.05)	0.005
Genito-urinary			
Urinary incontinence	5682 (5.07%)	3777 (3.37%)	<0.0001
Benign prostatic hyperplasia	2315 (2.07%)	1630 (1.46%)	<0.0001
Digestive			
Diverticular disease	3123 (2.79%)	1924 (1.72%)	<0.0001
Diaphragmatic hernia	4573 (4.08%)	2847 (2.54%)	<0.0001
Others			
Insomnia	10443 (9.33%)	6452 (5.76%)	<0.0001
Tinnitus	4638 (4.14%)	3278 (2.93%)	<0.0001
Scleroderma	54 (0.04%)	37 (0.03%)	0.07

COPD, chronic obstructive pulmonary disease, MSK, musculoskeletal, OA, osteoarthritis

Table 4-5 Association of comorbidities with chronic shoulder pain

Comorbidities	Crude OR (95% CI)	aOR[#] (95% CI)	aOR[##] (95% CI)
Metabolic/endocrine			
Diabetes	1.98 (1.93, 2.04)*	1.77 (1.72, 1.82)*	1.48 (1.43, 1.53)*
Hypothyroidism	1.41 (1.35, 1.47)*	1.34 (1.29, 1.40)*	1.21 (1.15, 1.26)*
Hyperlipidaemia	1.52 (1.47, 1.56)*	1.42 (1.38, 1.46)*	1.19 (1.15, 1.23)*
Cardiovascular/Circulatory			
Congestive heart failure	1.23 (1.18, 1.28)*	1.13 (1.08, 1.17)*	0.95 (0.91, 1.00)
Hypertension	1.30 (1.27, 1.33)*	1.19 (1.16, 1.22)*	1.01 (0.98, 1.04)
Ischemic heart diseases	1.56 (1.49, 1.64)*	1.41 (1.35, 1.48)*	1.08 (1.02, 1.14)*
Myocardial Infarction	1.54 (1.43, 1.66)*	1.38 (1.28, 1.49)*	1.05 (0.96, 1.16)
Respiratory			
COPD	1.46 (1.42, 1.5)*	1.39 (1.35, 1.43)*	1.20 (1.17, 1.24)*
Psychological			
Depression	1.71 (1.68,1.75)*	1.62 (1.59, 1.65)*	1.28 (1.25, 1.31)*
Anxiety	1.43 (1.39, 1.46)*	1.39 (1.36, 1.43)*	1.09 (1.06, 1.12)*
Musculoskeletal			
OA	2.29 (2.22, 2.36)*	2.15 (2.09, 2.22)*	1.76 (1.70, 1.82)*
Other MSK conditions	2.07 (2.03, 2.11)*	1.97 (1.94, 2.01)*	1.71 (1.68, 1.75)*
Fibromyalgia	2.13 (2.03, 2.24)*	1.94 (1.85, 2.04)*	1.40 (1.33, 1.48)*
Fatigue	1.56 (1.49, 1.64)*	1.52 (1.45, 1.60)*	1.19 (1.12, 1.25)*
Sarcopenia	1.60 (1.15, 2.24)*	1.58 (1.12, 2.21)*	1.16 (0.81, 1.66)
Genito-urinary			
Urinary incontinence	1.55 (1.49,1.62)*	1.47 (1.41, 1.53)*	1.19 (1.13,1.24)*
Benign prostatic hyperplasia	1.46 (1.37,1 .56)*	1.44 (1.34, 1.54)*	1.23 (1.14,1.32)*

Digestive			
Diverticular disease	1.66 (1.57, 1.76)*	1.58 (1.49, 1.68)*	1.30 (1.22, 1.38)*
Diaphragmatic hernia	1.65 (1.57, 1.73)*	1.56 (1.48, 1.63)*	1.31 (1.24, 1.38)*
Others			
Insomnia	1.70 (1.65, 1.76)*	1.63 (1.58, 1.69)*	1.26 (1.22, 1.31)*
Tinnitus	1.43 (1.37, 1.50)*	1.42 (1.36, 1.49)*	1.23 (1.17, 1.29)*
Scleroderma	1.45 (0.96, 2.21)	1.47 (0.96, 2.25)	1.33 (0.85, 2.09)

aOR, adjusted odds ratio for smoking, alcohol consumption, IMD, Ethnicity, and BMI, ## aOR, adjusted odds ratio for smoking, alcohol consumption, IMD, Ethnicity, BMI, and all other comorbidities, COPD, chronic obstructive pulmonary disease, MSK, musculoskeletal, # P value 0.05 adjusted for multiple testing using 'False discovery rate, * p-value<0.0001

4.4 Discussion

This chapter explored the risk factors and comorbidities prior to the diagnosis of CSP using a nationally representative large UK primary care database. The key findings were that smoking, a higher IMD, Asian and mixed ethnicity and a high BMI were significantly associated with CSP, while current alcohol drinking had a significantly lower risk of having CSP. Comorbidities that were associated retrospectively with CSP included other MSK conditions, OA, diabetes, fibromyalgia, depression, insomnia, COPD, and hypothyroidism.

Risk factors for chronic shoulder pain

Current alcohol consumption was found to have a significant negative association with CSP in both crude and adjusted models. Since alcohol is known to have analgesic effects, this might reduce the likelihood of someone presenting with CSP to their GP (Ferreira et al., 2013, Thompson et al., 2017, Zambelli et al., 2021). However, although a plausible hypothesis, other explanations such as reverse causation, are possible. Previous studies have investigated the relationship between alcohol consumption and MSK conditions. Leboeuf-Yde (2000) conducted a systemic review in 2000 that included nine studies (2 case-control and 7 cross-sectional studies) to evaluate the relationship between alcohol consumption and the risk of developing acute low back pain. The review found that drinking alcohol was not associated with LBP (Leboeuf-Yde, 2000). In contrast to Leboeuf-Yde (2000), Ferreira et al. (2013) conducted a later systematic review and meta-analysis in 2013 using a wider search

strategy. Twenty-six studies were included, 22 of which were retrospective cohort studies, two were case-control studies, and one was a longitudinal study employing a combination of cross-sectional, and cohort designs (Ferreira et al., 2013). Pooled results from the case control and retrospective cohort studies showed that alcohol consumption increased the risk of LBP (OR 1.3, 95% CI 1.1 to 1.5) (Ferreira et al., 2013). However, this association appeared only in people with chronic LBP, and in studies investigating alcohol as an abuse dependence substance (Ferreira et al., 2013). Only one longitudinal study in this review found a negative association between alcohol consumption and a future episode of low back pain (OR 0.7, 95% CI 0.5 to 0.9) (Hestbaek et al., 2006). Recently, Karimi et al. (2022) investigated whether alcohol drinking is related to the incidence of MSK chronic pain. Sixteen studies, comprising 13 cohort and 3 case control studies, were included with a total population of 642, 587 individuals (Karimi et al., 2022). The results showed that alcohol consumption was negatively associated with chronic pain (OR 0.76, 95% CI 0.61 to 0.95) (Karimi et al., 2022). The findings of the current study and the previous studies align with plausible biological explanations. Studies on animals have demonstrated that alcohol could partially inhibit pain receptors (Neddenriep et al., 2019), and the same effect was found in humans (Arout et al., 2016). Another theory is that ethanol acts like gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the brain, which binds to GABA receptors to block neuronal communication (Gatch, 1999). According to a different study, drinking alcohol causes a dose-related release of endogenous opioid ligands, which lowers the

transmission of pain signals to the central nervous system (Mitchell et al., 2012).

Another risk factor identified in current study was smoking. A history of previous smoking was found to have an association, albeit it relatively small, with CSP. This finding is consistent with previous studies (Mallon et al., 2004, Baumgarten et al., 2010, McRae et al., 2011, Tangtrakulwanich and Kapkird, 2012, Bishop et al., 2015). Baumgarten et al. (2010) found a dose-dependent and time-dependent relationship between smoking and RC tears. They retrospectively examined 584 patients, 473 of whom were smokers, who were referred for a diagnostic shoulder ultrasound for atraumatic unilateral shoulder pain. Diagnostic ultrasound determined 375 patients with RC tears and 211 did not (Baumgarten et al., 2010). Patients with RC tears had a higher daily tobacco smoking rate compared to those without RC tears (61.9% versus 48.3%) (Baumgarten et al., 2010). Results showed that the risk of RC tears increased when smoking occurred within 10 years of the shoulder pain complaint (OR 4.24, 95% CI 1.75 to 10.25; p-value= 0.0006), was significant in those with a history of smoking of one to two packs per day (OR 1.66; p-value= 0.009) and was greater for those who smoked more than two packs per day (OR 3.35; p-value = 0.0007) (Baumgarten et al., 2010). However, recall bias was a potential limitation in this study because participants were asked to self-report the dates of starting and stopping smoking and the amounts of tobacco use, and this may have led to some misclassification. Tangtrakulwanich and Kapbird (2012) conducted a case control study to evaluate the association between smoking and impingement syndrome.

The study group consisted of 111 cases with impingement syndrome and 191 healthy controls, with a mean age of 49.8 and 43 years, retrospectively. All included participants were interviewed to obtain basic demographic data in addition to information about smoking status (Tangtrakulwanich and Kapkird, 2012). They found that people who were currently smoking had 6.8 times greater risk of developing impingement syndrome than non-smokers (OR 6.8, 95% CI 1.2 to 39.8). However, one of the limitations of this study was that the control group differed in demographic characteristics in terms of age, sex and occupation. Therefore, selection bias of the control group might have influenced the strength of the association.

The results of the current study and the previous studies align with existing knowledge, and the hypothesis that tobacco can cause RC pathology is biologically plausible. Smoking may contribute to tendon degeneration because nicotine causes hypoxia, which reduces blood flow to the hypo-vascular area of the RC (Katzer et al., 1997). This hypoxic environment may alter the metabolism, lower mechanical resilience, and delay the healing process following a RC tear (Katzer et al., 1997). Similarly, nicotine might make tendons stiffer by increasing collagen synthesis and decreasing matrix metalloproteinase production (Ichinose et al., 2010).

Highly deprived people in this study had significantly higher risk of having CSP than less deprived people. This finding is in line with previous studies that have reported that low socioeconomic status is associated with MSK

pain (Urwin et al., 1998, Webb et al., 2003, Ayis and Dieppe, 2009, Bonathan et al., 2013, Nicolson et al., 2021). Urwin et al. investigated the self-reported prevalence of MSK pain in multiple sites by sending a postal questionnaire on demographics, MSK symptoms and physical disability to 6000 adults in three general practices in Manchester. The response rate was 78.5% (5752), and non-responders were more likely to be people who lived in high social deprivation areas. Using the Carstairs index as a measure of social deprivation, Urwin et al. found that MSK pain increased as the deprivation score increased, and people who were in more deprived areas were more likely to report MSK pain, especially back pain (X^2 test for trend = 11.46, p-value <0.001) (Urwin et al., 1998). Similarly, Webb et al. investigated the prevalence and the predictors of reported back and neck pain in a postal questionnaire mailed to 5752 adults in three general practices in the UK, Manchester. The response rate was 78.5%. Of the 4515 respondents, 1481 reported back pain, with 960 identifying this as their predominant pain site. Using the Townsend index as a marker for the socioeconomic status of the participants, they found that high deprivation was a strong predictor for back pain (adjusted for age, sex, BMI and additional pain sites) with an aOR of 1.7 (95% CI 1.1 to 2.7) (Webb et al., 2003). One possible explanation for the association between socioeconomic status and pain could be the differences in type of occupation, as people with lower socioeconomic status might work in more physically demanding jobs compared to people with high socioeconomic status. However, occupation was not taken into consideration as a potential confounder in the analysis. Another

explanation might be the educational inequalities that impact health through health literacy. There might be a conflict between a person's ability and level of education required to obtain health services and understand health information. Additionally, people in lower socioeconomic categories may be more likely to encounter barriers in accessing medical care compared to those in higher socioeconomic categories (Elstad, 2016).

Another risk factor identified in this study was ethnicity. Asian and mixed ethnic groups were at greater risk of having CSP compared to other ethnic groups. A possible explanation is that ethnicity might influence how a person experiences and responds to pain. Potential ethnic differences in endogenous pain regulatory mechanism have been proposed as a contributing factor that might explain racial differences in reporting pain (Campbell and Edwards, 2012). Comparing the current results to previous research, Malavolta et al. (2018) conducted a cross-sectional study in Brazil using medical records and found that Asian patients were more likely to develop adhesive capsulitis compared to other ethnic groups, with an adjusted OR of 3.6 (95% CI 2.0 to 6.5; p-value <0.001) (Malavolta et al., 2018). Similarly, Webb et al. (2003) found that Asian ethnicity was a significant predictor for both neck and back pain, each with disability, with an adjusted odds ratio of 2.15 (95% CI 1.62 to 2.85), and 1.85 (95% CI 1.27 to 2.67), respectively.

The current study found that high BMI is a significant risk factor for CSP. Previous epidemiological studies have shown that high BMI is a significant

and important risk factor for some MSK conditions such as knee and hip OA (Wearing et al., 2006, Jiang et al., 2011, Jiang et al., 2012, Viester et al., 2013). Increased hip and knee OA in obese people might be linked to increased biomechanical loading in these lower limb weight-bearing joints. However, several studies have demonstrated that higher BMI associates also with MSK conditions that affect non weight-bearing joints, such as hand OA (Gumina et al., 2014, Özkuk and Ateş, 2020). Therefore, it has been suggested that not only mechanical but also systemic factors might be involved in the pathogenesis of cartilage damage and OA related to obesity (Marshall et al., 2013, Sellam and Berenbaum, 2013, Visser et al., 2014, Visser et al., 2015). The demonstrated increase in serum inflammatory mediators, such as IL-6 and C-reactive protein (CRP), led to the suggested classification of obesity as a “low-grade inflammatory disease” (Greenberg and Obin, 2006, Sellam and Berenbaum, 2013).

Comorbidities

In this study, CSP was found to be associated with a large number of long-term conditions (i.e., comorbidities). As far as is known, this is the only study to examine the association of CSP with comorbidities in a large UK primary care database. Some of the MSK conditions that associated with CSP in this study have been reported in previous studies that have focused on individual conditions, including fibromyalgia (Guler et al., 1992, Gostine et al., 2018, Compagnoni et al., 2023), OA and other MSK conditions (Mäkela et al., 1991, Mäkelä et al., 1999, Wright et al., 2015, Laslett et al., 2016). A large observational study in the UK investigated the associations between incident shoulder pain at Year 4 and persistent knee

pain (pain in 1 or in 2 knees over years 0–3) (Laslett et al., 2016). Persistent pain in either 1 or 2 knees has found to be associated with the development of incident shoulder pain at Year 4 with an aRR of 1.59 (95% CI 0.97 to 2.61) and 2.02 (95% CI 1.17 to 3.49), respectively (adjusted for age, sex, BMI, depression score and lower limb pain). The relationship between incident shoulder pain and persistent pain in one or both knees might be mediated by functional weakness in the lower limbs, which may result in more reliance on the upper limbs for daily activities such as using stairs and getting out of a chair (Laslett et al., 2016). This appeared to be in line with current theoretical frameworks, which include the idea that abnormal joint loads or altered lifting patterns could result in biomechanical correlations (Radin et al., 1991, Frost, 1994, Back, 2001, Shakoor and Moisio, 2004, Fischer et al., 2015). However, the study by Laslett et al. (2016) included individuals with unspecified knee pain, which might restrict the generalisability to individuals who have knee OA or are at risk of developing knee OA.

In the current study, people with diabetes and hypothyroidism were at greater risk of having CSP. Endocrine diseases such as diabetes and hypothyroidism are well known to be associated with MSK symptoms (Mäkelä et al., 1999, Cakir et al., 2003, Cohen et al., 2020, Song et al., 2022, Chuang et al., 2023). Several studies have examined the association between diabetes and MSK conditions (Wyatt and Ferrance, 2006, Thomas et al., 2007, Wright et al., 2015, Sözen et al., 2018), and specifically adhesive capsulitis (Smith et al., 2003, Kiani et al., 2014). The development of MSK conditions in people with diabetes is thought to be

influenced by a number of factors, including increased collagen in the skin and MSK connective tissues, damage to vessels and nerves, and protein glycosylation (Kim, 2002). Some studies argued that the true causal association between diabetes and MSK pain results from the accumulation of advanced glycosylation end products (AGEs) in the joints (Aydeniz et al., 2008, Shirazi et al., 2016, Sözen et al., 2018). Both thyrotoxicosis and hypothyroidism may result in a wide range of symptomatic MSK conditions (Persellin and Rutstein, 1979, Ingbar et al., 2000). In a small prospective cohort study, 45 adults diagnosed with thyroid dysfunction were evaluated clinically using electrodiagnosis and hand-held dynamometry (Duyff et al., 2000). They found that 79% of hypothyroid patients had neuromuscular symptoms, 38% showed muscle weakness in one or more muscle groups, 42% showed indications of sensorimotor axonal neuropathy, and 29% had carpal tunnel syndrome (Duyff et al., 2000). However, the absence of a control group matched for age and sex is a significant limitation of this study. In another study, Cohen et al. (2020) assessed the association between self-reported thyroid disease and adhesive capsulitis. In that study, 166 patients diagnosed with adhesive capsulitis were compared with 129 patients with RC tears and 251 control subjects without shoulder problems (Cohen et al., 2020). They found that people with thyroid dysfunction had 2.69 times the likelihood of developing adhesive capsulitis compared to the two other groups. There was also a sex association, with females having a higher risk of developing adhesive capsulitis (Cohen et al., 2020).

In the current study, individuals who had depression were found to have an increased risk of CSP. A comparable result was observed with insomnia. These findings align with those of previous studies. Research has shown a high prevalence of sleep disturbance, anxiety and depression in people with chronic MSK pain, such as fibromyalgia, arthritis, and back pain. (Celiker et al., 1997, Wilson et al., 2002, Lin, 2008, Wilson et al., 2022). There is evidence for a bidirectional association between depression and MSK pain, that is that depression promotes pain and equally pain promotes depression (Magni et al., 1994, Bair et al., 2008). In a large observational study conducted by Generaal et al. (2017), insomnia and short sleep duration were significant risk factors for chronic MSK pain development, with an aHR for insomnia of 1.60 (95% CI 1.30 to 1.96) and an aHR for short sleep of 1.52 (95% CI 1.22 to 1.90). Additionally, previous observational studies have shown that shoulder disorders were associated with depression, anxiety, and sleep disturbance (Auvinen et al., 2010, Hoe et al., 2012, Cho et al., 2013, Mulligan et al., 2015). The relationship between poor sleep and pain in people with chronic pain may be explained by the mediation effect of negative mood (O'Brien et al., 2010), in that lack of delta sleep reduces descending pain inhibition, lowers mood, and can cause cognitive dysfunction (Lautenbacher et al., 2006, Haack et al., 2020).

In the current study, other comorbidities with a significant association with CSP were COPD, diverticular diseases and diaphragmatic hernia. COPD is a well-recognised risk factor for developing MSK pain. In cross-sectional population-based observational studies people with respiratory disorders

have reported a higher prevalence of MSK pain in different sites including the back, neck and shoulder areas (Janssen et al., 2016, Andenæs et al., 2018, Rasmussen-Barr et al., 2023). Referred pain to the shoulder can also be part of the presentation of diaphragmatic hernia and diverticular disease (Gray, 2011, Kohli et al., 2016, Hall, 2016).

Some of the comorbidities that associated with CSP in the current study have not been reported previously and are difficult to explain in terms of potential causal mechanisms, for example urinary incontinence, tinnitus and benign prostatic hyperplasia. There is some evidence that release of inflammatory substances in people with chronic pain may be associated with hearing loss. Takatsu et al. (2005) demonstrated that people with rheumatoid arthritis have higher rates of latent-type conductive hearing loss due to middle ear stiffness, and higher rates of sensorineural hearing loss, which might be due to systemic inflammation and tissue damage. However, no studies have been conducted to assess hearing impairment in patients with shoulder pain. Furthermore, one study has reported a significant relationship between the daily use of NSAIDs for MSK pain and the risk of having benign prostatic hyperplasia (HR 1.21, 95% CI 1.01 to 1.46) (Schenk et al., 2012). There are no previous studies regarding the associations between these comorbidities and shoulder pain. It is possible that the associations could be due to misdiagnosis or miscoding and further investigation of these associations is required.

Limitations of this study

Strengths of this study include the large sample size and the adjustments for other important confounders (age, sex, etc.). However, this study also has several caveats. Firstly, the case definition was based on diagnosis by the general practitioners, rather than a more rigorous diagnosis obtained by a physician with MSK expertise and use of imaging such as ultrasound to clarify the precise causal lesion, and this may have led to misclassification bias. However, a strict and narrow definition of CSP was used in this study to identify people with chronic pain. Another important limitation is the unavailability of data on risk factors such as occupation and physical activity to include in the analysis, since these are not consistently recorded in the CPRD database. Another limitation is that smoking, and alcohol data were self-reported, and not necessarily accurate. Finally, the missing data with respect to recording of BMI, alcohol intake, etc. might have reduced the statistical power of the study and produced biased estimates, leading to invalid conclusions. However, multiple imputation was conducted to address missing data, and this was followed by internal checks to ensure that the imputed data were reasonable. However, future studies are needed to explore other risk factors such as occupation and physical activity. Regarding comorbidities, the majority of the results were interpreted in the context of previously published research, so it is unlikely that false positive results had a significant impact on the conclusions. Most of the previously significant results remained significant even after applying Benjamini-Hochberg when

the multiple outcome measures under consideration were not independent.

4.5 Conclusion

In conclusion, the findings suggested that smoking, IMD, ethnicity and BMI were associated with CSP, whereas alcohol drinking associated with a significantly lower risk of CSP. Further studies are required to explore whether work-related risk factors are associated with CSP. This study provides important information on the comorbidities associated with CSP including other MSK conditions, COPD, diabetes, hypothyroidism, and depression. Understanding the possible association of other comorbidities with CSP, such as urinary incontinence, tinnitus and benign prostatic hyperplasia, merit further research. The findings of this study might have important implications for the development of health education and preventive strategies for targeted individuals who are at risk of CSP. Further studies are required to determine the causality of these associations with CSP.

Chapter 5. Outcomes associated with chronic shoulder pain: a prospective cohort study using the CPRD UK population

5.1 Introduction

As far as is known, no studies have been done in the UK to estimate the healthcare utilisations in people with CSP, and whether those people are more likely to have other long-term conditions. Exploring the health outcomes in people with CSP should provide a clear picture of the healthcare utilisations in this group. Therefore, the current study explored GP consultations, inpatient admissions, associated comorbidities, and all-cause mortality in people with CSP and in matched controls.

5.2 Methods

5.2.1 Study design

A cohort study was conducted to examine the outcomes and healthcare utilisations of people with CSP. Cases were defined as people with CSP identified between 2000 and 2020 (the first diagnosis date being the index date), whereas controls were defined as people without shoulder pain. Each case was matched with a control without shoulder pain by age, sex, and practice at the index date. See chapter 3 (pages 148) for further details about the inclusion and exclusion criteria. Selection of the study population and sample size are provided in Appendix 17 (pages 462-463).

5.2.2 External linkages

ONS Death Registration data on the date and causes of death were used to determine mortality (Herrett et al., 2015). HES Admitted Patient Care (HES APC) data, which contains information on hospital admissions, admission and discharge dates, and diagnoses (identifying primary diagnosis) in England was used to determine hospitalisations (Herbert et al., 2017). Records are coded using the International Classification of Diseases version 10 (ICD10) coding frame. In January 2022, 98% of the CPRD Aurum patients were linked to HES (Datalink, 2022).

5.2.3 Exposure and Outcomes

The exposure in this study was CSP.

The outcomes were:

- Comorbidities.

  All comorbidities investigated retrospectively in the case-control study (Chapter 4) were examined in this prospective study. Comorbidity was defined as the recording of a diagnosis of a predefined chronic condition in individuals in both groups.

- All-cause mortality.

  For mortality, all cause of deaths after the index date were captured to calculate mortality rates for the CSP group and the control group.

- GP consultations

  Information on GP consultations was derived from the consultation files. The number of consultations for any cause was used for the calculation of average consultations per year. The average number of

consultations per year was calculated by dividing the total number of GP consultations recorded after the index date, by the years of follow-up. For example, if a person had a total of 9 years of follow-up and had 120 consultations recorded during that period, then the average number of consultations for that person was 120/9 = 13.3 consultations per year.

- Hospitalisations

  The number of hospitalisations for any cause was used for the calculation of average hospitalisations per year. The average number of hospitalisations per year was calculated by dividing the total number of inpatients admissions recorded after the index date, by the years of follow-up. For example, if a person had a total of 9 years of follow-up and had 12 hospitalisations recorded during that period, then the average number of hospitalisations for that person was 12/9 = 1.3 hospitalisations per year.

5.2.4 Covariates

Owing to the longitudinal nature of the data, the health-related behaviours of participants could change over time. For example, during a 20-year follow-up period, BMI status, alcohol consumption, and smoking habits could vary considerably and research has shown that the occurrence of comorbidities is significantly influenced by these health-risk behaviours (Bhaskaran et al., 2013). Data on BMI, IMD, alcohol use and smoking status, together with age, sex, index date, and practice were used in the analysis.

5.2.5 Statistical analysis

Data management was conducted using R software (3.4.1) (Appendix 18, page 464). Data analysis was conducted using R software (3.4.1) (survival, and survminer) packages (Therneau and Lumley, 2015, Kassambara et al., 2017). Participant characteristics were presented using descriptive statistics, with mean and SD or median and interquartile range being used to summaries continuous variables, and frequency being used for categorical variables.

5.2.5.1 Comorbidities and all-cause mortality

For comorbidities, incident comorbidity at the earliest date of diagnosis after the index date was assessed. For each specific comorbidity, people without the comorbidity at the index date (i.e., people at risk of developing the comorbidity) in both the CSP and matched control group, were followed for up to 20 years after the index date. Participants were censored at the earliest date of comorbidity diagnosis, death, transfer out or end of the study date (31 December 2020) or last collection date, whichever occurred first. Hazard ratios (HRs) and 95% CIs were calculated for each comorbidity using the Cox proportional hazards model, adjusting for age, sex, practice, index date, BMI, IMD, ethnicity, smoking and alcohol consumption, and number of comorbidities at baseline. A sensitivity analysis was conducted for people with RC diseases to restrict the definition of CSP, and to assess whether RC diseases is associated with development of comorbidities (Appendix 19, Table 9-8, page 465).

For all-cause mortality, the people with CSP and the matched controls were followed up for up to 20 years after the index date. The follow-up of participants was censored at the earliest date of death, transfer out or end of the study date (31st December 2020), whichever occurred first. To evaluate simultaneously the effect of several factors on the rate of death, the hazard rate was calculated using the Cox regression. The univariate association between cases and controls and death was estimated using Cox proportional hazards regression analysis. All covariates that were statistically significantly (p-value < 0.05) associated with mortality were evaluated as potential confounders in the final analyses. Hazard ratios and 95% CIs were calculated using Cox regression adjusting for BMI, IMD, ethnicity, alcohol, smoking, and all comorbidities at baseline.

5.2.5.2 GP consultations and Hospitalisations

For GP consultations, descriptive statistics were reported as both mean (standard deviation) and median (inter quartile range). Normality distribution was tested using a histogram. As reported previously in the outcomes section, the average number of GP consultations per year was calculated by dividing the total number of consultations recorded after the index date by the years of follow-up. Due to evidence of overdispersion (the variance higher than average), Negative Binomial regression was used to allow for overdispersion. A similar method has been used before in the literature to analyse recurrent events in healthcare data (Thomsen and Parner, 2006, Banham et al., 2010, Korda et al., 2015). Negative binomial regression was applied to compute GP consultation risk ratio

(RR) and its 95% CI with follow-up time as an offset variable (Gwynn et al., 2000).

For hospitalisations, descriptive statistics were reported as both mean (standard deviation) and median (interquartile range). Normality distribution was tested using a histogram. The average of hospitalisation per year was calculated by dividing the total number of inpatients admissions recorded after index date, by years of follow-up. Due to evidence of overdispersion, negative binomial regression was applied to compute hospitalisations RR and its 95% CI with follow-up time as an offset variable.

Multicollinearity was checked using the Variance Inflation Factor (VIF) function in R (Shrestha, 2020). A value of VIF=1 indicates that there is no correlation between a predictor variable and any other predictor variables in the model. A value between 1 and 5 indicates moderate correlation between a predictor variable and other predictor variables in the model. A value > 5 indicates potentially severe correlation between a predictor variable and other predictor variables in the model. No multicollinearity was found between variables (Appendix 20, Tables 9-9 and 9-10, pages 466-468). To address the risk of a higher false discovery rate (FDR) due to multiple significance testing (Greenland, 2008), the FDR method proposed by Benjamini-Hochberg was used to calculate adjusted p-values (Benjamini and Hochberg, 1995, Benjamini and Yekutieli, 2001). The results were re-checked using the R built in function for calculating

adjusted p-values. The results were considered statistically significant when the p-value is less than the adjusted significance level of 0.05.

For all the previous outcomes, the survival between the two groups was compared using a Kaplan-Meier (KM) curve (Ranstam and Cook, 2017). The proportional hazard assumption (PH assumption) was assessed using KM curves, log-log plots and testing of scaled Schoenfeld residuals (Dessai and Patil, 2019, Kuitunen et al., 2021). Log-log plots are presented in Appendix 21 (pages 469-480).

5.3 Results

A total of 111,979 cases and 111,979 age, sex and practice matched controls were included in the analysis.

5.3.1 Comorbidities

The incidence of comorbidities in the CSP group and matched control group is shown in Table 5-1. The incidence of comorbidities was statistically significantly higher in people with incident CSP than in the controls. The crude and adjusted HR for incident comorbidities between CSP cases and controls are shown in Table 5-2. Of the 22 comorbidities studied, significant associations were seen with 18 comorbidities over the 20-year period (Table 5-2). The strongest associations were seen with fibromyalgia (aHR 1.71, 95% CI 1.62 to 1.81), sarcopenia (aHR 1.71, 95% CI 1.09 to 2.67), other MSK conditions (aHR 1.61, 95% CI 1.58 to 1.64), OA (aHR 1.60, 95% CI 1.55 to 1.64 and insomnia (aHR 1.54, 95% CI 1.47 to 1.61) (Table 5-2).

Table 5-1. Incidence of comorbidities in the incident chronic shoulder pain group and the matched controls

	Chronic shoulder pain (n=111,979)		Control group (n=111,979)	
Comorbidities	n	incidence/100 p-y (95% CI)	n	incidence/100 p-y (95% CI)
Diabetes	18507	2.62 (2.58, 2.66)	15222	1.99 (1.96, 2.02)
Hypothyroidism	3007	0.37 (0.36, 0.39)	2767	0.33 (0.32, 0.34)
Congestive heart failure	8900	1.14 (1.11, 1.16)	8041	1.00 (0.98, 1.02)
Hypertension	19072	2.84 (2.80, 2.88)	17572	2.47 (2.44, 2.51)
Ischemic heart disease	4829	0.60 (0.58, 0.61)	3362	0.40 (0.39, 0.41)
Myocardial infarction	1593	0.19 (0.18, 0.20)	1148	0.13 (0.12, 0.14)
Hyperlipidaemia	9618	1.31 (1.29, 1.34)	7589	0.98 (0.95,1.00)
COPD	7386	1.02 (1.00, 1.05)	5344	0.69 (0.67, 0.71)
Depression	19428	3.68 (3.63, 3.73)	14157	2.27 (2.24, 2.31)
Anxiety	9473	1.34 (1.31, 1.37)	6886	0.91 (0.89, 0.93)
OA	17137	2.45 (2.41, 2.48)	9699	1.25 (1.22, 1.27)
Other MSK conditions	29330	6.85 (6.78, 6.93)	21768	3.94 (3.88, 3.99)
Fibromyalgia	4496	0.56 (0.54, 0.58)	2288	0.27 (0.26, 0.28)
Insomnia	6079	0.80 (0.78, 0.83)	3677	0.45 (0.44, 0.47)
Fatigue	3390	0.42 (0.40, 0.43)	2203	0.26 (0.25, 0.27)
Sarcopenia	77	0.009 (0.007, 0.011)	35	0.004 (0.002, 0.008)
Tinnitus	3929	0.49 (0.47, 0.50)	2699	0.32 (0.31, 0.33)
Scleroderma	32	0.003 (0.002, 0.005)	28	0.003 (0.002, 0.004)
Urinary incontinence	3608	0.45 (0.43, 0.46)	2310	0.27 (0.26, 0.29)
Diverticular disease	4706	0.57 (0.56, 0.59)	3378	0.40 (0.38, 0.41)
Diaphragmatic hernia	4113	0.51 (0.49, 0.52)	2710	0.32 (0.31, 0.33)
Benign Prostatic Hyperplasia	2799	0.34 (0.32, 0.35)	2029	0.24 (0.23,0.25)

COPD, chronic obstructive pulmonary diseases. MSK, musculoskeletal

Table 5-2. HRs and 95% CIs for each comorbidity comparing the incident chronic shoulder pain and the control groups for a maximum of 20 years of follow-up.

Comorbidities	Crude HR, p-value	Adjusted HR*, p-value**
Metabolic/endocrine		
Diabetes	1.28 (1.25, 1.31), p<0.0001	1.19 (1.16, 1.22), p<0.0001
Hypothyroidism	1.21 (1.15,1.27), p<0.0001	1.13 (1.07, 1.19), p<0.0001
Hyperlipidaemia	1.31 (1.27, 1.36), p<0.0001	1.27 (1.23, 1.31), p<0.0001
Cardiovascular/Circulatory		
Congestive heart failure	1.12 (1.09, 1.16), p<0.0001	1.00 (0.97, 1.04), p=0.60
Hypertension	1.13 (1.11, 1.16), p<0.0001	1.03 (1.01, 1.05), p=0.002
Ischemic heart diseases	1.47 (1.41, 1.54), p<0.0001	1.27 (1.21, 1.33), p<0.0001
Myocardial Infarction	1.39 (1.28, 1.51), p<0.0001	1.22 (1.12, 1.32), p<0.0001
Respiratory		
COPD	1.46 (1.41, 1.52), p<0.0001	1.33 (1.28, 1.38), p<0.0001
Psychological		
Depression	1.58 (1.54, 1.62), p<0.0001	1.34 (1.31, 1.37), p<0.0001
Anxiety	1.44 (1.40, 1.49), p<0.0001	1.34 (1.30, 1.39), p<0.0001
Musculoskeletal		
OA	1.70 (1.66, 1.75), p<0.0001	1.60 (1.55, 1.64), p<0.0001
Other MSK conditions	1.75 (1.72, 1.79), p<0.0001	1.61 (1.58, 1.64), p<0.0001
Fibromyalgia	2.01 (1.90, 2.12), p<0.0001	1.71 (1.62, 1.81), p<0.0001
Fatigue	1.60 (1.51, 1.70), p<0.0001	1.42 (1.34, 1.51), p<0.0001
Sarcopenia	2.00 (1.29, 3.11), p=0.001	1.71 (1.09, 2.67), p=0.01
Genito-urinary		
Urinary incontinence	1.60(1.52, 1.70), p<0.0001	1.42(1.34, 1.50), p<0.0001
Benign Prostatic Hyperplasia[a]	1.40(1.32, 1.49), p<0.0001	1.36(1.28, 1.45), p<0.0001
Gastrointestinal		
Diverticular disease	1.43 (1.37, 1.50), p<0.0001	1.33 (1.27, 1.39), p<0.0001
Diaphragmatic hernia	1.56 (1.48, 1.64), p<0.0001	1.42 (1.34, 1.49), p<0.0001
Others		
Insomnia	1.71 (1.64, 1.79), p<0.0001	1.54 (1.47, 1.61), p<0.0001
Tinnitus	1.50 (1.42, 1.58), p<0.0001	1.42 (1.34, 1.49), p<0.0001
Scleroderma	0.98 (0.57, 1.68), p=0.95	0.96 (0.55, 1.66), p=0.89

*Adjusted for age, sex, practice, index date, BMI, IMD, smoking, alcohol and all comorbidities at baseline, a, for male only, COPD, chronic obstructive pulmonary diseases. MSK, musculoskeletal, **p-value <0.05 adjusted for multiple testing using 'False discovery rate'.

5.3.2 Mortality

During the study period, there were 3331(3.15%) deaths in the CSP group and 2802 (2.64%) deaths in the control group. The mortality rates were 0.39 (95% CI 0.37 to 0.40) per 100 person years in cases, and 0.32 (95% CI 0.31 to 0.33) per 100 person years in controls (Figure 5.1). After the adjustment for BMI, IMD, ethnicity, alcohol, and smoking, people with CSP had 16% higher risk of all-cause mortality (aHR 1.16, 95% CI 1.10 to 1.22). When additionally adjusting for all comorbidities at baseline, the CSP group had a 6% higher risk of all-cause mortality compared to the control group (aHR 1.06, 95% CI 1.00 to 1.11; p-value= 0.01) (Table 5-3).

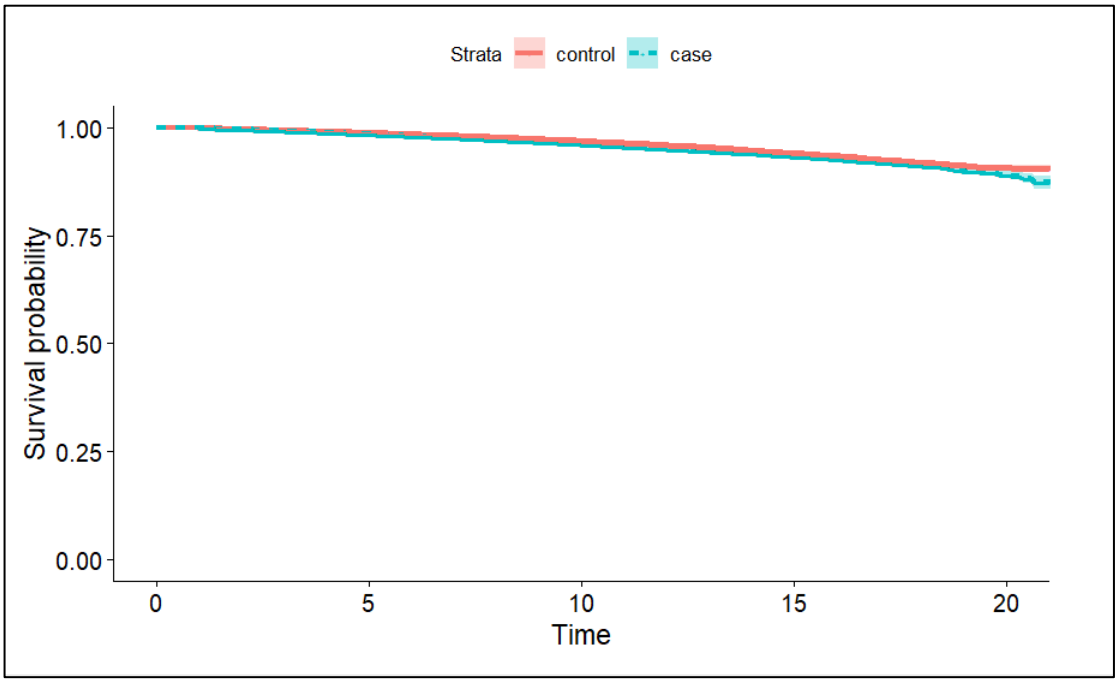


Figure 5.1 Survival probabilities of all-cause mortality in the CSP group and the control group.

Table 5-3. Mortality rate, and associations with all-cause mortality in the chronic shoulder pain group and the control group.

Group	Chronic shoulder pain (n=111,979)	Control group (n=111,979)
Total deaths (n)	3331	2802
Mortality rate per 100 person years (95% CI)	0.39 (0.37, 0.40)	0.32 (0.31, 0.33)
Crude HR (95% CI)	1.21 (1.15,1.27)	reference
Adjusted HR (95% CI) *	1.16 (1.10, 1.22)	reference
Adjusted HR (95% CI) **	1.06 (1.00, 1.11)	reference

n, number, *Adjusted for age, sex, index date, practice, BMI, IMD, ethnicity, alcohol, and smoking.
**Adjusted for age, sex, index date, practice, BMI, IMD, ethnicity, alcohol, smoking, and number of comorbidities at baseline, p-value<0.001

5.3.3 GP Consultations

The average number of GP consultations per year in people with CSP (23.60) was higher than in the control group (14.36). The negative binomial regression model showed that people with CSP were at 53% higher risk of having more GP consultations compared to the control group (aRR 1.53, 95% CI 1.52 to 1.54) (Table 5-4).

Table 5-4 Average number of (all-cause) GP consultations per year in the chronic shoulder pain group and the control group, and the negative binomial regression results

	Chronic shoulder pain (n= 111,979)	Control group (n= 111,979)
Average GP consultations per year		
Mean (SD)	23.60 (21.76)	14.36 (16.10)
Median (IQR)	17.96 (10.11- 20.15)	10.03 (4.06 - 15.18)
Number of GP consultations		
Mean (SD)	164.18 (182.43)	110.24 (143.67)
Median (IQR)	108 (46- 217)	64 (19 - 148)
Crude RR (95% CI)	1.63 (1.61, 1.64)	reference
Adjusted RR (95% CI)*	1.53 (1.52, 1.54) **	reference

SD- standard deviation, IQR- inter quartile range, *Adjusted for age, sex, practice, index-date, smoking, alcohol, BMI, and number of comorbidities at baseline, ** p-value <0.0001, RR- risk ratio

5.3.4 Hospitalisations

The mean average number of hospitalisations per year in people with CSP was higher (0.65) than in the controls (0.43) (Table 5-5). The negative binomial regression model showed that the number of hospitalisations in cases were 37% higher than in controls (aRR 1.37; 95% CI 1.35 to 1.39) (Table 5-5).

Table 5-5 Average number of (all-cause) hospitalisations per year in the chronic shoulder pain and the control groups.

	Chronic shoulder pain (n= 111,979)	Control group (n= 111,979)
Average hospitalisations per year		
Mean (SD)	0.65 (2.22)	0.43 (2.35)
Median (IQR)	0.28 (0-0.51)	0.13 (0-0.37)
Number of hospitalisations		
Mean (SD)	4.35 (17.09)	3.05 (13.08)
Median (IQR)	2 (1-5)	3 (0-3)
Crude RR (95% CI)	1.48 (1.45, 1.50)	reference
Adjusted RR (95% CI)*	1.37 (1.35, 1.39)**	reference

SD- standard deviation, IQR- inter quartile range, *Adjusted for age, sex, smoking, alcohol, BMI, and number of comorbidities at baseline, ** p-value <0.0001, RR-risk ratio

5.4 Discussion

Outcomes in CSP have been well studied with respect to quality of life, functional disability, psychological distress, and physical activity level (Alizadehkhaiyat et al., 2017, Walankar et al., 2020, Hwang and Oh, 2022). However, the burden and type of comorbidities associated with CSP and health services utilisation by people with CSP have not been well studied. Four outcomes were explored in this study using a large primary care database in the UK, specifically, the incidence of comorbidities and associations, all-cause mortality, GP consultations, and hospitalisations (inpatient admissions). The data demonstrated that people with CSP were at 53% higher risk of having more GP consultations, 37% higher risk of hospitalisations, 6% higher risk of all-

cause mortality, and a higher burden of comorbidities. The strongest associations observed were with sarcopenia (aHR1.71, 95% CI 1.09 to 2.67), fibromyalgia (aHR 1.71, 95% CI 1.62 to1.81), OA (aHR 1.60, 95% CI 1.55 to 1.64), other MSK conditions (aHR 1.61, 95% CI 1.58 to1.64), and insomnia (aHR 1.54, 95% CI 1.47 to 1.61).

Comorbidities and chronic shoulder pain

The study found that people with CSP were more likely to develop all of the examined comorbidities except for congestive heart failure and scleroderma. The association of CSP with other MSK conditions aligns with previous studies which reported associations between fibromyalgia (Guler et al., 1992, Gostine et al., 2018, Compagnoni et al., 2023), OA and other MSK conditions (Mäkela et al., 1991, Mäkelä et al., 1999, Wright et al., 2015, Laslett et al., 2016). Wright et al. (2015) found that shoulder pain was associated with cancer (aOR 1.4), diabetes (aOR 1.6), depression (aOR 4.0), cardiovascular diseases (aOR 2.2) and other MSK conditions (aOR 2.2) (Wright et al., 2015a). However, because of the cross-sectional nature of the study, it is difficult to draw firm conclusions about the temporal or causative relationships for the observed associations. In the current longitudinal study, it was found that people with CSP were at greater risk of developing diabetes and hypothyroidism. Previous studies have reported that endocrine diseases including diabetes and hypothyroidism may be associated with MSK pain (Mäkelä et al., 1999, Cakir et al., 2003, Cohen et al., 2020, Song et al., 2022, Chuang et al., 2023). Several studies have highlighted the association between diabetes

and MSK conditions such as adhesive capsulitis, tenosynovitis and Dupuytren's contracture (Wyatt and Ferrance, 2006, Thomas et al., 2007, Wright et al., 2015, Sözen et al., 2018). Thyroid diseases were also known to be associated with several MSK symptoms such as muscle weakness, muscle pain, and adhesive capsulitis (Persellin and Rutstein, 1979, Ingbar et al., 2000). There is a paucity of evidence on the underlying mechanism of the relationship between shoulder pain and thyroid disease. Some authors reported that the relationship between adhesive capsulitis and Hashimoto's thyroiditis, which is the most common cause of hypothyroidism, has an autoimmune aetiology (Cakir et al., 2003, Reuters et al., 2009, Wang et al., 2013, Schiefer et al., 2017). Histological findings have shown evidence of chronic nonspecific inflammation in people with adhesive capsulitis indicated by increased vascularity of tissues, increased tissue edema, proliferation of fibroblasts, and synovial membrane thickening (Jump et al., 2021). Metabolic findings in people with adhesive capsulitis showed increase in blood lipids (Jump et al., 2021). The association between adhesive capsulitis and other conditions such as diabetes, thyroid diseases, hyperlipidaemia and Dupuytren contracture may have similar basis (Jump et al., 2021). Like adhesive capsulitis, these conditions may create a proinflammatory environment, resulting in increased inflammatory response with elevated levels of inflammatory cytokines and fibrosis as well as elevated blood lipids (Bunker and Anthony, 1995, Bunker and Esler, 1995, Rizos et al., 2011). However, most of the previous studies were cross-sectional, or case-

control and they did not examine prospectively whether people with shoulder pain could develop these comorbidities.

As far as is known, only one prospective cohort studies have been undertaken recently in the UK to explore if people with adhesive capsulitis can develop type 2 diabetes in the future. This study was conducted by Dyer et al. (2024) using a large primary care electronic medical record (CPRD GOLD). The study included 31, 226 people with adhesive capsulitis matched by age, sex and practice with 31, 226 people without adhesive capsulitis. The findings showed that people with adhesive capsulitis were more likely to be diagnosed with type 2 diabetes compared to people without adhesive capsulitis (aHR 20.0, 95% CI 16.0 to 25.0) (Dyer et al., 2024). However, the association in this study might have been inflated if those with adhesive capsulitis were being tested more frequently than those without adhesive capsulitis. It is possible that people with adhesive capsulitis were already getting tested for type 2 diabetes more frequently since GPs are aware that these two conditions are associated. It is important also to state that this study do not support the theory that type 2 diabetes is caused by adhesive capsulitis (Losciale et al., 2023, Hernán et al., 2019). On the contrary, type 2 diabetes has been proposed as a cause of adhesive capsulitis (Hsu and Sheu, 2016, Dyer et al., 2023), which might explain the high prevalence of diabetes in people with adhesive capsulitis.

The finding that people with CSP have sleep disturbance, depression, and anxiety also aligns with previous reports regarding people with adhesive

capsulitis (Ding et al., 2014, Bagheri et al., 2016, Toprak and Erden, 2019). Sleep disturbance, depression, and anxiety are also well known to be associated with other forms of chronic MSK pain, such as fibromyalgia, arthritis, and back pain. (Celiker et al., 1997, Wilson et al., 2002, Lin, 2008, Wilson et al., 2022).

Cardiovascular diseases such as ischemic heart diseases and myocardial infarction have been found to be associated with chronic MSK pain, but few studies have examined their association specifically with shoulder pain. There is high-quality evidence that people with chronic MSK pain are more likely to have cardiovascular diseases compared with those without chronic MSK pain (RR 1.91, 95% CI 1.64 to 2.21) (Ryan et al., 2014, Oliveira et al., 2020). A possible explanation is that people with chronic MSK pain often have functional limitations that are commonly combined with psychological distress (Carvalho et al., 2017, Asavasopon, 2018), both of which could lead to reduced physical activity, a known risk factor for cardiovascular diseases (McBeth et al., 2010). Frequent use of nonsteroidal anti-inflammatory medicines (NSAIDs) is another example of a mechanism that might raise the risk of cardiovascular diseases in those with chronic MSK pain (Trelle et al., 2011, Lindhardsen et al., 2014, Bally et al., 2017). The use of NSAIDs for MSK pain may have impact on the cardiovascular system, including high blood pressure, thrombotic events, and congestive heart failure (Jüni et al., 2004). Both nonselective NSAIDs and selective COX-2 inhibitors increase the risk of congestive heart failure, which is attributed to vasoconstriction, blood pressure elevation, and sodium and water retention (Bhala et al., 2013). Large clinical trials

have found that rofecoxib increased the risk of myocardial infarction, which raised concerns about the potential cardiotoxicity of nonselective NSAIDs and selective COX-2 inhibitors (Jüni et al., 2004). One of the suggested explanations for the elevated risk of thrombotic events was the degree of inhibition of COX-2 in comparison to COX-1 (Dubreuil et al., 2018). This could lead to an imbalance between the pro-thrombotic vasoconstrictive effects of thromboxane A2, induced by COX-1 in platelets, and the antithrombotic vasodilatory actions of prostacyclin, induced by COX-2 in blood vessel walls (Braun et al., 2020). It is difficult to postulate mechanisms for some of the comorbidity associations that were found with CSP, for example, tinnitus, benign prostatic hyperplasia, and urinary incontinence. More studies are needed to determine the nature of these associations and whether they are direct or indirect.

A sensitivity analysis was conducted in this study for those who had RC diseases, and that analysis revealed no significant associations with congestive heart failure, hypertension, sarcopenia, or scleroderma. Restricting the definition did not greatly alter the findings but did suggest that the broad definition of shoulder pain might affect the results.

Mortality and chronic shoulder pain

Based on the existing evidence, this is the first study to examine the relationship between CSP and all-cause mortality. Some studies have reported positive associations between MSK pain and increased mortality, which aligns with the current results (Macfarlane et al., 2001, McBeth and Jones, 2007, Nitter and Forseth, 2013, Docking et al., 2015a, Macfarlane

et al., 2017). A large cohort study conducted by Macfarlane et al. (2017) examined the relationship between CWP and mortality using the UK Biobank database. Around half a million people aged 40–69 years who were registered with a general practitioner were recruited between 2006 and 2010. Participants reporting ’pain all over the body’ for more than 3 months were compared with participants without chronic pain. Information on death (with causes) was derived from the ONS records (Macfarlane et al., 2017). 7130 participants with CWP had excess mortality compared to participants without CWP (mortality RR 2.43). Specific causes for excess mortality were cancer (aRR 1.73), cardiovascular disease (aRR 3.24), and respiratory disease (aRR 5.66). After adjustment for low levels of physical activity, high BMI, smoking, and poor diet the mortality risk reduced (aRR 1.47, 95% CI 1.24 to 1.73) (Macfarlane et al., 2017). It is clear from the results that increased mortality in people with CWP could in part be explained by unfavourable lifestyle factors that could be addressed in the management of these participants. However, other studies have reported no significant association between MSK pain and mortality, especially after controlling for some demographic and behavioural factors (Smith and Leggat, 2004, Andersson, 2009, Andorsen et al., 2016, Fernandez et al., 2017). Torrance et al. (2010) examined the relationship between chronic pain and mortality using a cohort record linkage study over a 10-year period. The cohort consisted of 6940 people recruited from 29 practices across the UK with information being collected on chronic pain status, general health and sociodemographic information (Torrance et al., 2010). A record linkage between these data and the regularly gathered national

dataset for death registration was carried out ten years after its establishment. The analysis was conducted to determine HRs for all-cause, system-specific, and disease-specific mortality by chronic pain grade. Out of the initial cohort, 5858 (84.4%) people were linked, including 1557 who died. They found significant associations between chronic pain and all-cause mortality (HR 1.32), but when they adjusted for sociodemographic factors, this association was lost. However, those who reported severe chronic pain were at greater risk of mortality compared to people who reported mild or no chronic pain (HR 1.49) and after adjustment for sociodemographic factors, severe chronic pain remained significantly associated with all-cause mortality (aHR 1.49), and specific cause (circulatory system disease) mortality (aHR 1.68). However, this study had some limitations. For example, although they adjusted for several sociodemographic factors, they were unable to adjust for smoking and BMI, which are well established risk factors for conditions such as cardiovascular disease, cancer, and death.

Although the majority of previous studies adjusted only for age and sex, the primary findings of the current study align with their results, showing an increased risk of all-cause mortality in people with CSP (Macfarlane et al., 2001, Andersson, 2009, Nitter and Forseth, 2013, Docking et al., 2015a). Other covariates were also included such as risk factors and comorbidities, and although the HRs decreased when additional confounders were taken into account, the association remained significant. In general, the association between CSP and increased mortality might at least in part be explained by confounding caused by

socio-demographic factors, and comorbidities. Apart from these, the functional limitations, disability, and use of analgesics such as NSAIDs in people with CSP might explain the higher mortality rate (Badcock et al., 2003, Trelle et al., 2011, Roh et al., 2012, Luque-Suarez et al., 2020). Physical activity has been shown to enhance cardiorespiratory fitness, flexibility, balance, muscular endurance, and strength (Bai et al., 2022). People with disabilities are at higher risk for secondary conditions, such as cardiovascular disease, pressure sores, diabetes, and urinary tract infection, which will have a negative impact on overall health (Campbell et al., 1999). Previous studies have reported that functional limitations in daily activities associate with increased mortality (Forman-Hoffman et al., 2015, Bai et al., 2022, Gao et al., 2023, Smythe and Kuper, 2024). Additionally, NSAIDs use in people with chronic pain increases the risk of gastrointestinal (GI) bleeding, stroke, myocardial infarction, thrombotic events and hypertension, which might increase the risk of death (Stillman and Stillman, 2007, Roumie et al., 2008, Sabzwari et al., 2013).

GP consultations, hospitalisations and chronic shoulder pain

Chronic MSK pain previously has been found to be associated with higher use of healthcare services in several studies (Eriksen et al., 2004, Hartvigsen et al., 2014). However, healthcare utilisations for people specifically with shoulder pain have not been described thoroughly. GP consultations and hospitalisations for any reason in the CSP group compared to the matched control group were examined in this study. The average number of GP consultations per year was higher in people with

CSP compared to the control group, and people with CSP were at 53% higher risk of having more GP consultations. Shoulder pain is mainly managed in primary care (Urwin et al., 1998, Luime et al., 2004, Artus et al., 2017), which might explain the high number of GP consultations. However, all GP consultations were examined irrespective of the primary reason for the consultation. Similarly, the average number of hospitalisations per year was higher in people with CSP compared to the control group, and people with CSP were at 37% higher risk of more hospitalisations. Increased risk of hospitalisations in people with CSP could be due to multimorbidity (Soley-Bori et al., 2021), comorbidities (Lentz et al., 2019, Friebel and Maynou, 2022), opioid use (Friebel and Maynou, 2022), low socioeconomic status (Beyera et al., 2019, Lentz et al., 2019), poor general heath (Cornally and McCarthy, 2011, Emilson et al., 2020), and work-related injuries and associated disability (Wah et al., 2024). However, in the current study, after adjusting for comorbidities, the results did not change significantly.

Previous studies have demonstrated that long-term use of NSAIDs contributes to increased hospital admissions predominantly for GI bleeding (Laporte et al., 2004, Gupta and Eisen, 2009, Hnepa et al., 2021), and cardiovascular disease (Bhatnagar et al., 2015, Hemmo et al., 2021). Cassel et al. (2018) reported that multimorbidity was strongly associated with increased health services utilisation in the UK, people with multimorbidity accounting for 53% of all GP consultations and 56% of hospital admissions (Cassell et al., 2018). Few studies have explored the healthcare utilisations by people with CSP, and none have described GP

consultations and hospitalisations for CSP which makes it difficult to compare the results of this study to previous research. Matsen et al. (2014) found that advanced age and comorbidities were associated with readmission of people with primary shoulder arthroplasties after 90 days (Matsen et al., 2014). Another study in Korea investigated the medical services used and the usual care of common shoulder disorders, specifically, adhesive capsulitis, RC tendinopathy, and shoulder impingement syndrome (Joo et al., 2017). They found that people with RC syndrome had the highest overall and per-patient cost. Patients with RC tendinopathy were more likely than those with adhesive capsulitis to receive surgical management, and the number of in-patient admissions with RC tendinopathy was more than twice that of the other two groups (Joo et al., 2017). However, in that study there was no information on smoking status, drinking habits, educational level, socioeconomic status, and individual income, which could limit further investigations of person-specific causal relationships (Joo et al., 2017).

In summary, an in-depth analysis of the current trend of healthcare utilisation for the treatment of chronic shoulder disorders is warranted given the rise in the prevalence of this condition, and the variety of treatment options. Further studies are required to explore the causes of hospitalisations in this population.

Strengths and limitations

Major strengths of this study are the large sample size, the inclusion of 22 comorbidities, a long follow-up period (20 years), and adjustment for a number of confounders in the analysis. However, this study has some limitations. Only all- cause mortality was estimated in this study, whereas cause-specific mortality might provide further insights into specific causal pathways leading to the death of people with CSP. GP consultations and hospitalisations were calculated regardless of any specific causes, which could be influenced by the incidence of comorbidities. The GP consultation definition in this study might not be accurate as it includes recording of visits to the primary care for any cause. Potentially, people who visited their GP more frequently had higher chance of being diagnosed with long-term chronic conditions and vice versa. However, adjustments were made for a number of comorbidities in the analyses. Additionally, the associations with opioids or other oral drugs were not investigated which might explain the relationship between CSP and mortality, and hospitalisations. Although the majority of the comorbidities in the study have already been validated, misclassification bias for comorbidities remains a possibility. Additionally, the case definition for CSP was based on the diagnosis made by the GPs, rather than a specific diagnosis or to a 'gold standard' obtained by a physician with MSK expertise, and this may have led to misclassification bias. However, a sensitivity analysis was conducted restricted to one specific definition (RC diseases), which did not greatly alter the findings. Finally, the number of comorbidities examined in the current study was limited to just 22,

which could be interpreted as conservative, and it would be good to consider a more expanded list of comorbidities for use in future studies. Future longitudinal studies are required to investigate a causal relationship to determine whether some specific CSP conditions such as shoulder OA, adhesive capsulitis and bursitis can lead to long term comorbidities or vice versa.

5.5 Conclusion

In conclusion, this study found that people who have CSP had higher incidence rates of comorbidities, GP consultations and hospitalisations, and all-cause mortality. These findings provide information on the long-term effects of CSP and align with earlier findings about the associations between MSK pain in general and comorbidities, mortality, and hospitalisations. Understanding these associations may help healthcare practitioners evaluate and treat these people with shoulder pain more effectively. However, the association of CSP with some comorbidities could not be explained and might not be mechanistically linked to the shoulder pain but result indirectly from shared risk factors related to ageing. Further studies are required to investigate the aetiology and causality of these associations. The findings about the outcomes of CSP are expected to provide basic healthcare data for future research to aid policymakers as well as researchers.

Chapter 6. Patient and public involvement

Patient and public involvement (PPI) in healthcare research is increasingly essential and helps to ensure that research focuses on topics that are relevant to patients and the public (Staniszewska et al., 2012, Brett et al., 2014). Although this study did not require direct patient involvement, it is important for the public and patients to contribute to every stage in the research to ensure that the research priorities align with those of patients and healthcare service users.

Aims

To improve research quality and relevance by incorporating the viewpoint of the public. Involving patients and the public can reinforce and improve how research is applied in practice.

6.1 Methods

A sample of patients and public were identified people who had volunteered for such activities in the research website https://www.peopleinresearch.org. The People in Research is a free website that provides opportunities for members of the public to become actively and anonymously involved with the research process. For the first PPI input, a form was posted on the website that included a lay summary of the study, a brief description of the method used in the research, and six specific questions (Appendix 22, pages 481-483). For the final PPI input, a brochure that included the results of the study together with

questions was introduced through the same website (Appendix 23, pages 484-487).

6.2 Feedback

A total of nine responses were received in the first PPI input (Table 6-1). Eight out of nine respondents had CSP. Four people had one long-term condition, while five had more than two long-term conditions. All respondents stated that this project is worth doing and could benefit people with CSP. They also stated that this research will benefit patients with CSP in many ways, specifically:

- It would help care providers understand the severity of shoulder pain in the UK which could potentially lead to further research and treatment:
- To improve best practice for this condition, which will result in better health outcomes
- To understand the cause of shoulder pain
- To investigate if the trend of CSP is increasing
- To investigate how CSP can affect daily activities and the psychological effects of this condition.

For the final PPI input, a total of 9 responses were received. The responses are presented in Table 6-2. Most of the participants found that the project was worth doing and could benefit people with shoulder pain. Most of the participants found that the results were presented in a clear and understandable way. Only one participant found that the analysis

does not point to why the shoulder pain varied across UK regions. He reported that “this is a picture of what has happened rather than why this is what has happened”. Another participant reported that “Quantitative data rather than comparative would be better” and commented on the title “why UK, when only England and Northern Ireland are reported”. The same participant suggested that causes are more important than incidence (e.g. trauma, arthritis, occupation, long-term immobility etc.).

Table 6-1 First Patient and public involvement input

Question	Response
Have you had CSP ?	8 out of 9 people had CSP
What other conditions do you have?	Behcet’s disease, cancer, arthritis, sarcoidosis, ulcerative colitis, osteoporosis, diabetes, gout, hyperlipidemia, obesity, peripheral neuropathy; mixed dementia; medication-controlled hypertension, psoriasis, hypermobility, Lupus with Sjogren's, Antiphospholipid syndrome, fibromyalgia, OA 4 has one long term condition 5 has more than two long term conditions
Do you think this project is worth doing?	Yes (all respondents)
Do you think this research will benefit patients with CSP, Yes/No.' ' if so, how?'	Yes (all respondents) • To improve the best practice for this condition, better health outcomes and quality of life • To understand the cause of shoulder pain • To investigate if the trend of CSP is increasing • To investigate how CSP can affect daily activities and the psychological effects of CSP

	• To explore the treatment shared will be interesting It will help care providers understand the severity of shoulder pain in the UK, and it could potentially lead to further research and treatment options
Is there any part of this study that needs to be improved, or have we missed anything that you think more important?	• Consider psychological issues arising from this condition. Employment issues? Effect on the family? Effect on driving. Effect on personal care. • Ttreatments v. outcomes • "Perhaps those that have extreme shoulder pain could undergo radiographs which can be compared to radiographs of someone who has no pain to see what the differences are?" • Link of shoulder pain with other diseases e.g. osteoporosis Unsure as pain can be caused by different things
To make this research meaningful to people with CSP and public, we would like to have your inputs from time to time (September 2023). Are you happy for us to approach you again for this purpose?	8 out of 9 were happy to be contacted again

Table 6-2 Final Patient and public involvement input

Question	Response
Do you think the results were presented in a clear and understandable way? Yes/No. If no, how this could be improved	Yes (5 respondents)
Do you think this project is worth doing?	Yes (8 respondents), only one person found it not worth it
Do you think this research will benefit patients with CSP , Yes/No.	Yes (7 respondents) • Comprehensive knowledge of CSP is crucial to optimise practice and patient outcomes. • It may lead to patients better understanding of why they get this pain and how they can manage this condition
Is there any part of this study that needs to be improved, or have we missed anything that you think important?	Yes (7 respondents)

6.3 Discussion

Patient and public involvement in this study was effective, specifically for disseminating the results and to ensure that the results were presented in a clear and understandable way. The respondents highlighted several important aspects to consider in future research including psychological aspects, the work-related impact of shoulder pain, and management options for shoulder pain. The respondents recommended that the project would be significantly improved by analysis of why shoulder pain is different in various parts of the UK. For example, one of the respondents reported that while the South West area is heavily reliant on heritage and tourism, East Anglia and East Yorks have a higher proportion of

agricultural industry compared to other regions and that this might be a factor. The current study has suggested potential causes for varied prevalence among UK regions might include differences in life style, educational level and/or occupation. The PPI participants also proposed that some patients may not report pain to their GPs because of the difficulty of getting an appointment. However, it was suggested that the estimated prevalence might not accurately reflect the true prevalence of CSP because some people have symptoms but do not consult GPs, rather than specifying “difficulty in obtaining appointments” as an important cause. One participant observed that this research reported what happened rather than why it happened. However, this research provides basic information about the burden of CSP in the UK and might inform future research on why shoulder pain varies across UK regions, and which type of shoulder pain diagnosis is more common.

Although the PPI was effective, there were some limitations. There was a lack of complete information about respondents’ physical activity or the cause of their shoulder pain. Because of the nature of the website, and the fact that patient involvement was anonymised, it was not possible to confirm whether the people who responded to the second input were the same as those who had responded to the first input. In future studies, arranging face-to-face or on-line meetings with such individuals might overcome this limitation and allow for much fuller discussion of the study and its results.

6.4 Conclusion

PPI involvement is a crucial element in healthcare research. The PPI involvement in this study helped to facilitate the planning for future research. Other PPI approaches such as interviews or meetings should be considered in the future to ensure comprehensive feedback and involvement of the PPI group in each research phase. Future exploration of the causes of shoulder pain variations among UK regions is required.

Chapter 7. General Discussion

Shoulder pain was reported to be the third most common MSK condition in the UK (Jordan et al., 2010, Greving et al., 2012). It can arise from various causes, often overlapping with other MSK conditions, and can coexist with pain in other joints such as neck, back pain. Eight out of ten people in England reported that some of their chronic pain is MSK and in one of the following areas neck or shoulder, back, and limbs (Versus Arthritis, 2017). This chapter aims to provide a summary of this thesis and to propose clinical implications of the results and suggest future research questions.

7.1 Summary

The systematic review and meta-analysis have summarised the current evidence on the prevalence and incidence of shoulder pain, risk factors and associated comorbidities. It highlighted the variations of shoulder pain definition across the literature and the need for a standard protocol to diagnose and define CSP in future studies. The systematic review and meta-analysis helped to justify the need for longitudinal observational studies to explore the possible association between CSP and wide range of comorbidities.

This thesis focused on the epidemiology of CSP in the UK using a large nationally representative NHS database involving four different studies to explore CSP epidemiology, including prevalence and incidence, risk factors, comorbidities, mortality and healthcare utlisations.

The discrepancy in age-related inclusion criteria between the systematic review and meta-analysis, which included only adults aged 40 years and over, and the CPRD-based observational studies, which included all adults aged 18 years and above may be considered a potential limitation. The decision to restrict the systematic review to older adults was guided by the relative scarcity of studies focusing specifically on this age group, despite their elevated risk of chronic MSK conditions, including CSP. On the other hand, the broader inclusion criteria adopted in the CPRD studies were intended to provide a comprehensive view of the burden of CSP across the adult population. This inconsistency can limit the comparability of findings and may affect the generalisability of conclusions drawn from the systematic review to the population represented in the CPRD analyses. However, in the CPRD analyses, prevalence estimates stratified by age indicated a notable rise among adults aged 40 years and older, providing justification for the age threshold used in the systematic review.

The CPRD findings demonstrate an increase in the prevalence of CSP in the UK between the year 2000 and 2019 from 0.42% to 2%. While this may be considered a low burden compared to other chronic MSK conditions such as knee pain, which has shown an increased prevalence from 2.8% in 1997 to 18.6% in 2017 in the UK (Swain et al., 2020), it reflects an increase in the overall burden of MSK pain in the UK and the need for primary care to be prepared to handle this. The prevalence of all OA increased in the UK during 1997- 2017, from 6.15% to 10.77% (Swain

et al., 2020). Population growth, ageing, and other risk factors such as obesity and work-related factors can lead to a significant increase in the burden of MSK conditions, especially in developing countries (2010, Hoy et al., 2012, Murray et al., 2012, Cross et al., 2014). Carnes et al. (2007) found that in the UK general population more people had MSK chronic pain that was multi-site than single site (34% vs. 11.25%). This reflects that chronic MSK pain rarely presents as a single-site problem and commonly occurs as in various body joints simultaneously. Therefore, understanding the relationship between pain in different body sites and the health impact of multi-site pain is required to help inform management and meet healthcare needs (Carnes et al., 2007).

In the current study the prevalence and incidence of shoulder pain decreased in the year 2020, which might be influenced by reduced consultations during the COVID-19 pandemic and lockdown. Welsh et al. (2023) demonstrated that restrictions related to the pandemic resulted in a significant drop in rheumatic and MSK conditions consultations in primary care in March 2020 and a relative rise in the prescription of analgesics, including potent opioids, in the UK. This needs to be taken into consideration by policy makers when implementing future restrictions and consider preserving non-pharmacological approaches to pain management, such as exercise and physiotherapy.

In the current study, a high recording of “specific” shoulder pain was seen from the year 2012, which might be explained by possible change in coding. The findings confirmed that CSP increases with age above 40

years and is more common in female. However, the incidence of CSP started to decrease after the year 2011. This could be due to less incidence (less inputs) or improvement in management care, the last possibility is less likely because there was no clear evidence that the management for CSP in the UK has been improved.

The potential change in diagnostic recording aligns with a broader conceptual shift in how shoulder pain is classified in clinical practice. Due to the challenges of differential diagnosis for shoulder pain, many common shoulder pain presentations associated with subacromial pain (impingement), RC tendinopathy, subacromial bursitis and tears are recently more increasingly being grouped under a broader, more pragmatic diagnostic umbrella of “rotator cuff-related shoulder pain” (RCRSP) (Lewis, 2016, Requejo-Salinas et al., 2022, Lo et al., 2022). Lewis et al., (2016) suggested that because it may be difficult to derive a definitive structural pathognomonic label, terms such as rotator cuff related shoulder pain (RCRSP) or subacromial or RC pain syndrome may be more appropriate. Such an overarching term was proposed to help patients understand their experience of shoulder pain and weakness and to overcome the limitations and inconsistencies associated with previous diagnostic labels, such as subacromial impingement syndrome (SIS), and to replace potentially flawed pathoanatomical classifications such as bursitis and RC tears. (Lewis, 2016, Lo et al., 2022, Requejo-Salinas et al., 2022). The term RCRSP acknowledges that the underlying cause of the shoulder pain is currently unknown. It is one of many painful shoulder presentations that are characterised by pain and/or weakness during

shoulder elevation and external rotation, without evidence of referred pain (i.e. from cervical spine), and are associated with shoulder loading and lifestyle factors (Lewis, 2016, Burne et al., 2020, Requejo-Salinas et al., 2022).

However, although several diagnostic criteria for RCRSP have been proposed in the literature (Hermans et al., 2013, Diercks et al., 2014, Lewis, 2016), none have been supported by sufficiently robust methodology, which has hindered their acceptance as standardised diagnostic tools (Requejo-Salinas et al., 2022). Recently, Requejo-Salinas et al. (2022) identified the most relevant clinical descriptors for RCRSP based on the opinion of an international panel of experts with a high level of clinical, teaching, and research experience. A total of fifteen physical therapy experts participated in the Delphi survey. Following three rounds, consensus was achieved on 18 clinical descriptors. Of these, ten were allocated to the "subjective examination" domain, one to the "patient-reported outcome measures" domain, three to the "diagnostic examination" domain, two to the "physical examination" domain, and two to the "functional tests" domain. No descriptors reached consensus within the "special tests" domain. Among the items with the highest levels of agreement were the reproduction of symptoms under load, during overhead activities, and the importance of evaluating both active and resisted shoulder movements (Requejo-Salinas et al., 2022). Although this study utilised a panel of highly experienced experts, selected through a systematic search process aimed to minimise selection bias, the relatively low response rate in the initial Delphi round (26.8%) may limit the external

validity of the proposed clinical descriptors. Another limitation lies in the inclusion of physical therapists only, which may restrict the generalisability of the diagnostic criteria to other healthcare professionals involved in the management of shoulder pain, such as GPs, rheumatologists, sports medicine physicians, and orthopaedic surgeons. Further research is required to evaluate and validate these clinical descriptors across a broader range of clinical disciplines.

The conceptual shift toward using broader terms such as rotator cuff-related shoulder pain (RCRSP) can have implications on how shoulder pain is coded in primary care (Lewis, 2016). In the absence of a gold-standard diagnostic approach and given the limited reliability of clinical tests for specific shoulder pathologies, GPs often rely on symptom-based or nonspecific diagnostic codes. This reflects both diagnostic uncertainty and pragmatic decision-making in routine practice and may result in variability in coding between clinicians and practices, with the use of terms such as "shoulder disorder NOS," or "shoulder pain NOS (not otherwise specified) (Linsell et al., 2006).

The introduction of Musculoskeletal First Contact Practitioner (FCP) Physiotherapists into primary care represents a significant shift in the assessment and the management of MSK conditions within the UK healthcare system in 2018/19 (Goodwin et al., 2021, Bicker et al., 2024, Golding and Jackson, 2024). FCPs are specialised physiotherapists with enhanced skills embedded within general practice, who assess and manage patients with MSK conditions without the need for GP referral (Goodwin et al., 2020, Goodwin et al., 2021). The integration of FCPs into

primary care may influence the coding of shoulder pain conditions in several ways. Firstly, the direct access to physiotherapy services might result in an increase in the number of MSK consultations recorded in electronic health records by FCPS and at the same time reduce GP workload by decreasing repeated MSK consultations (Babatunde et al., 2020, Bishop et al., 2021), potentially affecting the prevalence and incidence estimates of this condition. Secondly, the clinical documentation of FCPS may differ from those of GPs, possibly affecting the consistency and accuracy of diagnostic coding. For instance, FCPs might use different terminologies or coding terms, which could lead to variations in how shoulder pain is recorded and classified in routinely collected data. Furthermore, FCPs are trained to accurately diagnose and treat MSK conditions. With their MSK expertise, the precision of coding for specific shoulder pain conditions terms may increase (Chartered Society of Physiotherapy, 2017, Langridge, 2019).

Additionally, the presence of FCPs may influence referral patterns and subsequent coding (Horne et al., 2019, Walsh et al., 2024). Patients seen by FCPs might be less likely to be referred to secondary care services, which could result in fewer cases of shoulder pain being coded in hospital records. This shift in referral patterns may contribute to changes in the overall coding landscape for MSK conditions. These potential shifts in coding practice should be considered when interpreting temporal trends in incidence and prevalence, especially in studies reliant on electronic health record data. Future research is needed to investigate whether the

introduction of FCP has affected the coding of shoulder pain diagnosis in primary care.

In the current study, the burden of CSP varied across UK regions, with the Yorkshire and the Humber being the highest area in terms of both prevalence and incidence. This might reflect the variations in environmental, genetic/racial, and lifestyle factors as discussed in Chapter 3. Although the prevalence and incidence estimates presented in this thesis are frequently referred to as 'UK' figures, it is important to acknowledge that the underlying data are predominantly derived from sources based in England and North Ireland. As such, these estimates may not fully reflect the epidemiological patterns in Scotland, and Wales, where demographic characteristics, healthcare systems, and disease recording practices can differ. This limitation restricts the generalisability of the findings to the entire UK population and should be taken into account when interpreting results or applying them in a broader national context.

People with CSP are more likely to have comorbidities both prior to and following the diagnosis of CSP, than people without shoulder pain. Sarcopenia, fibromyalgia, OA, other MSK conditions, insomnia, and diabetes were associated both before and after the diagnosis of shoulder pain, whereas myocardial infarction and hypertension only associated with CSP after its diagnosis. Further studies are needed to confirm causation.

People with CSP were at higher risk of having more GP consultations and hospitalisations (all-cause rather than specific to shoulder pain), but the reasons for hospitalisations and referrals to secondary care need to be

explored further. The findings of this thesis illustrate the trend of the burden of CSP in the UK, which might be considered as a baseline for programme design, relevant policies, and follow-up studies to potentially reduce the burden of CSP disorders.

One of the key issues highlighted throughout this thesis is the lack of a standardised definition for CSP and the variability of shoulder pain definitions in the literature. The systematic review and meta-analysis revealed a considerable variability in how shoulder pain is defined. Some studies defined chronicity based on symptom duration (e.g., >3 or >6 months) while others relied on clinical assessment or medical records, and some studies even lacked a clear definition. Such variability in definitions can result in misclassification, inconsistent reporting of prevalence and incidence rates, and difficulties in comparing results across populations. Also, it can affect clinical decision-making and guideline development. The research in this thesis addressed this issue by applying a consistent definition of CSP based on repeated consultations within a defined time frame (≥ 2 consultations within 6 months). By establishing this definition, this study clarified how CSP could be defined in primary healthcare records and also contributed to the growing body of evidence on its epidemiology. Although the definition applied in the current study provides a consistent and feasible method for identifying CSP, defining CSP solely based on healthcare consultations has important limitations. It may not fully account for the duration and severity of symptoms or their impact on a patient's function and quality of

life. The inclusion of patient-reported outcomes could greatly improve the clinical relevance and accuracy of the definition.

It has become clear that a more consistent and widely accepted gold-standard definition for CSP is needed. The next steps in addressing this issue should include the development of a standardised definition, which could be guided by both clinical expertise and research-based data. Future research could consider integrating patient-reported outcomes, such as pain duration and severity, functional limitations, and symptom persistence, into the definition of CSP. This could be achieved through:

• Establishing a consensus-based definition of CSP, potentially through Delphi studies involving both clinicians and researchers and patients.

• Validating case definitions in electronic healthcare records against gold-standard clinical assessments or consensus-derived definitions.

• Incorporating patient-reported outcome measures to capture symptom duration, functional limitations, and impact on daily activity and quality of life.

In conclusion, this research highlights the critical need for a standardised CSP definition and offers a framework that can guide the development of future consensus, helping to clarify how CSP might be defined and classified within large primary healthcare records. This standardisation is crucial for improving the comparability of research data as well as guiding clinical practice and policy development.

7.2 Clinical implications

This thesis has significant implications for both clinicians and policymakers. The most important clinical implication is the high prevalence of CSP in primary care, which was found to have increased from 2000 to 2020. Primary care facilities must be prepared to manage the future trends of CSP. People with CSP need to be considered for screening for early diagnosis of the related comorbidities and for management of the modifiable associated risk factors. Additionally, the management plan for people with shoulder pain might need to take into account the presence of comorbidities. An integrated person-centred care plan can be developed for people with CSP and take into account psychological aspects such as depression and anxiety. From a population health perspective, having insight into the frequency of CSP in the UK will help to understand the burden of this condition and the population at risk. There is no direct economic impact for this research, However, the output can potentially help to inform strategies to address modifiable risk factors and so reduce the occurrence of CSP, and to know the impact of CSP on healthcare utilisation. Furthermore, the prevalence of CSP and the variability in GP diagnostic coding suggest a possible need for improved education regarding clinical assessment of the shoulder in GP training.

7.3 Novel findings

As far as is known, this is the first study to use a large primary healthcare database to examine the prevalence and incidence of CSP in the UK, and geographical variations in these. The prevalence of CSP increased in the UK from 2000 to 2020. The incidence of CSP increased from 2000 to

2011, then decreased dramatically. Shoulder pain and RC syndrome codes were the most common codes used by GPs. In addition, the prevalence and incidence of specific CSP were examined for those patients with a specific diagnosis. It was found that after 2012, the prevalence of specific CSP continued to increase, and the use of non-specific CSP terms declined, which might suggest both improvements in the coding used by GPs and increased use of ultrasound imaging, which in recent years has become much more widely available outside of a hospital setting. With respect to incidence, after the year 2005 specific CSP decreased. From 2013 a remarkable decline was found in the incidence of non-specific CSP whereas the incidence of specific CSP increased, which might suggest coding improvement towards a specific diagnosis of shoulder pain.

Several risk factors were found to be associated with CSP including smoking (aOR 1.21, 95%CI 1.19, 1.24, p-value < 0.0001) a higher IMD (aOR 1.13, 95%CI 1.09, 1.17, p-value < 0.0001), Asian ethnicity (aOR 1.43, 95%CI 1.36,1.50, p-value < 0.0001) and having higher BMI ≥ 30 (kg/m2) (aOR 1.32, 95%CI 1.29, 1.35, p-value < 0.0001). Alcohol consumption was (significantly) negatively associated with CSP compared to controls (aOR 0.87, 95% CI 0.84 to 0.90; p-value <0.0001). Additionally, CSP was associated with 16 comorbidities retrospectively. The strongest associations were seen with OA (aOR 1.76, 95% CI 1.70 to 1.82), other MSK conditions (aOR 1.71, 95% CI 1.68 to 1.75), diabetes (aOR 1.48, 95% CI 1.43 to 1.53) and fibromyalgia (aOR 1.40, 95% CI 1.32 to 1.48). Other comorbidities found to be associated with CSP were depression,

insomnia, COPD, hypothyroidism, diverticular disease, and diaphragmatic hernia.

As far as is known, this is the first cohort study to examine a number of comorbidities associated prospectively with CSP. For all comorbidities, the incidence was statistically significantly higher in people with incident CSP than in the control group. People with CSP were at higher risk of developing 18 comorbidities. The strongest associations being with sarcopenia (aHR 1.74, 95% CI 1.11 to 2.71), fibromyalgia (aHR 1.71, 95% CI 1.62 to 1.81), OA (aHR 1.60, 95% CI 1.55 to 1.64), other MSK conditions (aHR 1.61, 95% CI 1.58 to 1.64), and insomnia (aHR 1.55, 95% CI 1.48 to 1.63).

In this thesis, several outcomes of CSP were examined including mortality, hospitalisations and GP consultations. The CSP group had a 6% higher risk of all-cause mortality compared to the control group (aHR 1.06, 95% CI 1.00 to 1.11; p-value= 0.02). Several reasons, apart from comorbidities, may help explain the higher risk of mortality in people with CSP, include obesity, pain, disability or functional limitations (Land and Yang, 2006, World Health Organization, 2009). However, this risk is lower compared to other MSK conditions discussed in the literature. Compared with CSP, Swain et al. (2023) found that people with OA in the UK had increased risk of all-cause mortality compared with people without OA (aHR 1.89, 95% CI 1.85 to 1.93). People with knee OA (HR 2.09, 95% CI 2.01 to 2.19) and hip OA (HR 2.08, 95% CI 1.95 to 2.21) had higher risk of mortality followed by wrist/hand OA (HR 1.80, 95% CI 1.58 to 2.06) in the

UK from the year 1997 to 2017 (Swain et al., 2023). The reason for higher risk of mortality in people with OA compared to CSP might be because OA is a more complex condition compared to CSP, and found to be associated with incidence of more long-term health conditions along with obesity, pain, and disability (Swain et al., 2021). The risk of all-cause mortality was found to be higher in people with pain in other body joints compared to those with shoulder joint pain alone. Chen et al. (2021) examined the association between chronic MSK pain and all-cause mortality in adult population using UK Biobank data from 2006 to 2010. The risk of all-cause mortality for people with neck or shoulder pain was aHR 1.07 (95% CI 1.02 to 1.13), which is similar to the results of the current study. However, in Chen et al.'s (2021) study, the multivariable adjusted HR for all-cause mortality for people with back pain was aHR 1.17 (95% CI 1.11 to 1.22), and aHR 1.15 (95% CI 1.07 to 1.24) for people with hip pain. Similarly, Docking et al. (2015b) found that disabling back pain was significantly associated with a higher risk of all-cause mortality in UK older adults' population with an adjusted HR of 1.5 (95% CI 1.2 to 1.9), which remained significant after further adjustment for health-related conditions, risk of falls, and use of medication (aHR 1.3, 95% CI 0.99 to 1.7). One possible explanation is that people with disabling chronic pain may have a lifestyle characterised by factors likely to increase mortality, such as poor diet, low physical activity, and professional hazards (e.g., manual work).

In the current study, the average number of GP consultations per year in people with CSP (23.60) was higher than in the control group (14.36) and

patients with CSP had 53% higher risk of GP consultations compared to the controls (aRR 1.53, 95% CI 1.52 to 1.54). The reasons for the increased consultations in the CSP group is multifactorial. MSK conditions considered to be the second highest reason for consultations in UK (Versus Arthritis, 2023). Also, the mean average number of hospitalisations per year in people with CSP was higher than in the control group. The aRR of hospitalisation in the CSP group being 1.37 (95% CI 1.35 to 1.39). The number and burden of other chronic conditions in people with CSP might be the cause of increased hospital admissions (Palladino et al., 2016). Additionally, increased risks of falls and injury (Eker and Kaygısız, 2019) and the requirement for shoulder joint arthroplasty could be the reasons for these rates of hospital admissions (Ben-Shlomo et al., 2021, Chung and Emery, 2025).

Although there was no direct patient involvement in this thesis, the PPI contribution in CPRD research considered meaningful and could add value to the research. The PPI was effective in terms of ensuring relevance and focus of the research question, disseminating the results and suggesting several aspects to be considered in future research.

7.4 Future work

This thesis addresses some important questions, but others need to be investigated.

- Although a recent improvement was found in the coding of CSP by GPs toward a specific shoulder pain diagnosis, validation studies are needed to confirm this. The prevalence of unspecified CSP in primary care, and the reasons for such recording, needs to be investigated further. Nevertheless, a more detailed validation of the SNOMED codes for shoulder pain could significantly improve the reliability of the CPRD Aurum in shoulder pain research.

- Regional variations were investigated in the prevalence and incidence of CSP, but this could be better studied using a more comprehensive primary care database of the UK that includes data on people in Scotland and Wales. The reasons for shoulder pain prevalence variations in UK regions need to be explored.

- Although individual comorbidities associated with CSP were examined, future studies could be undertaken to explore whether people with CSP are more likely to have multimorbidity (two or more concurrent chronic conditions).

- Further economic analysis studies should be carried out to understand the burden of CSP on specific healthcare utilisations such as surgical shoulder procedures (e.g., RC repair, shoulder total replacement), and the cost associated with each.

- This study showed that people with CSP have a higher risk of comorbidities, but further detailed studies are required to confirm causation and to further explore the reason for these associations. For

example, the association between CSP and tinnitus is interesting but needs further explanation and research. Epidemiological and biological research are required to confirm the associations found. A different research method in a different database might be useful to validate the findings. Furthermore, the possibility that oral analgesic (NSAIDS, opioids) use by people with CSP may be responsible for the development of certain comorbidities and for the increased mortality observed needs further investigations.

- The impact of CSP on work participation needs to be investigated to determine work productivity, sickness absence, and the association of this condition with risks of early retirement or permanent work disability in the UK.

- There is paucity of evidence available about the pattern and the prognosis of shoulder pain in the general population in the UK over time. Understanding the long-term prognosis of shoulder disorders is crucial for both researchers and clinicians because it could support the clinical judgements needed to make intervention decisions.

7.5 Conclusion

In conclusion, this study represents a significant contribution to the current evidence on the burden of shoulder pain in the UK and its association with comorbidities and risk factors. CPRD Aurum data have been used to investigate the burden of CSP, and address clinically relevant questions for primary care. The thesis presents evidence for the current epidemiology of CSP, associated risk factors and comorbidities. The

methodologies used in this thesis lay the foundation for future research in studying CSP using electronic medical records.

References

Adamson, J., Ebrahim, S., Dieppe, P. & Hunt, K. 2006. Prevalence and risk factors for joint pain among men and women in the West of Scotland Twenty-07 study. *Annals of the Rheumatic Diseases,* 65**,** 520-524.

Ahmad, Q., Yaseen, I., Sattar, R., Abbas, U. & Nawaz, U. 2020. Prevalence of frozen shoulder among patients with diabetes: A single center experience from Karachi, Pakistan. *Rawal Medical Journal,* 45**,** 838-841.

Ahmed, N., Saqlain, M., Kalam, M. N., Shah, S. N. H., Rasool, M. F. & Majeed, A. 2021. Prevalence of musculoskeletal complications of type-2 diabetes mellitus in population of southern Punjab, Pakistan. *International Journal of Diabetes in Developing Countries,* 41**,** 101-107.

Akhtar, A., Richards, J. & Monga, P. 2021. The biomechanics of the rotator cuff in health and disease–A narrative review. *Journal of clinical orthopaedics and trauma,* 18**,** 150-156.

Alderton, D. 2017. The Chicken or the Egg? The Relationship between Industry and Transport in East Anglia. *Understanding the Workplace: A Research Framework for Industrial Archaeology in Britain: 2005.* Routledge.

Alipour, A., Ghaffari, M., Shariati, B., Jensen, I. & Vingard, E. 2008. Occupational neck and shoulder pain among automobile manufacturing workers in Iran. *American Journal of Industrial Medicine,* 51**,** 372-9.

Alizadehkhaiyat, O., Roebuck, M. M., Makki, A. T. & Frostick, S. P. 2017. Pain, functional disability, psychological status, and health-related quality of life in patients with subacromial impingement syndrome. *Cogent Medicine,* 4**,** 1406631.

Allander, E. 1974. Prevalence, incidence, and remission rates of some common rheumatic diseases or syndromes. *Scandinavian journal of rheumatology,* 3**,** 145-153.

Alrowayeh, H. N., Alshatti, T. A., Aljadi, S. H., Fares, M., Alshamire, M. M. & Alwazan, S. S. 2010. Prevalence, characteristics, and impacts of work-related musculoskeletal disorders: A survey among physical therapists in the State of Kuwait. *BMC Musculoskeletal Disorders,* 11.

Andenæs, R., Momyr, A. & Brekke, I. 2018. Reporting of pain by people with chronic obstructive pulmonary disease (COPD): comparative

results from the HUNT3 population-based survey. *BMC Public Health,* 18**,** 1-10.

Andersen, J., Kaergaard, A., Mikkelsen, S., Jensen, U., Frost, P., Bonde, J., Fallentin, N. & Thomsen, J. 2003. Risk factors in the onset of neck/shoulder pain in a prospective study of workers in industrial and service companies. *Occupational and environmental medicine,* 60**,** 649-654.

Andersson, H. I. 2009. Increased mortality among individuals with chronic widespread pain relates to lifestyle factors: a prospective population-based study. *Disability and rehabilitation,* 31**,** 1980-1987.

Andorsen, O. F., Ahmed, L. A., Emaus, N. & Klouman, E. 2016. Musculoskeletal complaints (pain and/or stiffness) and their impact on mortality in the general population. The Tromsø Study. *PloS one,* 11**,** e0164341.

Andresen, E. M. & Miller, D. K. 2005. The future (history) of socioeconomic measurement and implications for improving health outcomes among African Americans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences,* 60**,** 1345-1350.

Ansok, C. B. & Muh, S. J. 2018. Optimal management of glenohumeral osteoarthritis. *Orthopedic Research and Reviews***,** 9-18.

Armitage, P., Berry, G. & Matthews, J. 1971. Statistical Methods in Medical Research. JohnWiley & Sons. *Inc., New York***,** 362-365.

Armstrong, T., Buckle, P., Fine, L., Hagberg, M., Jonsson, B., Kilborn, A., Kuorinka, I., Silverstein, B., Sjogaard, G. & Viikari-Juntura, E. 1993. A conceptual model for work-related neck and upper-limb musculoskeletal. *Scand J Work Environ Health,* 19**,** 73-84.

Arnander, M. & Tennent, D. 2014. Clinical assessment of the glenoid labrum. *Shoulder & elbow,* 6**,** 291-299.

Aronsson, G., Gustafsson, K. & Dallner, M. 2000. Sick but yet at work. An empirical study of sickness presenteeism. *Journal of Epidemiology & Community Health,* 54**,** 502-509.

Arout, C. A., Perrino Jr, A. C., Ralevski, E., Acampora, G., Koretski, J., Limoncelli, D., Newcomb, J. & Petrakis, I. L. 2016. Effect of intravenous ethanol on capsaicin-induced hyperalgesia in human subjects. *Alcoholism: Clinical and Experimental Research,* 40**,** 1425-1429.

Artus, M., van der Windt, D. A., Afolabi, E. K., Buchbinder, R., Chesterton, L. S., Hall, A., Roddy, E. & Foster, N. E. 2017. Management of

shoulder pain by UK general practitioners (GPs): a national survey. *BMJ Open,* 7**,** e015711.

Asavasopon, S. 2018. Chronification of low back pain: getting to the spine of the problem. *Brazilian Journal of Physical Therapy,* 22**,** 1.

Aurora, A., McCarron, J., Iannotti, J. P. & Derwin, K. 2007. Commercially available extracellular matrix materials for rotator cuff repairs: state of the art and future trends. *Journal of shoulder and elbow surgery,* 16**,** S171-S178.

Auvinen, J. P., Tammelin, T. H., Taimela, S. P., Zitting, P. J., Järvelin, M. R., Taanila, A. M. & Karppinen, J. I. 2010. Is insufficient quantity and quality of sleep a risk factor for neck, shoulder and low back pain? A longitudinal study among adolescents. *European Spine Journal,* 19**,** 641-649.

Averina, M., Nilssen, O., Brenn, T., Brox, J., Arkhipovsky, V. L. & Kalinin, A. G. 2005. Social and lifestyle determinants of depression, anxiety, sleeping disorders and self-evaluated quality of life in Russia--a population-based study in Arkhangelsk. *Soc Psychiatry Psychiatr Epidemiol,* 40**,** 511-8.

Aydeniz, A., Gursoy, S. & Guney, E. 2008. Which musculoskeletal complications are most frequently seen in type 2 diabetes mellitus? *Journal of International Medical Research,* 36**,** 505-511.

Ayis, S. & Dieppe, P. 2009. The natural history of disability and its determinants in adults with lower limb musculoskeletal pain. *The Journal of rheumatology,* 36**,** 583-591.

Azevedo, L. F., Costa-Pereira, A., Mendonça, L., Dias, C. C. & Castro-Lopes, J. M. 2012. Epidemiology of chronic pain: a population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. *The journal of pain,* 13**,** 773-783.

Babatunde, O. O., Bishop, A., Cottrell, E., Jordan, J. L., Corp, N., Humphries, K., Hadley-Barrows, T., Huntley, A. L. & van der Windt, D. A. 2020. A systematic review and evidence synthesis of non-medical triage, self-referral and direct access services for patients with musculoskeletal pain. *PLoS One,* 15**,** e0235364.

Babineau, J. 2014. Product review: Covidence (systematic review software). *Journal of the Canadian Health Libraries Association/Journal de l'Association des bibliothèques de la santé du Canada,* 35**,** 68-71.

Back, L. 2001. Musculoskeletal disorders and the workplace.

Badcock, L. J., Lewis, M., Hay, E. M. & Croft, P. R. 2003. Consultation and the outcome of shoulder-neck pain: a cohort study in the population. *Journal of Rheumatology,* 30**,** 2694-9.

Badcock, L., Lewis, M., Hay, E., McCarney, R. & Croft, P. 2002. Chronic shoulder pain in the community: a syndrome of disability or distress? *Annals of the rheumatic diseases,* 61**,** 128-131.

Badley, E. M. & Tennant, A. 1992. Changing profile of joint disorders with age: findings from a postal survey of the population of Calderdale, West Yorkshire, United Kingdom. *Annals of the rheumatic diseases,* 51**,** 366-371.

Baek, S.-R., Lim, J. Y., Lim, J.-Y., Park, J. H., Lee, J. J., Lee, S. B., Kim, K. W. & Paik, N.-J. 2010. Prevalence of musculoskeletal pain in an elderly Korean population: results from the Korean Longitudinal Study on Health and Aging (KLoSHA). *Archives of gerontology and geriatrics,* 51**,** e46-e51.

Bagheri, F., Ebrahimzadeh, M. H., Moradi, A. & Bidgoli, H. F. 2016. Factors associated with pain, disability and quality of life in patients suffering from frozen shoulder. *Archives of Bone and Joint Surgery,* 4**,** 243.

Bai, X., Soh, K. G., Omar Dev, R. D., Talib, O., Xiao, W. & Cai, H. 2022. Effect of brisk walking on health-related physical fitness balance and life satisfaction among the elderly: a systematic review. *Frontiers in public health,* 9**,** 829367.

Bair, M. J., Wu, J., Damush, T. M., Sutherland, J. M. & Kroenke, K. 2008. Association of depression and anxiety alone and in combination with chronic musculoskeletal pain in primary care patients. *Psychosomatic medicine,* 70**,** 890-897.

Bakhsh, W. & Nicandri, G. 2018. Anatomy and Physical Examination of the Shoulder. *Sports Med Arthrosc Rev,* 26**,** e10-e22.

Balke, M., Banerjee, M., Bouillon, B., Schmidt, C., Dedy, N. & Liem, D. 2013. Correlation of acromial morphology with impingement syndrome and rotator cuff tears. *Acta Orthopaedica,* 84**,** 178-183.

Bally, M., Dendukuri, N., Rich, B., Nadeau, L., Helin-Salmivaara, A., Garbe, E. & Brophy, J. M. 2017. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. *bmj,* 357.

Banham, D., Woollacott, T., Gray, J., Humphrys, B., Mihnev, A. & McDermott, R. 2010. Recognising potential for preventing hospitalisation. *Australian Health Review,* 34**,** 116-122.

Barendregt, J. J., Doi, S. A., Lee, Y. Y., Norman, R. E. & Vos, T. 2013. Meta-analysis of prevalence. *J Epidemiol Community Health,* 67**,** 974-978.

Baron, J. A. & Weiderpass, E. 2000. An introduction to epidemiological research with medical databases. *Annals of epidemiology,* 10**,** 200-204.

Barton, S. B., Kofoed, B. A. & Doleys, D. M. 1989. Smoking and narcotics use among chronic pain patients. *Psychol Rep,* 64**,** 1253-4.

Baumgarten, K. M., Gerlach, D., Galatz, L. M., Teefey, S. A., Middleton, W. D., Ditsios, K. & Yamaguchi, K. 2010. Cigarette smoking increases the risk for rotator cuff tears. *Clinical Orthopaedics and Related Research®,* 468**,** 1534-1541.

Belur, J., Tompson, L., Thornton, A. & Simon, M. 2021. Interrater reliability in systematic review methodology: exploring variation in coder decision-making. *Sociological methods & research,* 50**,** 837-865.

Benjamini, Y. & Hochberg, Y. 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (Methodological),* 57**,** 289-300.

Benjamini, Y. & Yekutieli, D. 2001. The control of the false discovery rate in multiple testing under dependency. *Annals of statistics***,** 1165-1188.

Ben-Shlomo, Y., Blom, A., Boulton, C., Brittain, R., Clark, E., Dawson-Bowling, S., Deere, K., Esler, C., Espinoza, O. & Goldberg, A. 2021. National joint registry annual reports. *The national joint registry 18th annual report***,** 2021.

Bergman, S. 2007. Management of musculoskeletal pain. *Best Practice & Research Clinical Rheumatology,* 21**,** 153-166.

Bergman, S., Herrström, P., Högström, K., Petersson, I. F., Svensson, B. & Jacobsson, L. T. 2001. Chronic musculoskeletal pain, prevalence rates, and sociodemographic associations in a Swedish population study. *The Journal of rheumatology,* 28**,** 1369-1377.

Bernard, B. P. & Putz-Anderson, V. 1997. Musculoskeletal disorders and workplace factors: a critical review of epidemiologic evidence for work-related musculoskeletal disorders of the neck, upper extremity, and low back.

Beyera, G. K., O'Brien, J. & Campbell, S. 2019. Health-care utilisation for low back pain: a systematic review and meta-analysis of population-based observational studies. *Rheumatology international,* 39**,** 1663-1679.

Bhala, N., Emberson, J., Merhi, A., Abramson, S., Arber, N., Baron, J., Bombardier, C., Cannon, C., Farkouh, M. & FitzGerald, G. 2013. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet (London, England),* 382**,** 769-779.

Bhaskaran, K., Forbes, H. J., Douglas, I., Leon, D. A. & Smeeth, L. 2013. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). *BMJ open,* 3**,** e003389.

Bhatnagar, P., Wickramasinghe, K., Williams, J., Rayner, M. & Townsend, N. 2015. The epidemiology of cardiovascular disease in the UK 2014. *Heart,* 101**,** 1182-1189.

Biberthaler, P., Wiedemann, E., Nerlich, A., Kettler, M., Mussack, T., Deckelmann, S. & Mutschler, W. 2003. Microcirculation associated with degenerative rotator cuff lesions: in vivo assessment with orthogonal polarization spectral imaging during arthroscopy of the shoulder. *JBJS,* 85**,** 475-480.

Bicker, G., Hadley-Barrows, T., Saunders, A., Mairs, H. & Stevenson, K. 2024. A narrative synthesis of the effectiveness and acceptability of musculoskeletal first contact physiotherapy practitioner roles in primary care. *Musculoskeletal Care,* 22**,** e1875.

Bigliani, L. 1986. The morphology of the acromion and its relationship to rotator cuff tears. *Orthop. Trans.,* 10**,** 228.

Bigliani, L. U., Ticker, J. B., Flatow, E. L., Soslotcsky, L. J. & Mow, V. C. 1991. The relationship of acromial architecture to rotator cuff disease. *Clinics in sports medicine,* 10**,** 823-838.

Bishop, A., Chen, Y., Protheroe, J., Ogollah, R. O., Bailey, J., Lewis, M., Jordan, K. & Foster, N. E. 2021. Providing patients with direct access to musculoskeletal physiotherapy: the impact on general practice musculoskeletal workload and resource use. The STEMS-2 study. *Physiotherapy,* 111**,** 48-56.

Bishop, J. Y., Santiago-Torres, J. E., Rimmke, N. & Flanigan, D. C. 2015. Smoking predisposes to rotator cuff pathology and shoulder dysfunction: a systematic review. *Arthroscopy: The Journal of Arthroscopic & Related Surgery,* 31**,** 1598-1605.

Blaine, T. A., Kim, Y.-S., Voloshin, I., Chen, D., Murakami, K., Chang, S.-S., Winchester, R., Lee, F. Y., O'Keefe, R. J. & Bigliani, L. U. 2005. The molecular pathophysiology of subacromial bursitis in rotator cuff disease. *Journal of Shoulder and Elbow Surgery,* 14**,** S84-S89.

Blyth, F. M., March, L. M., Nicholas, M. K. & Cousins, M. J. 2003. Chronic pain, work performance and litigation. *PAIN®,* 103**,** 41-47.

Bodin, J., Ha, C., Sérazin, C., Descatha, A., Leclerc, A., Goldberg, M. & Roquelaure, Y. 2012a. Effects of individual and work-related factors on incidence of shoulder pain in a large working population. *Journal of Occupational Health,* 54**,** 278-288.

Bodin, J., Serazin, C., Roquelaure, Y., Ha, C., Descatha, A., Leclerc, A. & Goldberg, M. 2012b. Effects of individual and work-related factors on incidence of shoulder pain in a large working population. *Journal of Occupational Health,* 54**,** 278-288.

Bonathan, C., Hearn, L. & Williams, A. C. d. C. 2013. Socioeconomic status and the course and consequences of chronic pain. *Pain management,* 3**,** 159-162.

Borenstein, M., Hedges, L. V., Higgins, J. P. T. & Rothstein, H. R. 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research synthesis methods,* 1**,** 97-111.

Borg, K., Hensing, G. & Alexanderson, K. 2001. Predictive factors for disability pension—an 11-year follow up of young persons on sick leave due to neck, shoulder, or back diagnoses. *Scandinavian journal of public health,* 29**,** 104-112.

Bot, S. D., van der Waal, J. M., Terwee, C. B., van der Windt, D. A., Scholten, R. J., Bouter, L. M. & Dekker, J. 2005. Predictors of outcome in neck and shoulder symptoms: a cohort study in general practice. *Spine,* 30**,** E459-E470.

Braun, J., Baraliakos, X. & Westhoff, T. Nonsteroidal anti-inflammatory drugs and cardiovascular risk–a matter of indication. Seminars in arthritis and rheumatism, 2020. Elsevier, 285-288.

Breivik, H., Collett, B., Ventafridda, V., Cohen, R. & Gallacher, D. 2006. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *European journal of pain,* 10**,** 287-333.

Brett, J., Staniszewska, S., Mockford, C., Herron-Marx, S., Hughes, J., Tysall, C. & Suleman, R. 2014. Mapping the impact of patient and public involvement on health and social care research: a systematic review. *Health expectations,* 17**,** 637-650.

Brewer, B. J. 1979. Aging of the rotator cuff. *The American journal of sports medicine,* 7**,** 102-110.

Brox, J. I. 2003. Shoulder pain. *Best Practice & Research Clinical Rheumatology,* 17**,** 33-56.

Buchan, I. E., Kontopantelis, E., Sperrin, M., Chandola, T. & Doran, T. 2017. North-South disparities in English mortality1965–2015: longitudinal population study. *J Epidemiol Community Health,* 71**,** 928-936.

Bunker, T. & Anthony, P. 1995. The pathology of frozen shoulder. A Dupuytren-like disease. *The Journal of Bone & Joint Surgery British Volume,* 77**,** 677-683.

Bunker, T. & Esler, C. 1995. Frozen shoulder and lipids. *The Journal of Bone & Joint Surgery British Volume,* 77**,** 684-686.

Bunt, C. W., Jonas, C. E. & Chang, J. G. 2018. Knee pain in adults and adolescents: the initial evaluation. *American family physician,* 98**,** 576-585.

Burbank, K. M., Stevenson, J. H., Czarnecki, G. R. & Dorfman, J. 2008. Chronic shoulder pain: part I. Evaluation and diagnosis. *Am Fam Physician,* 77**,** 453-60.

Burne, G., Mansfield, M., Gaida, J. & Lewis, J. 2020. Is there an association between metabolic syndrome and rotator cuff related shoulder pain? A systematic review. *Physiotherapy,* 107**,** e53-e53.

Burner, T., Abbott, D., Huber, K., Stout, M., Fleming, R., Wessel, B., Massey, E., Rosenthal, A. & Burns, E. 2014. Shoulder symptoms and function in geriatric patients. *Journal of Geriatric Physical Therapy,* 37**,** 154-8.

Cagliero, E., Apruzzese, W., Perlmutter, G. S. & Nathan, D. M. 2002. Musculoskeletal disorders of the hand and shoulder in patients with diabetes mellitus. *Am J Med,* 112**,** 487-90.

Cakir, M., Samanci, N., Balci, N. & Balci, M. K. 2003. Musculoskeletal manifestations in patients with thyroid disease. *Clinical endocrinology,* 59**,** 162-167.

Cala, S., Edyvean, J. & Engel, L. 1992. Chest wall and trunk muscle activity during inspiratory loading. *Journal of Applied Physiology,* 73**,** 2373-2381.

Caliş, M., Akgün, K., Birtane, M., Karacan, I., Caliş, H. & Tüzün, F. 2000. Diagnostic values of clinical diagnostic tests in subacromial impingement syndrome. *Ann Rheum Dis,* 59**,** 44-7.

Campbell, C. M. & Edwards, R. R. 2012. Ethnic differences in pain and pain management. *Pain management,* 2**,** 219-230.

Campbell, M. L., Sheets, D. & Strong, P. S. 1999. Secondary health conditions among middle-aged individuals with chronic physical disabilities: Implications for unmet needs for services. *Assistive Technology,* 11**,** 105-122.

Cao, S., Fisher, D. W., Yu, T. & Dong, H. 2019. The link between chronic pain and Alzheimer's disease. *Journal of neuroinflammation,* 16**,** 204.

Carnes, D., Parsons, S., Ashby, D., Breen, A., Foster, N., Pincus, T., Vogel, S. & Underwood, M. 2007. Chronic musculoskeletal pain rarely presents in a single body site: results from a UK population study.

Carvalho, F. A., Maher, C. G., Franco, M. R., Morelhao, P. K., Oliveira, C. B., Silva, F. G. & Pinto, R. Z. 2017. Fear of movement is not associated with objective and subjective physical activity levels in chronic nonspecific low back pain. *Archives of physical medicine and rehabilitation,* 98**,** 96-104.

Cassell, A., Edwards, D., Harshfield, A., Rhodes, K., Brimicombe, J., Payne, R. & Griffin, S. 2018. The epidemiology of multimorbidity in primary care: a retrospective cohort study. *British Journal of General Practice,* 68**,** e245-e251.

Cassou, B., Derriennic, F., Monfort, C., Norton, J. & Touranchet, A. 2002. Chronic neck and shoulder pain, age, and working conditions: longitudinal results from a large random sample in France. *Occupational & Environmental Medicine,* 59**,** 537-44.

Celiker, R., Borman, P., Öktem, F., Gökçe-Kutsal, Y. & Başgöze, O. 1997. Psychological disturbance in fibromyalgia: relation to pain severity. *Clinical rheumatology,* 16**,** 179-184.

Chapman, K. & Valdes, A. M. 2012. Genetic factors in OA pathogenesis. *Bone,* 51**,** 258-264.

Chard, M. D. & Hazleman, B. L. 1987. Shoulder disorders in the elderly (a hospital study). *Ann Rheum Dis,* 46**,** 684-7.

Chard, M. D., Hazleman, R., Hazleman, B. L., King, R. H. & Reiss, B. B. 1991. Shoulder disorders in the elderly: a community survey. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology,* 34**,** 766-769.

Chartered Society of Physiotherapy. 2017. *Physiotherapy in Primary Care – Summary Briefing* [Online]. Available: https://www.csp.org.uk/professional-clinical/improvement-innovation/first-contact-physiotherapy/physiotherapy-primary-care [Accessed 6 May 2025 2025].

Chaudhury, S., Gwilym, S. E., Moser, J. & Carr, A. J. 2010. Surgical options for patients with shoulder pain. *Nature Reviews Rheumatology,* 6**,** 217-226.

Chen, L., Ferreira, M. L., Nassar, N., Preen, D. B., Hopper, J. L., Li, S., Bui, M., Beckenkamp, P. R., Shi, B. & Arden, N. K. 2021. Association of chronic musculoskeletal pain with mortality among UK adults: A population-based cohort study with mediation analysis. *EClinicalMedicine,* 42.

Chen, S., Marshall, T., Jackson, C., Cooper, J., Crowe, F., Nirantharakumar, K., Saunders, C. L., Kirk, P., Richardson, S. & Edwards, D. 2023. Sociodemographic characteristics and longitudinal progression of multimorbidity: a multistate modelling

analysis of a large primary care records dataset in England. *PLoS Medicine,* 20**,** e1004310.

Chillemi, C. & Franceschini, V. 2013. Shoulder osteoarthritis. *Arthritis,* 2013**,** 370231.

Cho, C. H., Seo, H. J., Bae, K. C., Lee, K. J., Hwang, I. & Warner, J. J. 2013. The impact of depression and anxiety on self-assessed pain, disability, and quality of life in patients scheduled for rotator cuff repair. *Journal of Shoulder & Elbow Surgery,* 22**,** 1160-6.

Cho, H. J., Morey, V., Kang, J. Y., Kim, K. W. & Kim, T. K. 2015. Prevalence and Risk Factors of Spine, Shoulder, Hand, Hip, and Knee Osteoarthritis in Community-dwelling Koreans Older Than Age 65 Years. *Clinical Orthopaedics & Related Research,* 473**,** 3307-14.

Chuang, S.-H., Chen, Y.-P., Huang, S.-W. & Kuo, Y.-J. 2023. Association between adhesive capsulitis and thyroid disease: a meta-analysis. *Journal of Shoulder and Elbow Surgery,* 32**,** 1314-1322.

Chung, T. J. & Emery, R. J. 2025. Shoulder arthroplasty access in the United Kingdom. *Journal of Shoulder and Elbow Surgery,* 34**,** 325-327.

Coates, G., Clewes, P., Lohan, C., Stevenson, H., Wood, R., Tritton, T., Knaggs, R. D., Dickson, A. J. & Walsh, D. A. 2023. Chronic Low back pain with and without concomitant osteoarthritis: a retrospective, longitudinal cohort study of patients in England. *International Journal of Clinical Practice,* 2023**,** 5105810.

Cohen, C., Tortato, S., Silva, O. B. S., Leal, M. F., Ejnisman, B. & Faloppa, F. 2020. Association between frozen shoulder and thyroid diseases: strengthening the evidences. *Revista Brasileira de Ortopedia,* 55**,** 483-489.

Cole, A., Gill, T. K., Shanahan, E. M., Phillips, P., Taylor, A. W. & Hill, C. L. 2009. Is diabetes associated with shoulder pain or stiffness? Results from a population based study. *The Journal of rheumatology,* 36**,** 371-377.

Compagnoni, R., Suffritti, C., Fossati, C., Zanini, B., Gerace, F., Menon, A., Randelli, P. S. & Gualtierotti, R. 2023. Exploring the prevalence and clinical impact of fibromyalgia syndrome in patients with shoulder diseases: a cross-sectional study. *Clinical and Experimental Rheumatology,* 41**,** 1317-1322.

Consigliere, P., Haddo, O., Levy, O. & Sforza, G. 2018. Subacromial impingement syndrome: management challenges. *Orthopedic research and reviews,* 10**,** 83-91.

Conway, A., Rolley, J. X., Fulbrook, P., Page, K. & Thompson, D. R. 2013. Improving statistical analysis of matched case–control studies. *Research in nursing & health,* 36**,** 320-324.

Coppieters, I., Meeus, M., Kregel, J., Caeyenberghs, K., De Pauw, R., Goubert, D. & Cagnie, B. 2016. Relations between brain alterations and clinical pain measures in chronic musculoskeletal pain: a systematic review. *The Journal of Pain,* 17**,** 949-962.

Cornally, N. & McCarthy, G. 2011. Help-seeking behaviour for the treatment of chronic pain. *British journal of community nursing,* 16**,** 90-98.

Côté, J. N. 2014. Adaptations to neck/shoulder fatigue and injuries. *Progress in Motor Control: Skill Learning, Performance, Health, and Injury***,** 205-228.

Cimmino, M. A., Ferrone, C. & Cutolo, M. 2011. Epidemiology of chronic musculoskeletal pain. *Best practice & research Clinical rheumatology,* 25**,** 173-183.

Creech, J. A. & Silver, S. 2021. Shoulder Impingement Syndrome. *StatPearls.* Treasure Island (FL): StatPearls Publishing

Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., Bridgett, L., Williams, S., Guillemin, F. & Hill, C. L. 2014. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Annals of the rheumatic diseases,* 73**,** 1323-1330.

da Costa, B. R. & Vieira, E. R. 2010. Risk factors for work-related musculoskeletal disorders: A systematic review of recent longitudinal studies. *Am J Ind Med,* 53**,** 285-323.

da Rocha Motta, G., Amaral, M. V., Rezende, E., Pitta, R., dos Santos Vieira, T. C., Duarte, M. E. L., Vieira, A. R. & Casado, P. L. 2014. Evidence of genetic variations associated with rotator cuff disease. *Journal of shoulder and elbow surgery,* 23**,** 227-235.

Daigneault, J. & Cooney Jr, L. M. 1998. Shoulder pain in older people. *Journal of the American Geriatrics Society,* 46**,** 1144-1151.

Daneshmandi, H., Choobineh, A. R., Ghaem, H., Alhamd, M. & Fakherpour, A. 2017. The effect of musculoskeletal problems on fatigue and productivity of office personnel: A cross-sectional study. *Journal of Preventive Medicine and Hygiene,* 58**,** E252-E258.

Dang, A. & Davies, M. 2018. Rotator Cuff Disease: Treatment Options and Considerations. *Sports Med Arthrosc Rev,* 26**,** 129-133.

Datalink, C. P. R. 2022. *CPRD Aurum HES APC January 2022 (Version 2022.01.001)* [Online]. Clinical Practice Research Datalink. https://doi.org/10.48329/VAGX-9D96. [Accessed 03/09 2024].

De Vogli, R., Ferrie, J. E., Chandola, T., Kivimäki, M. & Marmot, M. G. 2007. Unfairness and health: evidence from the Whitehall II Study. *Journal of Epidemiology & Community Health,* 61**,** 513-518.

Dean, B. J. F., Gwilym, S. E. & Carr, A. J. 2013. Why does my shoulder hurt? A review of the neuroanatomical and biochemical basis of shoulder pain. *British journal of sports medicine,* 47**,** 1095-1104.

Dessai, S. & Patil, V. 2019. Testing and interpreting assumptions of COX regression analysis. *Cancer Research, Statistics, and Treatment,* 2**,** 108-111.

Diderichsen, F., Evans, T. & Whitehead, M. 2001. The social basis of disparities in health. *Challenging inequities in health: From ethics to action,* 1**,** 12-23.

Diercks, R., Bron, C., Dorrestijn, O., Meskers, C., Naber, R., De Ruiter, T., Willems, J., Winters, J. & Van Der Woude, H. J. 2014. Guideline for diagnosis and treatment of subacromial pain syndrome: a multidisciplinary review by the Dutch Orthopaedic Association. *Acta orthopaedica,* 85**,** 314-322.

Ding, H., Tang, Y., Xue, Y., Yang, Z., Li, Z., He, D., Zhao, Y. & Zong, Y. 2014. A report on the prevalence of depression and anxiety in patients with frozen shoulder and their relations to disease status. *Psychology Health & Medicine,* 19**,** 730-7.

Dinnes, J., Loveman, E., McIntyre, L. & Waugh, N. 2003. The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review. *Health Technology Assessment (Winchester, England),* 7**,** iii-1.

Djade, C. D., Porgo, T. V., Zomahoun, H. T. V., Perrault-Sullivan, G., Dionne, C. E. & Perrault-Sullivan, G. 2020. Incidence of shoulder pain in 40 years old and over and associated factors: A systematic review. *European Journal of Pain,* 24**,** 39-50.

Docking, R. E., Beasley, M., Steinerowski, A., Jones, E. A., Farmer, J., Macfarlane, G. J. & Jones, G. T. 2015a. The epidemiology of regional and widespread musculoskeletal pain in rural versus urban settings in those ≥55 years. *British Journal of Pain,* 9**,** 86-95.

Docking, R. E., Fleming, J., Brayne, C., Zhao, J., Macfarlane, G., Jones, G. & collaboration, C. C. o. s. C. s. 2015b. The relationship between back pain and mortality in older adults varies with disability and gender: R esults from the C ambridge C ity over-75s C ohort (CC75C) study. *European Journal of Pain,* 19**,** 466-472.

D'Onise, R., Shanahan, E. M., Gill, T. & Hill, C. L. 2010. Does leisure time physical activity protect against shoulder pain at work? *Occup Med (Lond),* 60**,** 383-8.

Doorn, P. F. v., Schepper, E. I. T. d., Rozendaal, R. M., Ottenheijm, R. P. G., van der Lei, J., Bindels, P. J., Schiphof, D., van Doorn, P. F. & de Schepper, E. I. T. 2021. The incidence and management of shoulder complaints in general practice: a retrospective cohort study. *Family Practice,* 38**,** 582-588.

D'Orsi, G. M., Via, A. G., Frizziero, A. & Oliva, F. 2012. Treatment of adhesive capsulitis: a review. *Muscles Ligaments Tendons J,* 2**,** 70-8.

Draghi, F., Scudeller, L., Draghi, A. G. & Bortolotto, C. 2015. Prevalence of subacromial-subdeltoid bursitis in shoulder pain: an ultrasonographic study. *Journal of ultrasound,* 18**,** 151-158.

Dubreuil, M., Louie-Gao, Q., Peloquin, C. E., Choi, H. K., Zhang, Y. & Neogi, T. 2018. Risk of myocardial infarction with use of selected non-steroidal anti-inflammatory drugs in patients with spondyloarthritis and osteoarthritis. *Annals of the rheumatic diseases,* 77**,** 1137-1142.

Dueñas, M., Ojeda, B., Salazar, A., Mico, J. A. & Failde, I. 2016. A review of chronic pain impact on patients, their social environment and the health care system. *Journal of pain research***,** 457-467.

Duffield, M. 2002. Trends in female employment. *Labour Market Trends,* 110**,** 605-16.

Duncan, R., Francis, R. M., Collerton, J., Davies, K., Jagger, C., Kingston, A., Kirkwood, T., Robinson, L. & Birrell, F. 2011. Prevalence of arthritis and joint pain in the oldest old-findings from the Newcastle 85+ study. *Age and Ageing,* 40.

Duyff, R. F., Van den Bosch, J., Laman, D. M., van Loon, B.-J. P. & Linssen, W. H. 2000. Neuromuscular findings in thyroid dysfunction: a prospective clinical and electrodiagnostic study. *Journal of Neurology, Neurosurgery & Psychiatry,* 68**,** 750-755.

Dyer, B. P., Burton, C., Rathod-Mistry, T., Blagojevic-Bucknall, M. & van der Windt, D. A. 2024. Are patients with newly diagnosed frozen shoulder more likely to be diagnosed with type 2 diabetes? A cohort study in UK electronic health records. *Diabetes, Obesity and Metabolism*.

Dyer, B. P., Rathod-Mistry, T., Burton, C., van der Windt, D. & Bucknall, M. 2023. Diabetes as a risk factor for the onset of frozen shoulder: a systematic review and meta-analysis. *BMJ open,* 13**,** e062377.

Eachus, J., Chan, P., Pearson, N., Propper, C. & Smith, G. D. 1999. An additional dimension to health inequalities: disease severity and socioeconomic position. *Journal of Epidemiology & Community Health,* 53**,** 603-611.

Ecklund, K. J., Lee, T. Q., Tibone, J. & Gupta, R. 2007. Rotator cuff tear arthropathy. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons,* 15**,** 340-349.

Eker, Y. & Kaygısız, B. B. 2019. The effect of pain severity on balance, postural stability and fall risk in patients with shoulder pathologies. *Archives of medical science: AMS,* 17**,** 390.

Elsharkawi, M., Cakir, B., Reichel, H. & Kappe, T. 2013. Reliability of radiologic glenohumeral osteoarthritis classifications. *Journal of Shoulder and Elbow Surgery,* 22**,** 1063-1067.

Elstad, J. I. 2016. Income inequality and foregone medical care in Europe during the great recession: multilevel analyses of EU-SILC surveys 2008–2013. *International journal for equity in health,* 15**,** 1-11.

Emilson, C., Åsenlöf, P., Demmelmaier, I. & Bergman, S. 2020. Association between health care utilization and musculoskeletal pain. A 21-year follow-up of a population cohort. *Scandinavian Journal of Pain,* 20**,** 533-543.

Engebretsen, K. B., Grotle, M. & Natvig, B. 2015. Patterns of shoulder pain during a 14-year follow-up: results from a longitudinal population study in Norway. *Shoulder and Elbow,* 7**,** 49-59.

Engebretsen, K., Grotle, M., Bautz-Holter, E., Ekeberg, O. M. & Brox, J. I. 2010. Predictors of Shoulder Pain and Disability Index (SPADI) and work status after 1 year in patients with subacromial shoulder pain. *BMC Musculoskeletal Disorders,* 11**,** 1-9.

Epstein, R. E., Schweitzer, M. E., Frieman, B. G., Fenlin Jr, J. & Mitchell, D. 1993. Hooked acromion: prevalence on MR images of painful shoulders. *Radiology,* 187**,** 479-481.

Eriksen, J., Sjøgren, P., Ekholm, O. & Rasmussen, N. K. 2004. Health care utilisation among individuals reporting long-term pain: an epidemiological study based on Danish National Health Surveys. *European Journal of Pain,* 8**,** 517-523.

Ezzati, A., Wang, C., Katz, M. J., Derby, C. A., Zammit, A. R., Zimmerman, M. E., Pavlovic, J. M., Sliwinski, M. J. & Lipton, R. B. 2019. The temporal relationship between pain intensity and pain interference and incident dementia. *Current Alzheimer Research,* 16**,** 109-115.

Farioli, A., Mattioli, S., Quaglieri, A., Curti, S., Violante, F. S. & Coggon, D. 2014. Musculoskeletal pain in Europe: role of personal,

occupational and social risk factors. *Scandinavian journal of work, environment & health,* 40**,** 36.

Faruqi, T. & Rizvi, T. J. 2021. Subacromial Bursitis. *StatPearls.* Treasure Island (FL): StatPearls Publishing

Farzad, M., MacDermid, J. C., Ring, D. C. & Shafiee, E. 2021. A scoping review of the evidence regarding assessment and management of psychological features of shoulder pain. *Rehabilitation Research and Practice,* 2021**,** 7211201.

Feinstein, A. R. 1970. The pre-therapeutic classification of co-morbidity in chronic disease. *Journal of chronic diseases,* 23**,** 455-468.

Fernandez, M., Boyle, E., Hartvigsen, J., Ferreira, M. L., Refshauge, K. M., Maher, C. G., Christensen, K., Hopper, J. L. & Ferreira, P. 2017. Is this back pain killing me? All-cause and cardiovascular-specific mortality in older Danish twins with spinal pain. *European Journal of Pain,* 21**,** 938-948.

Fernández-Moreno, M., Rego, I., Carreira-Garcia, V. & Blanco, F. J. 2008. Genetics in osteoarthritis. *Current genomics,* 9**,** 542-547.

Ferreira, P. H., Pinheiro, M. B., Machado, G. C. & Ferreira, M. L. 2013. Is alcohol intake associated with low back pain? A systematic review of observational studies. *Manual therapy,* 18**,** 183-190.

Feveile, H., Jensen, C. & Burr, H. 2002. Risk factors for neck-shoulder and wrist-hand symptoms in a 5-year follow-up study of 3,990 employees in Denmark. *International archives of occupational and environmental health,* 75**,** 243-251.

Fischer, S. L., Greene, H. P., Hampton, R. H., Cochran, M. G. & Albert, W. J. 2015. Gender-based differences in trunk and shoulder biomechanical changes caused by prolonged repetitive symmetrical lifting. *IIE Transactions on Occupational Ergonomics and Human Factors,* 3**,** 165-176.

Forman-Hoffman, V. L., Ault, K. L., Anderson, W. L., Weiner, J. M., Stevens, A., Campbell, V. A. & Armour, B. S. 2015. Disability status, mortality, and leading causes of death in the United States community population. *Medical care,* 53**,** 346-354.

Frérot, M., Lefebvre, A., Aho, S., Callier, P., Astruc, K. & Aho Glélé, L. S. 2018. What is epidemiology? Changing definitions of epidemiology 1978-2017. *PloS one,* 13**,** e0208442.

Friebel, R. & Maynou, L. 2022. Trends and characteristics of hospitalisations from the harmful use of opioids in England between 2008 and 2018: population-based retrospective cohort study. *Journal of the Royal Society of Medicine,* 115**,** 173-185.

Frost, H. M. 1994. Perspectives: a biomechanical model of the pathogenesis of arthroses. *The Anatomical Record,* 240**,** 19-31.

Fukunaga, J. Y., Quitschal, R. M., Doná, F., Ferraz, H. B., Ganança, M. M. & Caovilla, H. H. 2014. Postural control in Parkinson's disease. *Brazilian journal of otorhinolaryngology,* 80**,** 508-514.

Furlan, J. C., Singh, J., Hsieh, J. & Fehlings, M. G. 2011. Methodology of systematic reviews and recommendations. *Journal of neurotrauma,* 28**,** 1335-1339.

Furnée, C. A., Groot, W. & van Den Brink, H. M. 2008. The health effects of education: a meta-analysis. *European journal of public health,* 18**,** 417-421.

Gadgaard, N. R., Veres, K., Henderson, V. W. & Pedersen, A. B. 2024. Frozen Shoulder and the Risk of Parkinson's Disease: A Danish Registry-Based Cohort Study. *Clinical epidemiology***,** 447-459.

Gao, Y., Du, L., Cai, J. & Hu, T. 2023. Effects of functional limitations and activities of daily living on the mortality of the older people: a cohort study in China. *Frontiers in Public Health,* 10**,** 1098794.

Garving, C., Jakob, S., Bauer, I., Nadjar, R. & Brunner, U. H. 2017. Impingement Syndrome of the Shoulder. *Dtsch Arztebl Int,* 114**,** 765-776.

Gatch, M. B. 1999. Effects of benzodiazepines on acute and chronic ethanol-induced nociception in rats. *Alcoholism: Clinical and Experimental Research,* 23**,** 1736-1743.

Gavrielov-Yusim, N. & Friger, M. 2014. Use of administrative medical databases in population-based research. *J Epidemiol Community Health,* 68**,** 283-7.

Generaal, E., Vogelzangs, N., Penninx, B. W. & Dekker, J. 2017. Insomnia, sleep duration, depressive symptoms, and the onset of chronic multisite musculoskeletal pain. *Sleep,* 40**,** zsw030.

Ghafoor, A., Jemal, A., Ward, E., Cokkinides, V., Smith, R. & Thun, M. 2003. Trends in breast cancer by race and ethnicity. *CA: a cancer journal for clinicians,* 53**,** 342-355.

Gill, T. J., McIrvin, E., Kocher, M. S., Homa, K., Mair, S. D. & Hawkins, R. J. 2002. The relative importance of acromial morphology and age with respect to rotator cuff pathology. *J Shoulder Elbow Surg,* 11**,** 327-30.

Gill, T., Shanahan, E. M., Taylor, A., Buchbinder, R. & Hill, C. 2013. Shoulder pain in the community: an examination of associative factors using a longitudinal cohort study. *Arthritis care & research,* 65**,** 2000-2007.

Gillam, S. & Siriwardena, A. N. 2011. *The Quality and Outcomes Framework: QOF-transforming general practice*, Radcliffe Publishing.

Gimarc, D. C. & Lee, K. S. 2020. Shoulder MR imaging versus ultrasound: how to choose. *Magnetic Resonance Imaging Clinics,* 28**,** 317-330.

Girish, G., Lobo, L. G., Jacobson, J. A., Morag, Y., Miller, B. & Jamadar, D. A. 2011. Ultrasound of the shoulder: asymptomatic findings in men. *American Journal of Roentgenology,* 197**,** W713-W719.

Gismervik, S. Ø., Drogset, J. O., Granviken, F., Rø, M. & Leivseth, G. 2017. Physical examination tests of the shoulder: a systematic review and meta-analysis of diagnostic test performance. *BMC musculoskeletal disorders,* 18**,** 1-9.

Glousman, R., Jobe, F., Tibone, J., Moynes, D., Antonelli, D. & Perry, J. 1988. Dynamic electromyographic analysis of the throwing shoulder with glenohumeral instability. *JBJS,* 70**,** 220-226.

Goldin, A., Beckman, J. A., Schmidt, A. M. & Creager, M. A. 2006. Advanced glycation end products: sparking the development of diabetic vascular injury. *Circulation,* 114**,** 597-605.

Golding, S. R. & Jackson, J. 2024. First contact physiotherapists: are they able to reduce the burden on rheumatology services? A critical review of the evidence base. *Rheumatology Advances in Practice,* 8**,** rkad109.

Goodwin, R., Moffatt, F., Hendrick, P., Stynes, S., Bishop, A. & Logan, P. 2021. Evaluation of the First Contact Physiotherapy (FCP) model of primary care: a qualitative insight. *Physiotherapy,* 113**,** 209-216.

Goodwin, R., Moffatt, F., Hendrick, P., Timmons, S., Chadborn, N. & Logan, P. 2020. First point of contact physiotherapy; a qualitative study. *Physiotherapy,* 108**,** 29-36.

Gostine, M., Davis, F., Roberts, B. A., Risko, R., Asmus, M., Cappelleri, J. C. & Sadosky, A. 2018. Clinical Characteristics of Fibromyalgia in a Chronic Pain Population. *Pain Practice,* 18**,** 67-78.

Gray, J. C. 2011. Visceral Referred Pain to the Shoulder. *Physical Therapy of the Shoulder-E-Book***,** 267.

Greenberg, A. S. & Obin, M. S. 2006. Obesity and the role of adipose tissue in inflammation and metabolism. *The American journal of clinical nutrition,* 83**,** 461S-465S.

Greenberg, D. L. 2014. Evaluation and treatment of shoulder pain. *Med Clin North Am,* 98**,** 487-504.

Greenland, S. 2008. Multiple comparisons and association selection in general epidemiology. *International journal of epidemiology,* 37**,** 430-434.

Greving, K., Dorrestijn, O., Winters, J. C., Groenhof, F., Van Der Meer, K., Stevens, M. & Diercks, R. L. 2012. Incidence, prevalence, and consultation rates of shoulder complaints in general practice. *Scandinavian Journal of Rheumatology,* 41**,** 150-155.

Guler, M., Klroap, M. & Uremke, G. 1992. Clinical characteristics of patients with fibromyalgia. *Headache,* 28**,** 46.7.

Gumina, S., Candela, V., Passaretti, D., Latino, G., Venditto, T., Mariani, L. & Santilli, V. 2014. The association between body fat and rotator cuff tear: the influence on rotator cuff tear sizes. *Journal of shoulder and elbow surgery,* 23**,** 1669-1674.

Gupta, M. & Eisen, G. M. 2009. NSAIDs and the gastrointestinal tract. *Current gastroenterology reports,* 11**,** 345-353.

Gwynn, R. C., Burnett, R. T. & Thurston, G. D. 2000. A time-series analysis of acidic particulate matter and daily mortality and morbidity in the Buffalo, New York, region. *Environmental health perspectives,* 108**,** 125-133.

Haack, M., Simpson, N., Sethna, N., Kaur, S. & Mullington, J. 2020. Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. *Neuropsychopharmacology,* 45**,** 205-216.

Hagen, K. B., Tambs, K. & Bjerkedal, T. 2006. What mediates the inverse association between education and occupational disability from back pain?—A prospective cohort study from the Nord-Trøndelag health study in Norway. *Social science & medicine,* 63**,** 1267-1275.

Hagg, G. 1991. Static work loads and occupational myalgia-a new explanation model. *Electromyographical kinesiology***,** 141-144.

Halder, A. M., Itoi, E. & An, K.-N. 2000. Anatomy and biomechanics of the shoulder. *Orthopedic Clinics,* 31**,** 159-176.

Hall, J. 2016. Diverticular disease. *The ASCRS Textbook of Colon and Rectal Surgery***,** 645-667.

Hammad, A., Grinbaum, E., Chezar, A., Israeli, A., Rozen, N. & Rubin, G. 2022. The correlation between shoulder pathologies and sleep disorders. *The Journal of international medical research,* 50**,** 3000605221103543.

Hansen, J., Hansen, H., Nilsson, C., Ekholm, O. & Molsted, S. 2023. Association between educational level and self-reported musculoskeletal pain and physical functioning in Danes 60–70 years old from 2010 to 2017: A longitudinal analysis of trends over

time on data from the Danish Health and Morbidity Survey. *BMJ open,* 13**,** e073523.

Harkness, E., MacFarlane, G. J., Nahit, E., Silman, A. & McBeth, J. 2003. Mechanical and psychosocial factors predict new onset shoulder pain: a prospective cohort study of newly employed workers. *Occupational and environmental medicine,* 60**,** 850-857.

Hartling, L., Hamm, M., Milne, A., Vandermeer, B., Santaguida, P. L., Ansari, M., Tsertsvadze, A., Hempel, S., Shekelle, P. & Dryden, D. M. 2012. AHRQ Methods for Effective Health Care. *Validity and Inter-Rater Reliability Testing of Quality Assessment Instruments.* Rockville (MD): Agency for Healthcare Research and Quality (US).

Hartvigsen, J., Davidsen, M., Sogaard, K., Roos, E. M. & Hestbaek, L. 2014. Self-reported musculoskeletal pain predicts long-term increase in general health care use: a population-based cohort study with 20-year follow-up. *Scandinavian journal of public health,* 42**,** 698-704.

Harvie, P., Ostlere, S., Teh, J., McNally, E., Clipsham, K., Burston, B., Pollard, T. & Carr, A. 2004. Genetic influences in the aetiology of tears of the rotator cuff: sibling risk of a full-thickness tear. *The Journal of Bone & Joint Surgery British Volume,* 86**,** 696-700.

Hashimoto, T., Nobuhara, K. & Hamada, T. 2003. Pathologic evidence of degeneration as a primary cause of rotator cuff tear. *Clinical Orthopaedics and Related Research®,* 415**,** 111-120.

Haukka, E., Leino-Arjas, P., Solovieva, S., Ranta, R., Viikari-Juntura, E. & Riihimäki, H. 2006. Co-occurrence of musculoskeletal pain among female kitchen workers. *International Archives of Occupational and Environmental Health,* 80**,** 141-148.

Hayes, M. J., Smith, D. R. & Taylor, J. A. 2014. Musculoskeletal disorders in a 3 year longitudinal cohort of dental hygiene students. *Journal of Dental Hygiene,* 88**,** 36-41.

Hegedus, E. 2008. Physical examination tests of the shoulder: a syst.

Hegedus, E. J., Cook, C., Lewis, J., Wright, A. & Park, J.-Y. 2015. Combining orthopedic special tests to improve diagnosis of shoulder pathology. *Physical Therapy in Sport,* 16**,** 87-92.

Hegedus, E. J., Goode, A. P., Cook, C. E., Michener, L., Myer, C. A., Myer, D. M. & Wright, A. A. 2012. 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. *British journal of sports medicine,* 46**,** 964-978.

Hegedus, E. J., Goode, A., Campbell, S., Morin, A., Tamaddoni, M., Moorman, C. T. & Cook, C. 2008. Physical examination tests of the

shoulder: a systematic review with meta-analysis of individual tests. *British journal of sports medicine,* 42**,** 80-92.

Hemmo, S. I., Naser, A. Y., Alwafi, H., Mansour, M. M., Alanazi, A. F., Jalal, Z., Alsairafi, Z. K., Paudyal, V., Alomari, E. a. & Al-Momani, H. 2021. Hospital admissions due to ischemic heart diseases and prescriptions of cardiovascular diseases medications in England and Wales in the past two decades. *International journal of environmental research and public health,* 18**,** 7041.

Henkus, H.-E., Cobben, L. P., Coerkamp, E. G., Nelissen, R. G. & van Arkel, E. R. 2006. The accuracy of subacromial injections: a prospective randomized magnetic resonance imaging study. *Arthroscopy: The Journal of Arthroscopic & Related Surgery,* 22**,** 277-282.

Herbert, A., Wijlaars, L., Zylbersztejn, A., Cromwell, D. & Hardelid, P. 2017. Data resource profile: hospital episode statistics admitted patient care (HES APC). *International journal of epidemiology,* 46**,** 1093-1093i.

Herin, F., Soulat, J.-M., Vezina, M., Thaon, I. & Paris, C. 2012. Predictors of chronic shoulder pain after 5 years in a working population. *Pain,* 153**,** 2253-2259.

Hermans, J., Luime, J. J., Meuffels, D. E., Reijman, M., Simel, D. L. & Bierma-Zeinstra, S. M. 2013. Does this patient with shoulder pain have rotator cuff disease?: The Rational Clinical Examination systematic review. *Jama,* 310**,** 837-847.

Hernán, M. A., Hsu, J. & Healy, B. 2019. A second chance to get causal inference right: a classification of data science tasks. *Chance,* 32**,** 42-49.

Herrett, E., Gallagher, A. M., Bhaskaran, K., Forbes, H., Mathur, R., Van Staa, T. & Smeeth, L. 2015. Data resource profile: clinical practice research datalink (CPRD). *International journal of epidemiology,* 44**,** 827-836.

Hestbaek, L., Leboeuf-Yde, C. & Kyvik, K. O. 2006. Are lifestyle-factors in adolescence predictors for adult low back pain? A cross-sectional and prospective study of young twins. *BMC musculoskeletal disorders,* 7**,** 1-8.

Heward, E., Domzaridou, E., Gavan, S. P., Carr, M. J., Lunn, J., Molloy, J., Isba, R., Hay, A. D., Nichani, J. R. & Bruce, I. A. 2024. Incidence, antimicrobial prescribing practice and associated healthcare costs of paediatric otorrhoea in primary care in the UK: A longitudinal population study. *British Journal of General Practice*.

Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. 2003. Measuring inconsistency in meta-analyses. *Bmj,* 327**,** 557-60.

Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. & Welch, V. 2024. Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). Cochrane, 2024.

Hill, C. L., Gill, T. K., Shanahan, E. M. & Taylor, A. W. 2010. Prevalence and correlates of shoulder pain and stiffness in a population-based study: the North West Adelaide Health Study. *International Journal of Rheumatic Diseases,* 13**,** 215-22.

Hinsley, H., Ganderton, C., Arden, N. K. & Carr, A. J. 2022. Prevalence of rotator cuff tendon tears and symptoms in a Chingford general population cohort, and the resultant impact on UK health services: a cross-sectional observational study. *BMJ open,* 12**,** e059175.

Hirji, Z., Hunjun, J. S. & Choudur, H. N. 2011. Imaging of the bursae. *Journal of Clinical Imaging Science,* 1.

Hnepa, Y. Y., Chopey, I. V., Chubirko, K. I. & Bratasyuk, A. M. 2021. Short-and long-term effects of NSAIDs on the gastrointestinal mucosa: complex analysis of benefits and complications prevention. *Wiad Lek,* 74**,** 1011-1018.

Hodges, P. W. & Gandevia, S. C. 2000. Changes in intra-abdominal pressure during postural and respiratory activation of the human diaphragm. *Journal of applied Physiology*.

Hoe, V. C., Kelsall, H. L., Urquhart, D. M. & Sim, M. R. 2012. Risk factors for musculoskeletal symptoms of the neck or shoulder alone or neck and shoulder among hospital nurses. *Occupational and Environmental Medicine,* 69**,** 198-204.

Hoffman, B. M., Papas, R. K., Chatkoff, D. K. & Kerns, R. D. 2007. Meta-analysis of psychological interventions for chronic low back pain. *Health psychology,* 26**,** 1.

Holmström, E., Lindell, J. & Moritz, U. 1992. Low back and neck/shoulder pain in construction workers: occupational workload and psychosocial risk factors. *Spine,* 17**,** 672-677.

Honjo, Y., Nagai, K., Yuri, T., Nakai, H., Kawasaki, I., Harada, S., Suganuma, I. & Ogawa, N. 2024. Shoulder joint range of Motion related to Dementia. *Dementia and Geriatric Cognitive Disorders***,** 1-1.

Horne, L., Slade, V. & Evans, A. 2019. Transformation of MSK services in Halton Cheshire to first contact practitioner model. *Physiotherapy,* 105**,** e107.

Hoy, D., Bain, C., Williams, G., March, L., Brooks, P., Blyth, F., Woolf, A., Vos, T. & Buchbinder, R. 2012. A systematic review of the global prevalence of low back pain. *Arthritis & rheumatism,* 64**,** 2028-2037.

Hoy, D., Brooks, P., Blyth, F. & Buchbinder, R. 2010. The epidemiology of low back pain. *Best practice & research Clinical rheumatology,* 24**,** 769-781.

Hsiao, M. S., Cameron, K. L., Tucker, C. J., Benigni, M., Blaine, T. A. & Owens, B. D. 2015. Shoulder impingement in the United States military. *J Shoulder Elbow Surg,* 24**,** 1486-92.

Hsieh, F. Y., Bloch, D. A. & Larsen, M. D. 1998. A simple method of sample size calculation for linear and logistic regression. *Statistics in medicine,* 17**,** 1623-1634.

Hsu, C. L. & Sheu, W. H. H. 2016. Diabetes and shoulder disorders. *Journal of diabetes investigation,* 7**,** 649.

Huang, Y. P., Fann, C. Y., Chiu, Y. H., Yen, M. F., Chen, L. S., Chen, H. H. & Pan, S. L. 2013. Association of diabetes mellitus with the risk of developing adhesive capsulitis of the shoulder: a longitudinal population-based followup study. *Arthritis care & research,* 65**,** 1197-202.

Hudon, C., Fortin, M. & Soubhi, H. 2008. Chronic musculoskeletal conditions and comorbidities in primary care settings. *Canadian Family Physician,* 54**,** 74-75.

Huegel, J., Williams, A. A. & Soslowsky, L. J. 2015. Rotator cuff biology and biomechanics: a review of normal and pathological conditions. *Current rheumatology reports,* 17**,** 1-9.

Hwang, Y. & Oh, J. 2022. The relationship between shoulder pain and shoulder disability in women: The mediating role of sleep quality and psychological disorders. *Medicine,* 101**,** e31118.

Iannotti, J. P. & Kwon, Y. W. 2005. Management of persistent shoulder pain: a treatment algorithm. *American journal of orthopedics (Belle Mead, NJ),* 34**,** 16-23.

Ibounig, T., Simons, T., Launonen, A. & Paavola, M. 2020. Glenohumeral Osteoarthritis: An Overview of Etiology and Diagnostics. *Scandinavian Journal of Surgery*.

Ibounig, T., Simons, T., Launonen, A. & Paavola, M. 2021. Glenohumeral osteoarthritis: an overview of etiology and diagnostics. *Scandinavian Journal of Surgery,* 110**,** 441-451.

Ichinose, R., Sano, H., Kishimoto, K. N., Sakamoto, N., Sato, M. & Itoi, E. 2010. Alteration of the material properties of the normal

supraspinatus tendon by nicotine treatment in a rat model. *Acta Orthopaedica,* 81**,** 634-638.

Ijmker, S., Blatter, B. M., Van Der Beek, A. J., Van Mechelen, W. & Bongers, P. M. 2006. Prospective research on musculoskeletal disorders in office workers (PROMO): Study protocol. *BMC Musculoskeletal Disorders,* 7.

In, J., Kang, H., Kim, J. H., Kim, T. K., Ahn, E. J., Lee, D. K., Lee, S. & Park, J. H. 2020. Tips for troublesome sample-size calculation. *Korean journal of anesthesiology,* 73**,** 114-120.

Inderhaug, E., Kalsvik, M., Kollevold, K. H., Hegna, J. & Solheim, E. 2018. Long-term results after surgical treatment of subacromial pain syndrome with or without rotator cuff tear. *J Orthop,* 15**,** 757-760.

Ingbar, S. H., Braverman, L. E. & Utiger, R. D. 2000. *Werner & Ingbar's the thyroid: a fundamental and clinical text*, Lippincott Williams & Wilkins.

Inman, V. T., Saunders, J. d. M. & Abbott, L. C. 1944. Observations on the function of the shoulder joint. *JBJS,* 26**,** 1-30.

Jaggi, A. & Lambert, S. 2010. Rehabilitation for shoulder instability. *Br J Sports Med,* 44**,** 333-40.

Jain, N. B., Wilcox III, R. B., Katz, J. N. & Higgins, L. D. 2013. Clinical examination of the rotator cuff. *PM&R,* 5**,** 45-56.

Jan, A. & Weir, C. B. 2021. BMI classification percentile and cut off points. *StatPearls: Treasure Island, FL, USA***,** 1-4.

Janssen, D., Wouters, E., Parra, Y. L., Stakenborg, K. & Franssen, F. 2016. Prevalence of thoracic pain in patients with chronic obstructive pulmonary disease and relationship with patient characteristics: a cross-sectional observational study. *BMC pulmonary medicine,* 16**,** 1-8.

Janwantanakul, P., Pensri, P., Jiamjarasrangsri, V. & Sinsongsook, T. 2008. Prevalence of self-reported musculoskeletal symptoms among office workers. *Occupational Medicine,* 58**,** 436-438.

Jiang, L., Rong, J., Wang, Y., Hu, F., Bao, C., Li, X. & Zhao, Y. 2011. The relationship between body mass index and hip osteoarthritis: a systematic review and meta-analysis. *Joint bone spine,* 78**,** 150-155.

Jiang, L., Tian, W., Wang, Y., Rong, J., Bao, C., Liu, Y., Zhao, Y. & Wang, C. 2012. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. *Joint bone spine,* 79**,** 291-297.

Jick, S. S., Hagberg, K. W., Persson, R., Vasilakis-Scaramozza, C., Williams, T., Crellin, E. & Myles, P. 2020. Quality and completeness of diagnoses recorded in the new CPRD Aurum Database: evaluation of pulmonary embolism. *Pharmacoepidemiology and drug safety,* 29**,** 1134-1140.

Jick, S., Vasilakis-Scaramozza, C., Persson, R., Neasham, D., Kafatos, G. & Hagberg, K. W. 2023. Use of the CPRD aurum database: insights gained from new data quality assessments. *Clinical Epidemiology***,** 1219-1222.

Joensen, J., Couppe, C. & Bjordal, J. M. 2009. Increased palpation tenderness and muscle strength deficit in the prediction of tendon hypertrophy in symptomatic unilateral shoulder tendinopathy: an ultrasonographic study. *Physiotherapy,* 95**,** 83-93.

Jonasson, P., Halldin, K., Karlsson, J., Thoreson, O., Hvannberg, J., Sward, L. & Baranto, A. 2011. Prevalence of joint-related pain in the extremities and spine in five groups of top athletes. *Knee Surgery, Sports Traumatology, Arthroscopy,* 19**,** 1540-1546.

Jones, J. R. 1998. Self-reported work-related illness in 1995: Results from a household survey. *http://www. hse. gov. uk/statistics/2002/swi95. pdf*.

Jones, J., Rutledge, D. N., Jones, K. D., Matallana, L. & Rooks, D. S. 2008. Self-assessed physical function levels of women with fibromyalgia: a national survey. *Women's Health Issues,* 18**,** 406-412.

Joo, H., Lee, Y. J., Shin, J. S., Lee, J., Kim, M. R., Koh, W., Park, Y., Song, Y. K., Cho, J. H. & Ha, I. H. 2017. Medical service use and usual care of common shoulder disorders in Korea: a cross-sectional study using the Health Insurance Review and Assessment Service National Patient Sample. *BMJ Open,* 7**,** e015848.

Jordan, K. P., Kadam, U. T., Hayward, R., Porcheret, M., Young, C. & Croft, P. 2010. Annual consultation prevalence of regional musculoskeletal problems in primary care: an observational study. *BMC musculoskeletal disorders,* 11**,** 1-10.

Judge, A., Murphy, R. J., Maxwell, R., Arden, N. K. & Carr, A. J. 2014. Temporal trends and geographical variation in the use of subacromial decompression and rotator cuff repair of the shoulder in England. *Bone Joint J,* 96-b**,** 70-4.

Jump, C. M., Duke, K., Malik, R. A. & Charalambous, C. P. 2021. Frozen shoulder: a systematic review of cellular, molecular, and metabolic findings. *JBJS reviews,* 9**,** e19.

Jüni, P., Nartey, L., Reichenbach, S., Sterchi, R., Dieppe, P. A. & Egger, M. 2004. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *The lancet,* 364**,** 2021-2029.

Kaliniene, G., Ustinaviciene, R., Skemiene, L., Vaiciulis, V. & Vasilavicius, P. 2016. Associations between musculoskeletal pain and work-related factors among public service sector computer workers in Kaunas County, Lithuania. *BMC Musculoskeletal Disorders,* 17**,** 1-12.

Kao, P.-H., Jang, F.-L., Ho, C.-H., Chen, Y.-C., Hsu, C.-C., Lin, H.-J., Wang, J.-J. & Huang, C.-C. 2021. Chronic pain increases the risk of dementia: a nationwide population-based cohort study. *Pain Physician,* 24**,** E849-E856.

Karimi, R., Mallah, N., Nedjat, S., Beasley, M. J. & Takkouche, B. 2022. Association between alcohol consumption and chronic pain: a systematic review and meta-analysis. *British journal of anaesthesia,* 129**,** 355-365.

Kassambara, A., Kosinski, M., Biecek, P. & Fabian, S. 2017. Package 'survminer'. *Drawing Survival Curves using 'ggplot2'(R package version 03 1),* 3.

Katzer, A., Wening, J., Becker-Männich, H., Lorke, D. & Jungbluth, K. 1997. Rotator cuff rupture. Vascular supply and collagen fiber processes as pathogenetic factors. *Unfallchirurgie,* 23**,** 52-59.

Keefe, F. J. & Somers, T. J. 2010. Psychological approaches to understanding and treating arthritis pain. *Nature reviews rheumatology,* 6**,** 210-216.

Keefe, F. J., Lumley, M., Anderson, T., Lynch, T. & Carson, K. L. 2001. Pain and emotion: new research directions. *Journal of clinical psychology,* 57**,** 587-607.

Kennedy, M. S., Nicholson, H. D. & Woodley, S. J. 2017. Clinical anatomy of the subacromial and related shoulder bursae: A review of the literature. *Clinical Anatomy,* 30**,** 213-226.

Khosravi, F., Amiri, Z., Masouleh, N. A., Kashfi, P., Panjizadeh, F., Hajilo, Z., Shanayii, S., Khodakarim, S. & Rahnama, L. 2019. Shoulder pain prevalence and risk factors in middle-aged women: A cross-sectional study. *Journal of Bodywork & Movement Therapies,* 23**,** 752-757.

Kiani, J., Goharifar, H., Moghimbeigi, A. & Azizkhani, H. 2014. Prevalence and risk factors of five most common upper extremity disorders in diabetics. *Journal of Research in Health Sciences,* 14**,** 92-5.

Kim, H. J., Fay, M. P., Feuer, E. J. & Midthune, D. N. 2000. Permutation tests for joinpoint regression with applications to cancer rates. *Statistics in medicine,* 19**,** 335-351.

Kim, H. M., Caldwell, J. M. E., Buza, J. A., Fink, L. A., Ahmad, C. S., Bigliani, L. U. & Levine, W. N. 2014. Factors affecting satisfaction and shoulder function in patients with a recurrent rotator cuff tear. *Journal of Bone and Joint Surgery - Series A,* 96**,** 106-112.

Kim, R. P. 2002. The musculoskeletal complications of diabetes. *Current diabetes reports,* 2**,** 49-52.

Kim, Y. E. & Jeon, B. S. 2013. Musculoskeletal problems in Parkinson's disease. *Journal of Neural Transmission,* 120**,** 537-542.

Kindler, L. L., Valencia, C., Fillingim, R. B. & George, S. Z. 2011. Sex differences in experimental and clinical pain sensitivity for patients with shoulder pain. *European Journal of Pain,* 15**,** 118-123.

Kobayashi, T., Takagishi, K., Shitara, H., Ichinose, T., Shimoyama, D., Yamamoto, A., Osawa, T. & Tajika, T. 2014. Prevalence of and risk factors for shoulder osteoarthritis in Japanese middle-aged and elderly populations. *Journal of Shoulder & Elbow Surgery,* 23**,** 613-9.

Kohli, N., Mitreski, G., Yap, C.-H. & Leong, M. 2016. Massive symptomatic right-sided Bochdalek hernia in an adult man. *Case Reports,* 2016**,** bcr2016217432.

Kontopantelis, E., Springate, D., Reeves, D., Ashcroft, D. M., Valderas, J. M. & Doran, T. 2014. Withdrawing performance indicators: retrospective analysis of general practice performance under UK Quality and Outcomes Framework. *Bmj,* 348.

Kopec, J. A., Rahman, M. M., Berthelot, J.-M., Le Petit, C., Aghajanian, J., Sayre, E. C., Cibere, J., Anis, A. H. & Badley, E. M. 2007. Descriptive epidemiology of osteoarthritis in British Columbia, Canada. *The Journal of Rheumatology,* 34**,** 386-393.

Korda, R. J., Joshy, G., Paige, E., Butler, J. R., Jorm, L. R., Liu, B., Bauman, A. E. & Banks, E. 2015. The relationship between body mass index and hospitalisation rates, days in hospital and costs: findings from a large prospective linked data study. *PLoS One,* 10**,** e0118599.

Kuitunen, I., Ponkilainen, V. T., Uimonen, M. M., Eskelinen, A. & Reito, A. 2021. Testing the proportional hazards assumption in cox regression and dealing with possible non-proportionality in total joint arthroplasty research: methodological perspectives and review. *BMC musculoskeletal disorders,* 22**,** 489.

Kumagai, J., Sarkar, K. & Uhthoff, H. 1994. The collagen types in the attachment zone of rotator cuff tendons in the elderly: an immunohistochemical study. *The Journal of rheumatology,* 21**,** 2096-2100.

Kumar, S. 2001. Theories of musculoskeletal injury causation. *Ergonomics,* 44**,** 17-47.

Kumaradev, S., Fayosse, A., Dugravot, A., Dumurgier, J., Roux, C., Kivimäki, M., Singh-Manoux, A. & Sabia, S. 2021. Timeline of pain before dementia diagnosis: a 27-year follow-up study. *Pain,* 162**,** 1578-1585.

Kuo, C.-F., Grainge, M. J., Mallen, C., Zhang, W. & Doherty, M. 2015. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Annals of the rheumatic diseases,* 74**,** 661-667.

Lachenbruch, P. A. 2014. McNemar test. *Wiley StatsRef: Statistics Reference Online*.

Lafeber, F., Besselink, N., Mastbergen, S., Doherty, M., Bijlsma, J., Arden, N., Hunter, D. & Dalbeth, N. 2016. Oxford Textbook of Osteoarthritis and Crystal Arthropathy. *Oxford Textbook of Osteoarthritis and Crystal Arthropathy (3rd).* Oxford textbooks in Rheumatology.

Land, K. C. & Yang, Y. 2006. Morbidity, disability, and mortality. *Handbook of aging and the social sciences***,** 41-58.

Langridge, N. 2019. The skills, knowledge and attributes needed as a first-contact physiotherapist in musculoskeletal healthcare. *Musculoskeletal Care,* 17**,** 253-260.

Laporte, J.-R., Ibanez, L., Vidal, X., Vendrell, L. & Leone, R. 2004. Upper gastrointestinal bleeding associated with the use of NSAIDs: newer versus older agents. *Drug safety,* 27**,** 411-420.

Laslett, L. L., Burnet, S. P., Jones, J. A., Redmond, C. L. & McNeil, J. D. 2007. Musculoskeletal morbidity: the growing burden of shoulder pain and disability and poor quality of life in diabetic outpatients. *Clinical & Experimental Rheumatology,* 25**,** 422-9.

Laslett, L. L., Otahal, P., Hensor, E. M., Kingsbury, S. R. & Conaghan, P. G. 2016. Knee pain predicts subsequent shoulder pain and the association is mediated by leg weakness: Longitudinal observational data from the osteoarthritis initiative. *The Journal of rheumatology,* 43**,** 2049-2055.

Lautenbacher, S., Kundermann, B. & Krieg, J.-C. 2006. Sleep deprivation and pain perception. *Sleep medicine reviews,* 10**,** 357-369.

Leboeuf-Yde, C. 2000. Alcohol and low-back pain: a systematic literature review. *Journal of Manipulative and Physiological Therapeutics,* 23**,** 343-346.

Leclerc, A., Chastang, J., Niedhammer, I., Landre, M. & Roquelaure, Y. 2004. Incidence of shoulder pain in repetitive work. *Occupational and environmental medicine,* 61**,** 39-44.

Lee, H. J., Oh, J.-H., Yoo, J. R., Ko, S. Y., Kang, J. H., Lee, S. K., Jeong, W., Seong, G. M., Kang, C.-H. & Lim, C. 2024. Prevalence of shoulder pain and its correlates in Jeju agricultural population: A retrospective cross-sectional study. *Medicine,* 103**,** e37043.

Lehtinen, J. T., Kaarela, K., Belt, E. A., Kautiainen, H. J., Kauppi, M. J. & Lehto, M. 2000. Incidence of glenohumeral joint involvement in seropositive rheumatoid arthritis. A 15 year endpoint study. *The Journal of rheumatology,* 27**,** 347-350.

Leijon, O., Wahlstrom, J. & Mulder, M. 2009. Prevalence of self-reported neck-shoulder-arm pain and concurrent low back pain or psychological distress: time-trends in a general population, 1990-2006. *Spine,* 34**,** 1863-8.

Lentz, T. A., Harman, J. S., Marlow, N. M., Beneciuk, J. M., Fillingim, R. B. & George, S. Z. 2019. Factors associated with persistently high-cost health care utilization for musculoskeletal pain. *PLoS One,* 14**,** e0225125.

Leong, H.-T., Tsui, S., Ying, M., Leung, V. Y.-f. & Fu, S. N. 2012. Ultrasound measurements on acromio-humeral distance and supraspinatus tendon thickness: test–retest reliability and correlations with shoulder rotational strengths. *Journal of science and medicine in sport,* 15**,** 284-291.

Lerman, S. F., Rudich, Z., Brill, S., Shalev, H. & Shahar, G. 2015. Longitudinal associations between depression, anxiety, pain, and pain-related disability in chronic pain patients. *Psychosomatic medicine,* 77**,** 333-341.

Levitz, C. & Iannotti, J. 1995. Overuse injuries of the shoulder. *Repetitive motions disorders of the upper extremity*.

Lewis, J. 2016. Rotator cuff related shoulder pain: assessment, management and uncertainties. *Manual therapy,* 23**,** 57-68.

Lewis, J. S. 2009. Rotator cuff tendinopathy. *British journal of sports medicine,* 43**,** 236-241.

Lewis, J. S. 2011. Subacromial impingement syndrome: a musculoskeletal condition or a clinical illusion? *Physical Therapy Reviews,* 16**,** 388-398.

Lewis, J. S., Raza, S. A., Pilcher, J., Heron, C. & Poloniecki, J. D. 2009. The prevalence of neovascularity in patients clinically diagnosed with rotator cuff tendinopathy. *BMC Musculoskeletal Disorders,* 10**,** 1-14.

Lewis, J., McCreesh, K., Roy, J.-S. & Ginn, K. 2015. Rotator cuff tendinopathy: navigating the diagnosis-management conundrum. *Journal of orthopaedic & sports physical therapy,* 45**,** 923-937.

Licher, S., Leening, M. J., Yilmaz, P., Wolters, F. J., Heeringa, J., Bindels, P. J., Initiative, A. s. D. N., Vernooij, M. W., Stephan, B. C. & Steyerberg, E. W. 2019. Development and validation of a dementia risk prediction model in the general population: an analysis of three longitudinal studies. *American Journal of Psychiatry,* 176**,** 543-551.

Lin, E. H. 2008. Depression and osteoarthritis. *The American journal of medicine,* 121**,** S16-S19.

Lindhardsen, J., Gislason, G. H., Jacobsen, S., Ahlehoff, O., Olsen, A.-M. S., Madsen, O. R., Torp-Pedersen, C. & Hansen, P. R. 2014. Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study. *Annals of the rheumatic diseases,* 73**,** 1515-1521.

Linsell, L., Dawson, J., Zondervan, K., Rose, P., Randall, T., Fitzpatrick, R. & Carr, A. 2006. Prevalence and incidence of adults consulting for shoulder conditions in UK primary care; patterns of diagnosis and referral. *Rheumatology,* 45**,** 215-21.

Linton, S. J. & Shaw, W. S. 2011. Impact of psychological factors in the experience of pain. *Physical therapy,* 91**,** 700-711.

Litaker, D., Pioro, M., Bilbeisi, H. E. & Brems, J. 2000. Returning to the bedside: using the history and physical examination to identify rotator cuff tears. *Journal of the American Geriatrics Society,* 48**,** 1633-1637.

Littlewood, C., Malliaras, P., Bateman, M., Stace, R., May, S. & Walters, S. 2013. The central nervous system–an additional consideration in 'rotator cuff tendinopathy'and a potential basis for understanding response to loaded therapeutic exercise. *Manual therapy,* 18**,** 468-472.

Liu, S. H., Henry, M. H. & Nuccion, S. L. 1996. A prospective evaluation of a new physical examination in predicting glenoid labral tears. *Am J Sports Med,* 24**,** 721-5.

Lluch, E., Torres, R., Nijs, J. & Van Oosterwijck, J. 2014. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. *European journal of pain,* 18**,** 1367-1375.

Lo, C. K.-L., Mertz, D. & Loeb, M. 2014. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC medical research methodology,* 14**,** 1-5.

Lo, C. N., van Griensven, H. & Lewis, J. 2022. Rotator cuff related shoulder pain: An update of potential pathoaetiological factors. *New Zealand Journal of Physiotherapy,* 50**,** 82-93.

Lock, C., Allgar, V., Jones, K., Marples, G., Chandler, C. & Dawson, P. 1999. Prevalence of back, neck and shoulder problems in the inner city: implications for the provision of physiotherapy services in primary healthcare. *Physiotherapy Research International,* 4**,** 161-169.

Loew, M., Doustdar, S., Drath, C., Weber, M. A., Bruckner, T., Porschke, F., Raiss, P., Schiltenwolf, M., Almansour, H. & Akbar, M. 2019. Could long-term overhead load in painters be associated with rotator cuff lesions? A pilot study. *PLoS ONE [Electronic Resource],* 14**,** e0213824.

Longo, U. G., Facchinetti, G., Marchetti, A., Candela, V., Risi Ambrogioni, L., Faldetta, A., De Marinis, M. G. & Denaro, V. 2019. Sleep disturbance and rotator cuff tears: a systematic review. *Medicina,* 55**,** 453.

Losciale, J. M., Bullock, G. S., Collins, G. S., Arundale, A. J., Hughes, T., Arden, N. K. & Whittaker, J. L. 2023. Description, prediction, and causation in sport and exercise medicine research: resolving the confusion to improve research quality and patient outcomes. *journal of orthopaedic & sports physical therapy,* 53**,** 381-387.

Loughlin, J. 2015. Genetic contribution to osteoarthritis development: current state of evidence. *Current opinion in rheumatology,* 27**,** 284-288.

Loza, E., Jover, J. A., Rodriguez, L., Carmona, L. & Group, E. S. Multimorbidity: prevalence, effect on quality of life and daily functioning, and variation of this effect when one condition is a rheumatic disease. Seminars in arthritis and rheumatism, 2009. Elsevier, 312-319.

Lucas, J., van Doorn, P., Hegedus, E., Lewis, J. & van der Windt, D. 2022. A systematic review of the global prevalence and incidence of shoulder pain.

Luchini, C., Stubbs, B., Solmi, M. & Veronese, N. 2017. Assessing the quality of studies in meta-analyses: Advantages and limitations of the Newcastle Ottawa Scale. *World Journal of Meta-Analysis,* 5**,** 80-84.

Lugo, R., Kung, P. & Ma, C. B. 2008. Shoulder biomechanics. *European journal of radiology,* 68**,** 16-24.

Luime, J., Koes, B., Hendriksen, I., Burdorf, A., Verhagen, A., Miedema, H. & Verhaar, J. 2004. Prevalence and incidence of shoulder pain in the general population; a systematic review. *Scandinavian journal of rheumatology,* 33**,** 73-81.

Lunardi, A. C., Marques da Silva, C. C. B., Rodrigues Mendes, F. A., Marques, A. P., Stelmach, R. & Fernandes Carvalho, C. R. 2011. Musculoskeletal dysfunction and pain in adults with asthma. *Journal of asthma,* 48**,** 105-110.

Lundberg, U., Dohns, I. E., Melin, B., Sandsjo, L., Palmerud, G., Kadefors, R., Ekstrom, M. & Parr, D. 1999. Psychophysiological stress responses, muscle tension, and neck and shoulder pain among supermarket cashiers. *Journal of Occupational Health Psychology,* 4**,** 245-55.

Lundberg, U., Kadefors, R., Melin, B., Palmerud, G., Hassmén, P., Engström, M. & Elfsberg Dohns, I. 1994. Psychophysiological stress and EMG activity of the trapezius muscle. *International journal of behavioral medicine,* 1**,** 354-370.

Luque-Suarez, A., Martinez-Calderon, J., Navarro-Ledesma, S., Morales-Asencio, J. M., Meeus, M. & Struyf, F. 2020. Kinesiophobia is associated with pain intensity and disability in chronic shoulder pain: a cross-sectional study. *Journal of Manipulative and Physiological Therapeutics,* 43**,** 791-798.

Macfarlane, G. J. 1999. Generalized pain, fibromyalgia and regional pain: an epidemiological view. *Best Practice & Research Clinical Rheumatology,* 13**,** 403-414.

Macfarlane, G. J., Barnish, M. S. & Jones, G. T. 2017. Persons with chronic widespread pain experience excess mortality: longitudinal results from UK Biobank and meta-analysis. *Annals of the rheumatic diseases,* 76**,** 1815-1822.

Macfarlane, G. J., Beasley, M., Smith, B. H., Jones, G. T. & Macfarlane, T. V. 2015. Can large surveys conducted on highly selected populations provide valid information on the epidemiology of common health conditions? An analysis of UK Biobank data on musculoskeletal pain. *British Journal of Pain,* 9**,** 203-212.

Macfarlane, G. J., Crombie, I., McBeth, J. & Silman, A. J. 2001. Widespread body pain and mortality: prospective population based studyCommentary: An interesting finding, but what does it mean? *Bmj,* 323**,** 662.

Macfarlane, G. J., Norrie, G., Atherton, K., Power, C. & Jones, G. T. 2009. The influence of socioeconomic status on the reporting of regional and widespread musculoskeletal pain: results from the 1958 British Birth Cohort Study. *Annals of the Rheumatic Diseases,* 68**,** 1591-1595.

Madadizadeh, F., Vali, L., Rafiei, S. & Akbarnejad, Z. 2017. Risk factors associated with musculoskeletal disorders of the neck and shoulder in the personnel of Kerman University of Medical Sciences. *Electronic physician,* 9**,** 4341.

Madden, M. B. & Hall, D. A. 2010. Shoulder pain in Parkinson's disease: a case-control study. *Movement Disorders,* 25**,** 1105-6.

Magni, G., Moreschi, C., Rigatti-Luchini, S. & Merskey, H. 1994. Prospective study on the relationship between depressive symptoms and chronic musculoskeletal pain. *Pain,* 56**,** 289-297.

Mäkelä, M., Heliövaara, M., Sainio, P., Knekt, P., Impivaara, O. & Aromaa, A. 1999. Shoulder joint impairment among Finns aged 30 years or over: prevalence, risk factors and co-morbidity. *Rheumatology (Oxford, England),* 38**,** 656-662.

Mäkela, M., Heliövaara, M., Sievers, K., Impivaara, O., Knekt, P. & Aromaa, A. 1991. Prevalence, determinants, and consequences of chronic neck pain in Finland. *American journal of epidemiology,* 134**,** 1356-1367.

Malanga, G. A., Chu, S. K., Del Toro, J. R., Karnaugh, R. D., Dentico, R. & Komaroff, E. 2012. Sonographic evaluation of supraspinatus cross-sectional area in collegiate baseball players. *PM&R,* 4**,** 488-492.

Malavolta, E. A., Gracitelli, M. E. C., Pinto, G. d. M. R., Silveira, A. Z. F. d., Assunção, J. H. & Ferreira Neto, A. A. 2018. Asian ethnicity: a risk factor for adhesive capsulitis? *Revista Brasileira de Ortopedia,* 53**,** 602-606.

Mallon, W. J., Misamore, G., Snead, D. S. & Denton, P. 2004. The impact of preoperative smoking habits on the results of rotator cuff repair. *Journal of shoulder and elbow surgery,* 13**,** 129-132.

Mannerkorpi, K., Burckhardt, C. S. & Bjelle, A. 1994. Physical performance characteristics of women with fibromyalgia. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology,* 7**,** 123-129.

Marshall, M., Peat, G., Nicholls, E., van der Windt, D., Myers, H. & Dziedzic, K. 2013. Subsets of symptomatic hand osteoarthritis in community-dwelling older adults in the United Kingdom: prevalence, inter-relationships, risk factor profiles and clinical

characteristics at baseline and 3-years. *Osteoarthritis and cartilage,* 21**,** 1674-1684.

Marston, L., Carpenter, J. R., Walters, K. R., Morris, R. W., Nazareth, I., White, I. R. & Petersen, I. 2014. Smoker, ex-smoker or non-smoker? The validity of routinely recorded smoking status in UK primary care: a cross-sectional study. *BMJ open,* 4**,** e004958.

Martimo, K. P., Shiri, R., Miranda, H., Ketola, R., Varonen, H. & Viikari-Juntura, E. 2009. Self-reported productivity loss among workers with upper extremity disorders. *Scandinavian Journal of Work, Environment and Health,* 35**,** 301-308.

Martin, J. A. & Buckwalter, J. A. 2003. The role of chondrocyte senescence in the pathogenesis of osteoarthritis and in limiting cartilage repair. *JBJS,* 85**,** 106-110.

Martinez-Calderon, J., Meeus, M., Struyf, F., Morales-Asencio, J. M., Gijon-Nogueron, G. & Luque-Suarez, A. 2018. The role of psychological factors in the perpetuation of pain intensity and disability in people with chronic shoulder pain: a systematic review. *BMJ open,* 8**,** e020703.

Matharu, G. S., Mouchti, S., Twigg, S., Delmestri, A., Murray, D. W., Judge, A. & Pandit, H. G. 2019. The effect of smoking on outcomes following primary total hip and knee arthroplasty: a population-based cohort study of 117,024 patients. *Acta orthopaedica,* 90**,** 559-567.

Matsen, F. A., Li, N., Gao, H., Yuan, S., Russ, S. M. & Sampson, P. D. 2014. Factors affecting length of stay, readmission, and revision after shoulder arthroplasty a population-based study. *Journal of Bone and Joint Surgery - American Volume,* 97**,** 1255-1263.

May, T. & Garmel, G. M. 2021. Rotator Cuff Injury. *StatPearls.* Treasure Island (FL): StatPearls Publishing

McBeth, J. & Jones, K. 2007. Epidemiology of chronic musculoskeletal pain. *Best Practice and Research: Clinical Rheumatology,* 21**,** 403-425.

McBeth, J., Nicholl, B. I., Cordingley, L., Davies, K. A. & Macfarlane, G. J. 2010. Chronic widespread pain predicts physical inactivity: results from the prospective EPIFUND study. *European Journal of Pain,* 14**,** 972-979.

McCreesh, K. M., Purtill, H., Donnelly, A. E. & Lewis, J. S. 2017. Increased supraspinatus tendon thickness following fatigue loading in rotator cuff tendinopathy: potential implications for exercise therapy. *BMJ open sport & exercise medicine,* 3**,** e000279.

McDonald, J. 2014. Handbook of Biological Statistics 3rd ed Sparky House Publishing. *Baltimore, MD: Available http://www. biostathandbook. com/transformation. html,* 3.

McDonald, J. H. 2009. *Handbook of biological statistics*, sparky house publishing Baltimore, MD.

McRae, S., Leiter, J., Walmsley, C., Rehsia, S. & MacDonald, P. 2011. Relationship between self-reported shoulder function/quality of life, body mass index, and other contributing factors in patients awaiting rotator cuff repair surgery. *Journal of shoulder and elbow surgery,* 20**,** 57-61.

Meeus, M. & Nijs, J. 2007. Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clinical rheumatology,* 26**,** 465-473.

Meeus, M., Nijs, J., Van de Wauwer, N., Toeback, L. & Truijen, S. 2008. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. *Pain,* 139**,** 439-448.

Meeus, M., Vervisch, S., De Clerck, L. S., Moorkens, G., Hans, G. & Nijs, J. Central sensitization in patients with rheumatoid arthritis: a systematic literature review. Seminars in arthritis and rheumatism, 2012. Elsevier, 556-567.

Menge, T. J., Boykin, R. E., Byram, I. R. & Bushnell, B. D. 2014. A comprehensive approach to glenohumeral arthritis. *South Med J,* 107**,** 567-73.

Menotti, A., Mulder, I., Nissinen, A., Giampaoli, S., Feskens, E. J. & Kromhout, D. 2001. Prevalence of morbidity and multimorbidity in elderly male populations and their impact on 10-year all-cause mortality: The FINE study (Finland, Italy, Netherlands, Elderly). *Journal of clinical epidemiology,* 54**,** 680-686.

Michener, L. A., McClure, P. W. & Karduna, A. R. 2003. Anatomical and biomechanical mechanisms of subacromial impingement syndrome. *Clinical biomechanics,* 18**,** 369-379.

Michener, L. A., Subasi Yesilyaprak, S. S., Seitz, A. L., Timmons, M. K. & Walsworth, M. K. 2015. Supraspinatus tendon and subacromial space parameters measured on ultrasonographic imaging in subacromial impingement syndrome. *Knee Surgery, Sports Traumatology, Arthroscopy,* 23**,** 363-369.

Michener, L. A., Walsworth, M. K., Doukas, W. C. & Murphy, K. P. 2009. Reliability and diagnostic accuracy of 5 physical examination tests and combination of tests for subacromial impingement. *Archives of physical medicine and rehabilitation,* 90**,** 1898-1903.

Mikkonen, P., Leino-Arjas, P., Remes, J., Zitting, P., Taimela, S. & Karppinen, J. 2008. Is smoking a risk factor for low back pain in adolescents?: A prospective cohort study. *Spine,* 33**,** 527-532.

Milgrom, C., Novack, V., Weil, Y., Jaber, S., Radeva-Petrova, D. R. & Finestone, A. 2008. Risk factors for idiopathic frozen shoulder. *Israel Medical Association Journal: Imaj,* 10**,** 361-4.

Milgrom, C., Schaffler, M., Gilbert, S. & van Holsbeeck, M. 1995. Rotator-cuff changes in asymptomatic adults. The effect of age, hand dominance and gender. *The Journal of Bone & Joint Surgery British Volume,* 77**,** 296-298.

Millett, P. J., Gobezie, R. & Boykin, R. E. 2008. Shoulder osteoarthritis: diagnosis and management. *Am Fam Physician,* 78**,** 605-11.

Mills, S., Torrance, N. & Smith, B. H. 2016. Identification and management of chronic pain in primary care: a review. *Current psychiatry reports,* 18**,** 1-9.

Ministry of Housing/Communities & Local Government. 2019. *English indices of deprivation 2019* [Online]. Available: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019 [Accessed 6 May 2025 2025].

Miranda, H., Punnett, L., Viikari-Juntura, E., Heliövaara, M. & Knekt, P. 2008. Physical work and chronic shoulder disorder. Results of a prospective population-based study. *Annals of the rheumatic diseases,* 67**,** 218-223.

Miranda, H., Viikari-Juntura, E., Heistaro, S., Heliövaara, M. & Riihimäki, H. 2005. A population study on differences in the determinants of a specific shoulder disorder versus nonspecific shoulder pain without clinical findings. *American Journal of Epidemiology,* 161**,** 847-855.

Miranda, H., Viikari-Juntura, E., Martikainen, R., Takala, E. & Riihimäki, H. 2001. A prospective study of work related factors and physical exercise as predictors of shoulder pain. *Occupational and environmental medicine,* 58**,** 528-534.

Mitchell, C., Adebajo, A., Hay, E. & Carr, A. 2005. Shoulder pain: diagnosis and management in primary care. *Bmj,* 331**,** 1124-1128.

Mitchell, J. M., O'Neil, J. P., Janabi, M., Marks, S. M., Jagust, W. J. & Fields, H. L. 2012. Alcohol consumption induces endogenous opioid release in the human orbitofrontal cortex and nucleus accumbens. *Science translational medicine,* 4**,** 116ra6-116ra6.

Mitchell, M. D., Mannino, D. M., Steinke, D. T., Kryscio, R. J., Bush, H. M. & Crofford, L. J. 2011. Association of smoking and chronic pain syndromes in Kentucky women. *J Pain,* 12**,** 892-9.

Morelli, K. M., Martin, B. R., Charakla, F. H., Durmisevic, A. & Warren, G. L. 2019. Acromion morphology and prevalence of rotator cuff tear: A systematic review and meta-analysis. *Clinical Anatomy,* 32**,** 122-130.

Morley, S., Eccleston, C. & Williams, A. 1999. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain,* 80**,** 1-13.

Morris, S. B. 2008. Book Review: Hunter, JE, & Schmidt, FL (2004). Methods of Meta-Analysis: Correcting Error and Bias in Research Findings . Thousand Oaks, CA: Sage. *Organizational Research Methods,* 11**,** 184-187.

Morse, T., Bruneau, H., Michalak-Turcotte, C., Sanders, M., Warren, N., Dussetschleger, J., Diva, U., Croteau, M. & Cherniack, M. 2007. Musculoskeletal disorders of the neck and shoulder in dental hygienists and dental hygiene students. *Journal of Dental Hygiene,* 81**,** 10.

Muckelt, P. E., Roos, E., Stokes, M., McDonough, S., Grønne, D., Ewings, S. & Skou, S. 2020. Comorbidities and their link with individual health status: A cross-sectional analysis of 23,892 people with knee and hip osteoarthritis from primary care. *Journal of Comorbidity,* 10**,** 2235042X20920456.

Mulligan, E. P., Brunette, M., Shirley, Z. & Khazzam, M. 2015. Sleep quality and nocturnal pain in patients with shoulder disorders. *Journal of Shoulder and Elbow Surgery,* 24**,** 1452-1457.

Murphy, R. J. & Carr, A. J. 2010. Shoulder pain. *BMJ Clin Evid,* 2010.

Murray, C. J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A. & Abdalla, S. 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet,* 380**,** 2197-2223.

Murrell, G. A. & Walton, J. R. 2001. Diagnosis of rotator cuff tears. *The Lancet,* 357**,** 769-770.

musculoskeletal conditions in numbers.

Musumeci, G., Szychlinska, M. A. & Mobasheri, A. 2015. Age-related degeneration of articular cartilage in the pathogenesis of osteoarthritis: molecular markers of senescent chondrocytes.

Neddenriep, B., Bagdas, D., Contreras, K. M., Ditre, J. W., Wolstenholme, J. T., Miles, M. F. & Damaj, M. I. 2019. Pharmacological

mechanisms of alcohol analgesic-like properties in mouse models of acute and chronic pain. *Neuropharmacology,* 160**,** 107793.

Neer, C. 1972. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. *JBJS,* 54**,** 41-50.

Neer, C. S. 1983. Impingement lesions. *Clinical Orthopaedics and Related Research (1976-2007),* 173**,** 70-77.

Neviaser, A. S. & Hannafin, J. A. 2010. Adhesive capsulitis: a review of current treatment. *Am J Sports Med,* 38**,** 2346-56.

Neviaser, R. J. & Neviaser, T. J. 1987. The Frozen Shoulder Diagnosis and Management. *Clinical Orthopaedics and Related Research (1976-2007),* 223**,** 59-64.

Ngamjarus, C. 2016. n4Studies: sample size calculation for an epidemiological study on a smart device. *Siriraj Medical Journal,* 68**,** 160-170.

Nguyen, C. D., Carlin, J. B. & Lee, K. J. 2017. Model checking in multiple imputation: an overview and case study. *Emerging themes in epidemiology,* 14**,** 1-12.

NHS. 2018. *Body Mass index (BMI) in UK population* [Online]. Available: https://www.nhs.uk/conditions/obesity/ [Accessed 6 May 2025 2025].

NICE 2022. Osteoarthritis in over 16s: diagnosis and management.

NICE, N. I. f. H. a. C. E. 2021. *Shoulder pain* [Online]. Available: https://cks.nice.org.uk/topics/shoulder-pain/ [Accessed 05/08 2024].

Nicolson, P. J., Williamson, E., Morris, A., Sanchez-Santos, M. T., Bruce, J., Silman, A. & Lamb, S. E. 2021. Musculoskeletal pain and loneliness, social support and social engagement among older adults: Analysis of the Oxford Pain, Activity and Lifestyle cohort. *Musculoskeletal Care,* 19**,** 269-277.

Niedhammer, I., Landre, M., Leclerc, A., Bourgeois, F., Franchi, P., Chastang, J., Marignac, G., Mereau, P., Quinton, D., Du Noyer, C. R., Schmaus, A. & Vallayer, C. 1998. Shoulder disorders related to work organization and other occupational factors among supermarket cashiers. *International Journal of Occupational & Environmental Health,* 4**,** 168-178.

Nijs, J., Meeus, M., Van Oosterwijck, J., Ickmans, K., Moorkens, G., Hans, G. & De Clerck, L. S. 2012. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. *European journal of clinical investigation,* 42**,** 203-212.

Nikiphorou, E., De Lusignan, S., Mallen, C., Roberts, J., Khavandi, K., Bedarida, G., Buckley, C. D., Galloway, J. & Raza, K. 2020. Prognostic value of comorbidity indices and lung diseases in early rheumatoid arthritis: a UK population-based study. *Rheumatology,* 59**,** 1296-1305.

Nitter, A. K. & Forseth, K. Ø. 2013. Mortality rate and causes of death in women with self-reported musculoskeletal pain: Results from a 17-year follow-up study. *Scandinavian journal of pain,* 4**,** 86-92.

Noordzij, M., Dekker, F. W., Zoccali, C. & Jager, K. J. 2010. Measures of disease frequency: prevalence and incidence. *Nephron Clinical Practice,* 115**,** c17-c20.

Noten, S., Struyf, F., Lluch, E., D'Hoore, M., Van Looveren, E. & Meeus, M. 2017. Central Pain Processing in Patients with Shoulder Pain: A Review of the Literature. *Pain Pract,* 17**,** 267-280.

Novati, A., Roman, V., Cetin, T., Hagewoud, R., den Boer, J. A., Luiten, P. G. & Meerlo, P. 2008. Chronically restricted sleep leads to depression-like changes in neurotransmitter receptor sensitivity and neuroendocrine stress reactivity in rats. *Sleep,* 31**,** 1579-1585.

O'Kane, J. W. & Toresdahl, B. G. 2014. The evidenced-based shoulder evaluation. *Current sports medicine reports,* 13**,** 307-313.

Ogawa, K., Yoshida, A., Inokuchi, W. & Naniwa, T. 2005. Acromial spur: relationship to aging and morphologic changes in the rotator cuff. *Journal of shoulder and elbow surgery,* 14**,** 591-598.

Oh, J. H., Chung, S. W., Oh, C. H., Kim, S. H., Park, S. J., Kim, K. W., Park, J. H., Lee, S. B. & Lee, J. J. 2011. The prevalence of shoulder osteoarthritis in the elderly Korean population: association with risk factors and function. *J Shoulder Elbow Surg,* 20**,** 756-63.

Oh, J.-h., Jung, B., Kim, E.-S., Kim, N. & Ha, I.-H. 2021. The effect of continuity of care on medical costs in patients with chronic shoulder pain. *Scientific Reports,* 11**,** 4077.

Oh, L. S., Wolf, B. R., Hall, M. P., Levy, B. A. & Marx, R. G. 2007. Indications for rotator cuff repair: a systematic review. *Clin Orthop Relat Res,* 455**,** 52-63.

Oha, K., Animagi, L., Paasuke, M., Coggon, D. & Merisalu, E. 2014. Individual and work-related risk factors for musculoskeletal pain: a cross-sectional study among Estonian computer users. *BMC Musculoskeletal Disorders,* 15**,** 181.

Oliveira, C. B., Maher, C. G., Franco, M. R., Kamper, S. J., Williams, C. M., Silva, F. G. & Pinto, R. Z. 2020. Co-occurrence of chronic musculoskeletal pain and cardiovascular diseases: a systematic review with meta-analysis. *Pain Medicine,* 21**,** 1106-1121.

Orenius, T., Koskela, T., Koho, P., Pohjolainen, T., Kautiainen, H., Haanpää, M. & Hurri, H. 2013. Anxiety and depression are independent predictors of quality of life of patients with chronic musculoskeletal pain. *Journal of health psychology,* 18**,** 167-175.

Ortego, G., Villafane, J. H., Domenech-Garcia, V., Berjano, P., Bertozzi, L. & Herrero, P. 2016. Is there a relationship between psychological stress or anxiety and chronic nonspecific neck-arm pain in adults? A systematic review and meta-analysis. *Journal of Psychosomatic Research,* 90**,** 70-81.

Östergren, P., Hanson, B. S., Balogh, I., Ektor-Andersen, J., Isacsson, A., Örbaek, P., Winkel, J. & Isacsson, S. 2005. Incidence of shoulder and neck pain in a working population: effect modification between mechanical and psychosocial exposures at work? Results from a one year follow up on the Malmö shoulder and neck study cohort. *Journal of Epidemiology & Community Health,* 59**,** 721-728.

Otoshi, K., Sekiguchi, M., Otani, K., Shishido, H., Kikuchi, S., Konno, S., Takegami, M., Onishi, Y. & Yamazaki, S. 2014. Association between kyphosis and subacromial impingement syndrome: LOHAS study. *Journal of Shoulder and Elbow Surgery,* 23**,** e300-e307.

Ouzzani, M., Hammady, H., Fedorowicz, Z. & Elmagarmid, A. 2016. Rayyan—a web and mobile app for systematic reviews. *Systematic reviews,* 5**,** 1-10.

Ozaki, J., Fujimoto, S., Nakagawa, Y., Masuhara, K. & Tamai, S. 1988. Tears of the rotator cuff of the shoulder associated with pathological changes in the acromion. A study in cadavera. *JBJS,* 70**,** 1224-1230.

Özkuk, K. & Ateş, Z. 2020. The effect of obesity on pain and disability in chronic shoulder pain patients. *Journal of back and musculoskeletal rehabilitation,* 33**,** 73-79.

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A. & Brennan, S. E. 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *bmj,* 372.

Palladino, R., Tayu Lee, J., Ashworth, M., Triassi, M. & Millett, C. 2016. Associations between multimorbidity, healthcare utilisation and health status: evidence from 16 European countries. *Age and ageing,* 45**,** 431-435.

Pandya, J., Johnson, T. & Low, A. K. 2018. Shoulder replacement for osteoarthritis: a review of surgical management. *Maturitas,* 108**,** 71-76.

Papalia, R., Torre, G., Papalia, G., Baums, M., Narbona, P., Di Lazzaro, V. & Denaro, V. 2019. Frozen shoulder or shoulder stiffness from Parkinson disease? *Musculoskeletal surgery,* 103**,** 115-119.

Park, H. B., Yokota, A., Gill, H. S., El Rassi, G. & McFarland, E. G. 2005. Diagnostic accuracy of clinical tests for the different degrees of subacromial impingement syndrome. *JBJS,* 87**,** 1446-1455.

Park, S., Kim, Y.-H., Bang, H. I. & Park, Y. 2023. Sample size calculation in clinical trial using R. *Journal of minimally invasive surgery,* 26**,** 9.

Parsons Iv, I., Apreleva, M., Fu, F. H. & Woo, S. L. Y. 2002. The effect of rotator cuff tears on reaction forces at the glenohumeral joint. *Journal of orthopaedic research,* 20**,** 439-446.

Parsons, S., Breen, A., Foster, N. E., Letley, L., Pincus, T., Vogel, S. & Underwood, M. 2007. Prevalence and comparative troublesomeness by age of musculoskeletal pain in different body locations. *Fam Pract,* 24**,** 308-16.

Patel, A. S., Farquharson, R., Carroll, D., Moore, A., Phillips, C. J., Taylor, R. S. & Barden, J. 2012. The impact and burden of chronic pain in the workplace: a qualitative systematic review. *Pain Practice,* 12**,** 578-589.

Persellin, R. & Rutstein, J. 1979. Rheumatic aspects of endocrinopathies. Lea & Febiger Philadelphia.

Persson, R., Vasilakis-Scaramozza, C., Hagberg, K. W., Sponholtz, T., Williams, T., Myles, P. & Jick, S. S. 2020. CPRD Aurum database: Assessment of data quality and completeness of three important comorbidities. *Pharmacoepidemiol Drug Saf,* 29**,** 1456-1464.

Picavet, H. S. & Schouten, J. S. 2003. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. *Pain,* 102**,** 167-78.

Piette, J. D. & Kerr, E. A. 2006. The impact of comorbid chronic conditions on diabetes care. *Diabetes care,* 29.

Popchak, A. J., Hogaboom, N. S., Vyas, D., Abt, J. P., Delitto, A., Irrgang, J. J. & Boninger, M. L. 2017. Acute Response of the Infraspinatus and Biceps Tendons to Pitching in Youth Baseball. *Medicine and science in sports and exercise,* 49**,** 1168-1175.

Pope, D. P., Croft, P. R., Pritchard, C. M. & Silman, A. J. 1997. Prevalence of shoulder pain in the community: the influence of case definition. *Annals of the Rheumatic Diseases,* 56**,** 308-12.

Porter, K. N., Blanch, P. D., Walker, H. M. & Shield, A. J. 2020. The effect of previous shoulder pain on supraspinatus tendon thickness

changes following swimming practice. *Scandinavian journal of medicine & science in sports,* 30**,** 1442-1448.

Posch, M., Schranz, A., Lener, M., Senn, W., Ang, B. O., Burtscher, M. & Ruedl, G. 2019. Prevalence and potential risk factors of flight-related neck, shoulder and low back pain among helicopter pilots and crewmembers: a questionnaire-based study. *BMC Musculoskeletal Disorders,* 20**,** 44.

Pourhoseingholi, M. A., Vahedi, M. & Rahimzadeh, M. 2013. Sample size calculation in medical studies. *Gastroenterol Hepatol Bed Bench,* 6**,** 14-7.

Pribicevic, M. 2012. The epidemiology of shoulder pain: A narrative review of the literature. *Pain in perspective*.

Putrik, P., Ramiro, S., Chorus, A., Keszei, A. & Boonen, A. 2015. Socioeconomic inequities in perceived health among patients with musculoskeletal disorders compared with other chronic disorders: results from a cross-sectional Dutch study. *RMD open,* 1**,** e000045.

Radin, E., Burr, D., Caterson, B., Fyhrie, D., Brown, T. & Boyd, R. Mechanical determinants of osteoarthrosis. Seminars in arthritis and rheumatism, 1991. Elsevier, 12-21.

Ramirez, J. 2019. Adhesive Capsulitis: Diagnosis and Management. *Am Fam Physician,* 99**,** 297-300.

Ranstam, J. & Cook, J. 2017. Kaplan–meier curve. *Journal of British Surgery,* 104**,** 442-442.

Rasmussen-Barr, E., Grooten, W. J., Hallqvist, J., Holm, L. W. & Skillgate, E. 2014. Are job strain and sleep disturbances prognostic factors for neck/shoulder/arm pain? A cohort study of a general population of working age in Sweden. *BMJ Open,* 4**,** e005103.

Rasmussen-Barr, E., Nordin, M. & Skillgate, E. 2023. Are respiratory disorders risk factors for troublesome neck/shoulder pain? A study of a general population cohort in Sweden. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society,* 32**,** 659-666.

Rathbun, J. B. & Macnab, I. 1970. The microvascular pattern of the rotator cuff. *The Journal of Bone & Joint Surgery British Volume,* 52**,** 540-553.

Razmjou, H., Lincoln, S., Macritchie, I., Richards, R. R., Medeiros, D. & Elmaraghy, A. 2016. Sex and gender disparity in pathology, disability, referral pattern, and wait time for surgery in workers with shoulder injury. *BMC Musculoskelet Disord,* 17**,** 401.

Rechardt, M., Shiri, R., Karppinen, J., Jula, A., Heliovaara, M. & Viikari-Juntura, E. 2010. Lifestyle and metabolic factors in relation to shoulder pain and rotator cuff tendinitis: a population-based study. *BMC Musculoskeletal Disorders,* 11**,** 165.

Redler, L. H. & Dennis, E. R. 2019. Treatment of Adhesive Capsulitis of the Shoulder. *J Am Acad Orthop Surg,* 27**,** e544-e554.

Requejo-Salinas, N., Lewis, J., Michener, L. A., La Touche, R., Fernández-Matías, R., Tercero-Lucas, J., Camargo, P. R., Bateman, M., Struyf, F. & Roy, J.-S. 2022. International physical therapists consensus on clinical descriptors for diagnosing rotator cuff related shoulder pain: a Delphi study. *Brazilian journal of physical therapy,* 26**,** 100395.

Reuters, V. S., Patrícia de Fátima, S. T., Vigário, P. S., Almeida, C. P., Buescu, A., Ferreira, M. M., Vaisman, M., de Castro, C. L. & Gold, J. 2009. Functional capacity and muscular abnormalities in subclinical hypothyroidism. *The American journal of the medical sciences,* 338**,** 259-263.

Riley, D., Lang, A., Blair, R., Birnbaum, A. & Reid, B. 1989. Frozen shoulder and other shoulder disturbances in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry,* 52**,** 63-66.

Riley, G., Harrall, R., Constant, C., Chard, M., Cawston, T. & Hazleman, B. 1994. Glycosaminoglycans of human rotator cuff tendons: changes with age and in chronic rotator cuff tendinitis. *Annals of the rheumatic diseases,* 53**,** 367-376.

Rizos, C., Elisaf, M. & Liberopoulos, E. 2011. Effects of thyroid dysfunction on lipid profile. *The open cardiovascular medicine journal,* 5**,** 76.

Robles-Ribeiro, P. G., Ribeiro, M. & Lianza, S. 2005. Relationship between peak expiratory flow rate and shoulders posture in healthy individuals and moderate to severe asthmatic patients. *Journal of Asthma,* 42**,** 783-786.

Rodeo, S. A., Hannafin, J. A., Tom, J., Warren, R. F. & Wickiewicz, T. L. 1997. Immunolocalization of cytokines and their receptors in adhesive capsulitis of the shoulder. *Journal of Orthopaedic Research,* 15**,** 427-436.

Roh, Y. H., Lee, B. K., Noh, J. H., Oh, J. H., Gong, H. S. & Baek, G. H. 2012. Effect of depressive symptoms on perceived disability in patients with chronic shoulder pain. *Archives of orthopaedic and trauma surgery,* 132**,** 1251-1257.

Roland, M. 2004. Linking physicians' pay to the quality of care—a major experiment in the United Kingdom. *N Engl J Med,* 351**,** 1448-54.

Rouch, I., Edjolo, A., Laurent, B., Pongan, E., Dartigues, J.-F. & Amieva, H. 2021. Association between chronic pain and long-term cognitive decline in a population-based cohort of elderly participants. *Pain,* 162**,** 552-560.

Roumie, C. L., Mitchel Jr, E. F., Kaltenbach, L., Arbogast, P. G., Gideon, P. & Griffin, M. R. 2008. Nonaspirin NSAIDs, cyclooxygenase 2 inhibitors, and the risk for stroke. *Stroke,* 39**,** 2037-2045.

Rubin, D. B. 2004. *Multiple imputation for nonresponse in surveys*, John Wiley & Sons.

Rubin, D. B. 2018. Multiple imputation. *Flexible Imputation of Missing Data, Second Edition.* Chapman and Hall/CRC.

Ryall, C., Coggon, D., Peveler, R., Poole, J. & Palmer, K. T. 2007. A prospective cohort study of arm pain in primary care and physiotherapy--prognostic determinants. *Rheumatology,* 46**,** 508-15.

Ryan, C., McDonough, S., Kirwan, J., Leveille, S. & Martin, D. 2014. An investigation of association between chronic musculoskeletal pain and cardiovascular disease in the H ealth S urvey for E ngland (2008). *European journal of pain,* 18**,** 740-750.

Ryan, V., Brown, H., Minns Lowe, C. J. & Lewis, J. S. 2016. The pathophysiology associated with primary (idiopathic) frozen shoulder: A systematic review. *BMC musculoskeletal disorders,* 17**,** 1-21.

Sabzwari, S. R., Qidwai, W. & Bhanji, S. 2013. Polypharmacy in elderly: a cautious trail to tread. *Journal of Pakistan Medical Association,* 63**,** 624.

Salamh, P. & Lewis, J. 2020. It is time to put special tests for rotator cuff–related shoulder pain out to pasture. *Journal of Orthopaedic & Sports Physical Therapy,* 50**,** 222-225.

Sanchez Santos, M. T., Williamson, E., Bruce, J., Ward, L., Mallen, C. D., Garrett, A., Morris, A. & Lamb, S. E. 2020. Cohort profile: Oxford pain, activity and lifestyle (OPAL) Study, a prospective cohort study of older adults in England. *BMJ Open,* 10.

Sanchez-Adams, J., Leddy, H. A., McNulty, A. L., O'Conor, C. J. & Guilak, F. 2014. The mechanobiology of articular cartilage: bearing the burden of osteoarthritis. *Current rheumatology reports,* 16**,** 1-9.

Sanchis, M. N., Lluch, E., Nijs, J., Struyf, F. & Kangasperko, M. The role of central sensitization in shoulder pain: a systematic literature review. Seminars in arthritis and rheumatism, 2015. Elsevier, 710-716.

Sansone, V., Bonora, C., Boria, P. & Meroni, R. 2014. Women performing repetitive work: Is there a difference in the prevalence of shoulder pain and pathology in supermarket cashiers compared to the general female population? *International Journal of Occupational Medicine and Environmental Health,* 27**,** 722-735.

Sansone, V., Maiorano, E., Galluzzo, A. & Pascale, V. 2018. Calcific tendinopathy of the shoulder: clinical perspectives into the mechanisms, pathogenesis, and treatment. *Orthopedic research and reviews***,** 63-72.

Sarakbi, H. A., Alsaed, O., Hammoudeh, M., Lutf, A., Poil, A. R., Al-Emadi, S. & Ziyada, A. 2020. Epidemiology of musculoskeletal complaints and diseases in Qatar: A cross-sectional study. *Qatar Medical Journal,* 2020**,** 29.

Scarlat, M. & Florescu, A. 2005. [Shoulder function and scores in 180 asymptomatic individuals aged over 75 years]. *Revue de Chirurgie Orthopedique et Reparatrice de l Appareil Moteur,* 91**,** 502-7.

Schenk, J. M., Calip, G. S., Tangen, C. M., Goodman, P., Parsons, J. K., Thompson, I. M. & Kristal, A. R. 2012. Indications for and use of nonsteroidal antiinflammatory drugs and the risk of incident, symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *American journal of epidemiology,* 176**,** 156-163.

Schiefer, M., Teixeira, P. F. S., Conceicao, F. L., Fontenelle, C., Carminatti, T., Santos, D. A. & Righi, L. D. 2017. Prevalence of hypothyroidism in patients with frozen shoulder. *Journal of Shoulder and Elbow Surgery,* 26**,** 49-55.

Schwarzer, G. 2007. meta: An R package for meta-analysis. *R news,* 7**,** 40-45.

Scibek, J. S. & Carcia, C. R. 2012. Assessment of scapulohumeral rhythm for scapular plane shoulder elevation using a modified digital inclinometer. *World J Orthop,* 3**,** 87-94.

Seidler, A., Starke, K. R., Freiberg, A., Hegewald, J., Nienhaus, A. & Bolm-audorff, U. 2020. Dose–response relationship between physical workload and specific shoulder diseases—a systematic review with meta-analysis. *International Journal of Environmental Research and Public Health,* 17.

Sein, M. L., Walton, J., Linklater, J., Appleyard, R., Kirkbride, B., Kuah, D. & Murrell, G. A. 2010. Shoulder pain in elite swimmers: primarily due to swim-volume-induced supraspinatus tendinopathy. *British journal of sports medicine,* 44**,** 105-113.

Seitz, A. L., McClure, P. W., Finucane, S., Boardman III, N. D. & Michener, L. A. 2011. Mechanisms of rotator cuff tendinopathy: intrinsic, extrinsic, or both? *Clinical biomechanics,* 26**,** 1-12.

Sellam, J. & Berenbaum, F. 2013. Is osteoarthritis a metabolic disease? *Joint bone spine,* 80**,** 568-573.

Shah, K. M., Clark, B. R., McGill, J. B. & Mueller, M. J. 2015. Upper extremity impairments, pain and disability in patients with diabetes mellitus. *Physiotherapy,* 101**,** 147-54.

Shahabpour, M., Kichouh, M., Laridon, E., Gielen, J. L. & De Mey, J. 2008. The effectiveness of diagnostic imaging methods for the assessment of soft tissue and articular disorders of the shoulder and elbow. *European journal of radiology,* 65**,** 194-200.

Shakoor, N. & Moisio, K. 2004. A biomechanical approach to musculoskeletal disease. *Best Practice & Research Clinical Rheumatology,* 18**,** 173-186.

Shei, R.-J., Paris, H. L., Wilhite, D. P., Chapman, R. F. & Mickleborough, T. D. 2016. The role of inspiratory muscle training in the management of asthma and exercise-induced bronchoconstriction. *The Physician and sportsmedicine,* 44**,** 327-334.

Shirazi, A. A., Nasiri, M. & Yazdanpanah, L. 2016. Dermatological and musculoskeletal assessment of diabetic foot: A narrative review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews,* 10**,** S158-S164.

Shrestha, N. 2020. Detecting multicollinearity in regression analysis. *American Journal of Applied Mathematics and Statistics,* 8**,** 39-42.

Shultz, S. J. & Fegley, J. 2023. The effect of sex hormones on ligament structure, joint stability and ACL injury risk. *Sex Hormones, Exercise and Women: Scientific and Clinical Aspects.* Springer.

Shy, C. M. 1986. Epidemiologic principles and methods for occupational health studies. *Occupational Respiratory Diseases: DHHS (NIOSH) Publication,* 86**,** 103-136.

Silman, A. J. & Hochberg, M. C. 1993. *Epidemiology of the rheumatic diseases*, Oxford University Press.

Silva, F. D., Ramachandran, S. & Chhabra, A. 2023. Glenohumeral osteoarthritis: What the surgeon needs from the radiologist. *Skeletal radiology,* 52**,** 2283-2296.

Sim, J., Lacey, R. J. & Lewis, M. 2006. The impact of workplace risk factors on the occurrence of neck and upper limb pain: a general population study. *BMC Public Health,* 6**,** 234.

Smalley, H. & Edwards, K. 2023. Understanding the burden of chronic back pain: a spatial microsimulation of chronic back pain at small area level across England. *European Spine Journal*, 1-9.

Smith, D. R. & Leggat, P. A. 2004. Musculoskeletal disorders among rural Australian nursing students. *Australian Journal of Rural Health,* 12, 241-245.

Smith, L., Burnet, S. & McNeil, J. 2003. Musculoskeletal manifestations of diabetes mellitus. *British journal of sports medicine,* 37, 30.

Smith, P. M., Chen, C. & Mustard, C. 2009. Differential risk of employment in more physically demanding jobs among a recent cohort of immigrants to Canada. *Injury Prevention,* 15, 252-258.

Smythe, T. & Kuper, H. 2024. The association between disability and all-cause mortality in low-income and middle-income countries: a systematic review and meta-analysis. *The Lancet Global Health,* 12, e756-e770.

Soley-Bori, M., Ashworth, M., Bisquera, A., Dodhia, H., Lynch, R., Wang, Y. & Fox-Rushby, J. 2021. Impact of multimorbidity on healthcare costs and utilisation: a systematic review of the UK literature. *British Journal of General Practice,* 71, e39-e46.

Somathilake, G., Ford, E., Armes, J., Moschoyiannis, S., Collins, M., Francsics, P. & Lemanska, A. 2025. Evaluating the quality of prostate cancer diagnosis recording in CPRD GOLD and CPRD Aurum primary care databases for observational research: A study using linked English electronic health records. *Cancer Epidemiology,* 94, 102715.

Song, A., Cannon, D., Kim, P., Ayers, G. D., Gao, C., Giri, A. & Jain, N. B. 2022. Risk factors for degenerative, symptomatic rotator cuff tears: a case-control study. *Journal of shoulder and elbow surgery,* 31, 806-812.

Sözen, T., Başaran, N. Ç., Tınazlı, M. & Özışık, L. 2018. Musculoskeletal problems in diabetes mellitus. *European journal of rheumatology,* 5, 258.

Speed, C. A. & Crisp, A. J. 2005. Referrals to hospital-based rheumatology and orthopaedic services: seeking direction. *Rheumatology (Oxford),* 44, 469-71.

Squires, G. R., Okouneff, S., Ionescu, M. & Poole, A. R. 2003. The pathobiology of focal lesion development in aging human articular cartilage and molecular matrix changes characteristic of osteoarthritis. *Arthritis & Rheumatism,* 48, 1261-1270.

Stamey, W., Davidson, A. & Jankovic, J. 2008. Shoulder pain: a presenting symptom of Parkinson disease. *JCR: Journal of Clinical Rheumatology,* 14**,** 253-254.

Staniszewska, S., Haywood, K. L., Brett, J. & Tutton, L. 2012. Patient and public involvement in patient-reported outcome measures: evolution not revolution. *The Patient-Patient-Centered Outcomes Research,* 5**,** 79-87.

Staud, R., Craggs, J. G., Robinson, M. E., Perlstein, W. M. & Price, D. D. 2007. Brain activity related to temporal summation of C-fiber evoked pain. *Pain,* 129**,** 130-142.

Stillman, M. J. & Stillman, M. T. 2007. Appropriate use of NSAIDs: considering cardiovascular risk in the elderly. *Geriatrics,* 62**,** 16-21.

Straker, L. M., O'Sullivan, P. B., Smith, A. J. & Perry, M. C. 2009. Relationships between prolonged neck/shoulder pain and sitting spinal posture in male and female adolescents. *Manual Therapy,* 14**,** 321-9.

Strom, B. L. & Kimmel, S. E. 2006. Textbook of pharmacoepidemiology/editors, Brian L. Strom and Stephen E. Kimmel.

Struyf, F. & Meeus, M. 2014. Current evidence on physical therapy in patients with adhesive capsulitis: what are we missing? *Clinical rheumatology,* 33**,** 593-600.

Struyf, F., Lluch, E., Falla, D., Meeus, M., Noten, S. & Nijs, J. 2015. Influence of shoulder pain on muscle function: implications for the assessment and therapy of shoulder disorders. *European journal of applied physiology,* 115**,** 225-234.

Su, Y. C., Chung, C. H., Ke, M. J., Chen, L. C., Chien, W. C. & Wu, Y. T. 2021. Increased risk of shoulder calcific tendinopathy in diabetes mellitus: A nationwide, population-based, matched cohort study. *International Journal of Clinical Practice,* 75**,** e14549.

Sun, J., Li, Y., Liu, L., Jiang, Z. & Liu, G. 2019. Aspirin use and pancreatic cancer risk: A systematic review of observational studies. *Medicine,* 98.

Svendsen, S. W., Dalbøge, A., Andersen, J. H., Thomsen, J. F. & Frost, P. 2013. Risk of surgery for subacromial impingement syndrome in relation to neck-shoulder complaints and occupational biomechanical exposures: A longitudinal study. *Scandinavian Journal of Work, Environment and Health,* 39**,** 568-577.

Swain, S., Coupland, C., Mallen, C., Kuo, C. F., Sarmanova, A., Bierma-Zeinstra, S. M., Englund, M., Prieto-Alhambra, D., Doherty, M. & Zhang, W. 2021. Temporal relationship between osteoarthritis and

comorbidities: a combined case control and cohort study in the UK primary care setting. *Rheumatology,* 60**,** 4327-4339.

Swain, S., Coupland, C., Sarmanova, A., Kuo, C. F., Mallen, C., Doherty, M. & Zhang, W. 2023. Healthcare utilisation and mortality in people with osteoarthritis in the UK: findings from a national primary care database. *British Journal of General Practice,* 73**,** e615-e622.

Swain, S., Coupland, C., Strauss, V., Mallen, C., Kuo, C., Sarmanova, A., Bierma-Zeinstra, S., Englund, M., Prieto-Alhambra, D. & Doherty, M. 2022. Clustering of comorbidities and associated outcomes in people with osteoarthritis-A UK Clinical Practice Research Datalink study. *Osteoarthritis and Cartilage,* 30**,** 702-713.

Swain, S., Sarmanova, A., Mallen, C., Kuo, C. F., Coupland, C., Doherty, M. & Zhang, W. 2020. Trends in incidence and prevalence of osteoarthritis in the United Kingdom: findings from the Clinical Practice Research Datalink (CPRD). *Osteoarthritis and cartilage,* 28**,** 792-801.

Tagliaferri, S. D., Fitzgibbon, B. M., Owen, P. J., Miller, C. T., Bowe, S. J. & Belavy, D. L. 2022. Brain structure, psychosocial, and physical health in acute and chronic back pain: a UK Biobank study. *Pain,* 163**,** 1277-1290.

Takahashi, A., Kitamura, K., Watanabe, Y., Kobayashi, R., Saito, T., Takachi, R., Kabasawa, K., Oshiki, R., Tsugane, S. & Iki, M. 2018. Epidemiological profiles of chronic low back and knee pain in middle-aged and elderly Japanese from the Murakami cohort. *Journal of pain research***,** 3161-3169.

Takala, J. 1982. Rheumatic symptoms in the middle-aged population in southwestern Finland. *Scand J Rheumatol,* 47**,** 15-29.

Tangtrakulwanich, B. & Kapkird, A. 2012. Analyses of possible risk factors for subacromial impingement syndrome. *World Journal of Orthopedics,* 3**,** 5-9.

Tashjian, R. Z. 2012. Epidemiology, natural history, and indications for treatment of rotator cuff tears. *Clin Sports Med,* 31**,** 589-604.

Tekavec, E., Jöud, A., Rittner, R., Mikoczy, Z., Nordander, C., Petersson, I. F. & Englund, M. 2012. Population-based consultation patterns in patients with shoulder pain diagnoses. *BMC Musculoskeletal Disorders,* 13.

Tekeoglu, I., Ediz, L., Hiz, O., Toprak, M., Yazmalar, L. & Karaaslan, G. 2013. The relationship between shoulder impingement syndrome and sleep quality. *European Review for Medical & Pharmacological Sciences,* 17**,** 370-4.

Tempelhof, S., Rupp, S. & Seil, R. 1999. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. *J Shoulder Elbow Surg,* 8**,** 296-9.

Tennent, T. D., Beach, W. R. & Meyers, J. F. 2003. A review of the special tests associated with shoulder examination: part I: the Rotator Cuff tests. *The American journal of sports medicine,* 31**,** 154-160.

Therneau, T. M. & Lumley, T. 2015. Package 'survival'. *R Top Doc,* 128**,** 28-33.

Thomas, S. J., McDougall, C., Brown, I. D., Jaberoo, M. C., Stearns, A., Ashraf, R., Fisher, M. & Kelly, I. G. 2007. Prevalence of symptoms and signs of shoulder problems in people with diabetes mellitus. *Journal of Shoulder & Elbow Surgery,* 16**,** 748-51.

Thomsen, J. L. & Parner, E. T. 2006. Methods for analysing recurrent events in health care data. Examples from admissions in Ebeltoft Health Promotion Project. *Family practice,* 23**,** 407-413.

Titchener, A. G., White, J. J., Hinchliffe, S. R., Tambe, A. A., Hubbard, R. B. & Clark, D. I. 2014. Comorbidities in rotator cuff disease: a case-control study. *Journal of shoulder and elbow surgery,* 23**,** 1282-1288.

Toprak, M. & Erden, M. 2019. Sleep quality, pain, anxiety, depression and quality of life in patients with frozen shoulder1. *Journal of Back & Musculoskeletal Rehabilitation,* 32**,** 287-291.

Torrance, N., Elliott, A. M., Lee, A. J. & Smith, B. H. 2010. Severe chronic pain is associated with increased 10 year mortality. A cohort record linkage study. *European journal of pain,* 14**,** 380-386.

Tran, G., Fascia, D., Askew, J., Cabry, F., Talbot, C., Copas, D. & Conaghan, P. G. 2022. The prevalence of glenohumeral joint osteoarthritis in a primary care shoulder pain population referred for radiographs. *Rheumatology,* 61**,** 1290-1292.

Treede, R.-D., Rief, W., Barke, A., Aziz, Q., Bennett, M. I., Benoliel, R., Cohen, M., Evers, S., Finnerup, N. B. & First, M. B. 2019. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *pain,* 160**,** 19-27.

Trelle, S., Reichenbach, S., Wandel, S., Hildebrand, P., Tschannen, B., Villiger, P. M., Egger, M. & Jüni, P. 2011. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *Bmj,* 342.

Tu, Y., Cao, J., Bi, Y. & Hu, L. 2021. Magnetic resonance imaging for chronic pain: diagnosis, manipulation, and biomarkers. *Science China Life Sciences,* 64**,** 879-896.

Uhthoff, H. K. & Loehr, J. W. 1997. Calcific tendinopathy of the rotator cuff: pathogenesis, diagnosis, and management. *JAAOS-Journal of the American Academy of Orthopaedic Surgeons,* 5**,** 183-191.

UK Government. 2021. *List of ethnic groups* [Online]. [Accessed 6 May 2026 2025].

Urwin, M., Symmons, D., Allison, T., Brammah, T., Busby, H., Roxby, M., Simmons, A. & Williams, G. 1998. 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,* 57**,** 649-55.

Valderas, J. M., Starfield, B., Sibbald, B., Salisbury, C. & Roland, M. 2009. Defining comorbidity: implications for understanding health and health services. *The Annals of Family Medicine,* 7**,** 357-363.

Van Buuren, S. & Groothuis-Oudshoorn, K. 2011. mice: Multivariate imputation by chained equations in R. *Journal of statistical software,* 45**,** 1-67.

Van Buuren, S. & Oudshoorn, C. 2005. MICE: Multiva riate imputation by chained equations. R package 1.14 version. h ttp. *web. inter. nl. net/users/S. van. Buuren/mi/hmtl/mice. htm*.

van den Heuvel, S. G., Ijmker, S., Blatter, B. M. & de Korte, E. M. 2007. Loss of productivity due to neck/shoulder symptoms and hand/arm symptoms: results from the PROMO-Study. *Journal of Occupational Rehabilitation,* 17**,** 370-382.

van der Windt, D. A., Burke, D. L., Babatunde, O., Hattle, M., McRobert, C., Littlewood, C., Wynne-Jones, G., Chesterton, L., van der Heijden, G., Winters, J. C., Rhon, D. I., Bennell, K., Roddy, E., Heneghan, C., Beard, D., Rees, J. L. & Riley, R. D. 2019. Predictors of the effects of treatment for shoulder pain: protocol of an individual participant data meta-analysis. *Diagn Progn Res,* 3**,** 15.

van der Windt, D. A., Koes, B. W., Boeke, A. J., Devillé, W., De Jong, B. A. & Bouter, L. M. 1996. Shoulder disorders in general practice: prognostic indicators of outcome. *Br J Gen Pract,* 46**,** 519-23.

van der Windt, D. A., Koes, B. W., de Jong, B. A. & Bouter, L. M. 1995. Shoulder disorders in general practice: incidence, patient characteristics, and management. *Annals of the rheumatic diseases,* 54**,** 959-964.

van der Windt, D. A., Thomas, E., Pope, D. P., de Winter, A. F., Macfarlane, G. J., Bouter, L. M. & Silman, A. J. 2000. Occupational risk factors for shoulder pain: a systematic review. *Occupational & Environmental Medicine,* 57**,** 433-42.

van Enst, W. A., Ochodo, E., Scholten, R. J., Hooft, L. & Leeflang, M. M. 2014. Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study. *BMC Med Res Methodol,* 14**,** 70.

Varacallo, M., El Bitar, Y. & Mair, S. D. 2021. Rotator Cuff Syndrome. *StatPearls.* Treasure Island (FL): StatPearls Publishing

Vaz, S., Soyer, J., Pries, P. & Clarac, J. 2000. Subacromial impingement: influence of coracoacromial arch geometry on shoulder function. *Joint Bone Spine,* 67**,** 305-309.

Versus Arthritis 2023. The state of musculoskeletal health 2023: arthritis and other

Versus Arthritis. 2017. *Chronic Pain in England: Unseen, unequal, unfair* [Online]. Versus Arthritis. Available: https://www.versusarthritis.org/about-arthritis/data-and-statistics/chronic-pain-in-england/ [Accessed 2024].

Viester, L., Verhagen, E. A., Hengel, K. M. O., Koppes, L. L., van der Beek, A. J. & Bongers, P. M. 2013. The relation between body mass index and musculoskeletal symptoms in the working population. *BMC musculoskeletal disorders,* 14**,** 1-9.

Vincent, K. & Tracey, I. 2008. Hormones and their interaction with the pain experience. *Reviews in pain,* 2**,** 20-24.

Virta, L., Joranger, P., Brox, J. I. & Eriksson, R. 2012. Costs of shoulder pain and resource use in primary health care: a cost-of-illness study in Sweden. *BMC musculoskeletal disorders,* 13**,** 1-11.

Visser, A. W., Ioan-Facsinay, A., de Mutsert, R., Widya, R. L., Loef, M., de Roos, A., le Cessie, S., den Heijer, M., Rosendaal, F. R. & Kloppenburg, M. 2014. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study. *Arthritis research & therapy,* 16**,** 1-7.

Visser, A., De Mutsert, R., Le Cessie, S., Den Heijer, M., Rosendaal, F. & Kloppenburg, M. 2015. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. *Annals of the rheumatic diseases,* 74**,** 1842-1847.

Visser, B. & van Dieën, J. H. 2006. Pathophysiology of upper extremity muscle disorders. *Journal of electromyography and kinesiology,* 16**,** 1-16.

Vogt, M. T., Simonsick, E. M., Harris, T. B., Nevitt, M. C., Kang, J. D., Rubin, S. M., Kritchevsky, S. B. & Newman, A. B. 2003. Neck and shoulder pain in 70- to 79-year-old men and women: findings from the Health, Aging and Body Composition Study. *Spine J,* 3**,** 435-41.

Wærsted, M., Koch, M. & Veiersted, K. B. 2020. Work above shoulder level and shoulder complaints: a systematic review. *International Archives of Occupational and Environmental Health,* 93**,** 925-954.

Wah, W., Berecki-Gisolf, J. & Walker-Bone, K. 2024. In-hospital complications of work-related musculoskeletal injuries. *Injury,* 55**,** 111211.

Walankar, P. P., Panhale, V. P. & Patil, M. M. 2020. Psychosocial factors, disability and quality of life in chronic shoulder pain patients with central sensitization. *Health psychology research,* 8.

Walker-Bone, K., Palmer, K. T., Reading, I., Coggon, D. & Cooper, C. 2004. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. *Arthritis Care and Research,* 51**,** 642-651.

Walsh, N., Halls, S., Thomas, R., Berry, A., Liddiard, C., Cupples, M. E., Gage, H., Jackson, D., Cramp, F. & Stott, H. 2024. First contact physiotherapy: an evaluation of clinical effectiveness and costs. *British Journal of General Practice*.

Wang, H. K., Lin, J. J., Pan, S. L. & Wang, T. G. 2005. Sonographic evaluations in elite college baseball athletes. *Scandinavian journal of medicine & science in sports,* 15**,** 29-35.

Wang, K., Ho, V., Beh, P. S., Weber, A. B., Hunter-Smith, D. J. & Smith, K. M. 2013. Risk factors in idiopathic adhesive capsulitis: A case control study. *Journal of Shoulder and Elbow Surgery,* 22**,** e24-e29.

Wearing, S. C., Hennig, E. M., Byrne, N. M., Steele, J. R. & Hills, A. P. 2006. Musculoskeletal disorders associated with obesity: a biomechanical perspective. *Obesity reviews,* 7**,** 239-250.

Webb, R., Brammah, T., Lunt, M., Urwin, M., Allison, T. & Symmons, D. 2003. Prevalence and predictors of intense, chronic, and disabling neck and back pain in the UK general population. *Spine,* 28**,** 1195-1202.

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. & Tugwell, P. 2000. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Oxford.

Welsh, V., Mason, K., Bailey, J., Bajpai, R., Jordan, K., Mallen, C. D. & Burton, C. 2023. Trends in musculoskeletal consultations and prescribing: an electronic primary care records study. *British Journal of General Practice*.

Wetherell, J. L., Afari, N., Rutledge, T., Sorrell, J. T., Stoddard, J. A., Petkus, A. J., Solomon, B. C., Lehman, D. H., Liu, L. & Lang, A. J. 2011. A randomized, controlled trial of acceptance and commitment

therapy and cognitive-behavioral therapy for chronic pain. *Pain,* 152**,** 2098-2107.

Wheeler, P. C. 2022. Nearly half of patients with chronic tendinopathy may have a neuropathic pain component, with significant differences seen between different tendon sites: a prospective cohort of more than 300 patients. *BMJ open sport & exercise medicine,* 8**,** e001297.

White, D., Choi, H., Peloquin, C., Zhu, Y. & Zhang, Y. 2011. Secular trend of adhesive capsulitis. *Arthritis care & research,* 63**,** 1571-5.

White, J., Titchener, A., Fakis, A., Tambe, A., Hubbard, R. & Clark, D. 2014. An epidemiological study of rotator cuff pathology using The Health Improvement Network database. *The bone & joint journal,* 96**,** 350-353.

Whitehead, M., Bambra, C., Barr, B., Bowles, J., Caulfield, R., Doran, T., Harrison, D., Lynch, A., Pleasant, S. & Weldon, J. 2014. Due North: report of the inquiry on health equity for the North.

Wiley, A. 1991. Arthroscopic appearance of frozen shoulder. *Arthroscopy: The Journal of Arthroscopic & Related Surgery,* 7**,** 138-143.

Wilkinson, R. 2010. *The Spirit Level: Why equality is better for everyone*, Penguin.

Wilson, J. M., Colebaugh, C. A., Flowers, K. M., Edwards, R. R., Partridge, A. H., Dominici, L. S. & Schreiber, K. L. 2022. Early postoperative psychological distress as a mediator of subsequent persistent postsurgical pain outcomes among younger breast cancer patients. *Breast cancer research and treatment,* 196**,** 363-370.

Wilson, K. G., Eriksson, M. Y., Joyce, L., Mikail, S. F. & Emery, P. C. 2002. Major depression and insomnia in chronic pain. *The Clinical journal of pain,* 18**,** 77-83.

Wolf, A., Dedman, D., Campbell, J., Booth, H., Lunn, D., Chapman, J. & Myles, P. 2019. Data resource profile: clinical practice research Datalink (CPRD) aurum. *International journal of epidemiology,* 48**,** 1740-1740g.

Wolf, J. M., Cameron, K. L. & Owens, B. D. 2011. Impact of joint laxity and hypermobility on the musculoskeletal system. *Journal of the American Academy of Orthopaedic Surgeons,* 19**,** 463-71.

Woo, S. 2000. Anatomy, biology, and biomechanics of tendon and ligament. *Orthopaedic basic science: biology and blamechanics of the musculoskeletal system***,** 582-616.

Wood, G., Neilson, J., Cottrell, E. & Hoole, S. P. 2023. Osteoarthritis in people over 16: diagnosis and management—updated summary of NICE guidance. *bmj,* 380.

Woodward, T. W. & Best, T. M. 2000. The painful shoulder: part I. Clinical evaluation. *American family physician,* 61**,** 3079-3088.

Woolf, A. D. & Pfleger, B. 2003. Burden of major musculoskeletal conditions. *Bulletin of the world health organization,* 81**,** 646-656.

Woolf, A. D. 2012. Bone and Joint Decade report: moving together beyond the decade. Preface. *Best Pract Res Clin Rheumatol,* 26**,** 167-8.

Worland, R., Lee, D., Orozco, C., SozaRex, F. & Keenan, J. 2003. Correlation of age, acromial morphology, and rotator cuff tear pathology diagnosed by ultrasound in asymptomatic patients. *Journal of the Southern Orthopaedic Association,* 12**,** 23-26.

World Health Organization 2009. Global health risks: mortality and burden of disease attributable to selected major risks. *World Health Organization*.

Wright, A. R., Shi, X. A., Busby-Whitehead, J., Jordan, J. M. & Nelson, A. E. 2015. The Prevalence of Neck and Shoulder Symptoms and Associations with Comorbidities and Disability: The Johnston County Osteoarthritis Project. *Myopain,* 23**,** 34-44.

Wu, W.-T., Hsu, P.-C., Han, D.-S., Chang, H.-C., Huang, K.-C. & Chang, K.-V. 2021. Sarcopenia Is Associated With Increased Risks of Rotator Cuff Tendon Diseases Among Community-Dwelling Elders: A Cross-Sectional Quantitative Ultrasound Study. *Frontiers in Medicine,* 8**,** 630009.

Wyatt, L. H. & Ferrance, R. J. 2006. The musculoskeletal effects of diabetes mellitus. *The Journal of the Canadian Chiropractic Association,* 50**,** 43.

Xu, F., Xie, N., Ji, D., Gao, Q. & Liu, C. 2024. Risk Factors Analysis and Prediction of Rotator Cuff Tears: A Retrospective Study. *Annali Italiani Di Chirurgia,* 95**,** 708-714.

Xu, L., Kanasaki, K., Kitada, M. & Koya, D. 2012. Diabetic angiopathy and angiogenic defects. *Fibrogenesis & tissue repair,* 5**,** 1-9.

Yang, S., Kim, T. U., Kim, D. H. & Chang, M. C. 2021. Understanding the physical examination of the shoulder: a narrative review. *Annals of palliative medicine,* 10**,** 2293303-2292303.

Yanik, E. L., Keener, J. D., Stevens, M. J., Walker-Bone, K. E., Dale, A. M., Ma, Y., Colditz, G. A., Wright, R. W., Saccone, N. L. & Jain, N. B. 2023. Occupational demands associated with rotator cuff

disease surgery in the UK Biobank. *Scandinavian Journal of Work, Environment & Health,* 49**,** 53.

Yenipınar, A., Koç, Ş., Çanga, D. & Kaya, F. 2019. Determining sample size in logistic regression with G-Power. *Black Sea Journal of Engineering and Science,* 2**,** 16-22.

Yip, M., Francis, A. M., Roberts, T., Rokito, A., Zuckerman, J. D. & Virk, M. S. 2018. Treatment of Adhesive Capsulitis of the Shoulder: A Critical Analysis Review. *JBJS Rev,* 6**,** e5.

Yu, D., Peat, G., Jordan, K. P., Bailey, J., Prieto-Alhambra, D., Robinson, D. E., Strauss, V. Y., Walker-Bone, K., Silman, A. & Mamas, M. 2021. Estimating the population health burden of musculoskeletal conditions using primary care electronic health records. *Rheumatology,* 60**,** 4832-4843.

Zhao, J., Luo, M., Liang, G., Pan, J., Han, Y., Zeng, L., Yang, W. & Liu, J. 2022. What factors are associated with symptomatic rotator cuff tears: a meta-analysis. *Clinical Orthopaedics and Related Research®,* 480**,** 96-105.

Zhao, W., Zhao, L., Chang, X., Lu, X. & Tu, Y. 2023. Elevated dementia risk, cognitive decline, and hippocampal atrophy in multisite chronic pain. *Proceedings of the National Academy of Sciences of the United States of America,* 120**,** e2215192120.

Zheng, Y.-N., Liu, H., Chen, P.-J. & Wang, X.-Q. 2024. Association of persistent musculoskeletal pain with dementia risk score in adults aged 45 years or older: the China health and retirement longitudinal study. *Brain, Behavior, and Immunity,* 116**,** 185-192.

Zreik, N. H., Malik, R. A. & Charalambous, C. P. 2016. Adhesive capsulitis of the shoulder and diabetes: a meta-analysis of prevalence. *Muscles, Ligaments & Tendons Journal (MLTJ),* 6**,** 26-34.

Appendices

9.1 Appendix 1. Published conference abstracts

PP032

Epidemiology

Epidemiology of chronic shoulder pain in people aged 40 or older – a systematic review and meta-analysis of observational studies

Nouf Alotaibi, Subhashisa Swain, Monirah Shuaib, Michael Doherty, Weiya Zhang, Michelle Hall

Academic Rheumatology department, The University of Nottingham, Clinical Sciences Building City Hospital, Nottingham, UK; Medical Sciences Division, The University of Oxford, Oxford,UK; School of Health Sciences, Queen's Medical Centre Campus, The University of Nottingham, Nottingham,UK

BACKGROUND: Chronic shoulder pain (CSP) is a common musculoskeletal complaint. However, variations exist in reported prevalence and populations and reported risk factors. It affects between 5% and 47% of the adult population annually worldwide. In the United Kingdom (UK), it is estimated that 2.4% of people aged between 18 and 60 years old consulted their general practitioners (GPs) for shoulder pain in 2005. In Finland, the prevalence of shoulder pain was approximately 17% among adults aged between 40-64 years.

AIMS: (1) Determine the pooled prevalence and incidence of CSP in people aged > 40 years; (2) explore the risk factors and comorbidities associated with CSP; and (3) examine the prevalence of CSP according to specific populations and specific diagnoses of shoulder pain.

METHODS: Medline (OVID), Scopus and CINAHL (EBSCO) and Google Scholar were searched from their inception to Sep 2021 for observational studies of adults aged 40 or more with chronic shoulder pain. Quality was assessed using the Newcastle Ottawa Scale (NOS). Data were extracted on prevalence and incidence. The secondary outcome included potential risk factors and associated comorbidities. Meta-analysis was conducted using random-effects model where sufficient data was available, and effect sizes and

variances were calculated accordingly. Heterogeneity was examined using I2 test and potential reasons explored.

RESULTS: Of 5203 studies retrieved, 27 met the inclusion criteria. Studies consisted of 19 cross-sectional, 4 case-control, and 4 cohort studies (2 retrospective and 2 prospective cohort studies). The quality analysis was conducted by a single reviewer and validated by a second reviewer. Of the 27 studies, 24 had a high quality, and 3 had moderate quality.

Overall the pooled prevalence of CSP was 27% (95% Confidence interval (CI) 19, 34). The prevalence in the general population was (19%, 95%CI 13, 25). and was higher in people with diabetes (35%, 95%CI 0, 85), and those with physically demanding jobs (34%, 95% CI 22, 46). Common risk factors identified were age (odds ratio (OR) 2.34, 95%CI 1.27, 4.30), female sex (OR 2.10, 95%CI 1.16, 3.80), lower educational level (OR 1.80, 95%CI 1.35, 2.38), and manual work (OR 3.55, 95%CI 1.68, 7.49), and pain in other joints was also significantly associated (OR 2.73, 95%CI 1.73, 4.30).

CONCLUSIONS: Over a quarter of people aged 40 years old or more have chronic shoulder pain worldwide. The major risk factors include age, female sex, lower education, manual worker and pain elsewhere. The results are main derived from cross-sectional/case control studies. There are limited prospective studies and they are quite small. Therefore larger prospective cohort studies are needed in the future to examine risk factors and comorbidities associated with shoulder pain.

This systematic review will help us understand the burden of chronic shoulder pain, and the population at risk, in order to inform the planning of effective management of shoulder pain in primary care

Keywords: shoulder pain, prevalence, incidence, risk factors, associations

Abstract published in Annals of the rheumatic diseases journal (EULAR European Congress of Rheumatology 2024)

HPR Epidemiology and public health

POS1458-HPR

TRENDS OF PREVALENCE AND INCIDENCE OF CHRONIC SHOULDER PAIN IN THE UNITED KINGDOM: FINDINGS FROM THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

Keywords: Pain, Epidemiology

N. Alotaibi[1], S. Swain[2,3], Y. Vinogradova[4], B. Iyen[5], M. Doherty[6], W. Zhang[1], M. Hall[7]. [1]*University of Nottingham, School of Medicine, Academic Rheumatology, Pain Centre Versus Arthritis, Nottingham, United Kingdom*; [2]*University of Oxford, Primary Care Health Sciences, Medical Sciences Division, Oxford, United Kingdom*; [3]*Keele University, School of Medicine, Center for Musculoskeletal Health Research, Keele, United Kingdom*; [4]*University of Nottingham, Faculty of Medicine & Health Sciences, Division of Primary Care, Nottingham, United Kingdom*; [5]*University of Nottingham, School of Medicine & Health Sciences, Division of Primary Care, Nottingham, United Kingdom*; [6]*University of Nottingham, School of Medicine, Academic Rheumatology, Pain Centre Versus Arthritis, Nottingham, United Kingdom*; [7]*University of Nottingham, School of Health Sciences, Queen's Medical Centre Campus, Nottingham, United Kingdom*

Background: Chronic shoulder pain (CSP) is a common musculoskeletal condition that can lead to sleeping difficulties, work disability and functional limitations in daily activities [1,2]. There is a gap in the evidence on the current prevalence and incidence of CSP in the UK, any variation that may exist between regions, and whether the occurrence of shoulder pain has changed in the past 20 years.

Objectives: To investigate the prevalence and incidence of CSP in the UK in the year 2019 by age, sex and geographical regions and to examine the trends of prevalence and incidence of CSP from 2000 to 2020.

Methods: We conducted cross-sectional and cohort studies using a large nationally representative primary care database (CPRD) to examine the prevalence and incidence of CSP in people in the UK aged 18 years and above. CSP was defined as having at least 2 General Practitioner (GP) consultations for shoulder pain within a 6 month period. We excluded severe acute trauma, including fracture, in the 6 months prior to the first consultation and shoulder surgery within the previous 3 months. We used the data in 2019 (prior to the COVID-19 pandemic) to estimate the current prevalence and incidence of shoulder pain UK. The trend of prevalence and incidence was examined using Joinpoint regression analysis. Prevalence and incidence for each year from 2000 until 2020 was standardised according to the age and sex structure of the 2019 CPRD population. Additionally, we examined the prevalence of shoulder pain using different codes used by GPs.

Results: The prevalence of CSP in 2019 in 11,092,332 eligible adults was 1.91% (95%CI 1.91-1.92%). It increased with age and was higher in women (2.04 %,95%CI 2.03 -2.05%) than men (1.68%, 95%CI 1.67-1.69%) (Figure 1). There was a total of 11,164,066 person years of follow-up in 2019 of which 13,514 incident cases of CSP were identified, giving an incidence of 1.2 (95%CI 1.19-1.23) per 1,000 person-years. The incidence was higher in women than men, being 1.35 (95%CI 1.32-1.38) and 1.06 (95%CI 1.04-1.09) per 1,000 person-years, respectively (Figure 1). The age and sex standardised prevalence of CSP increased over the study period from 0.42% (95%CI 0.42-0.43) in 2000 to 1.83% (95%CI 1.83-1.84) in 2020. The age and sex-standardised incidence also increased from 0.88 (95%CI 0.86-0.9) in 2000 to 2.00 (95%CI 1.96-2.00) in 2011, then subsequently decreased. Shoulder pain and rotator cuff syndrome were most commonly coded by GPs with prevalence of 0.75% (95% CI 0.75-0.76) and 0.49% (95% CI 0.49-0.50), respectively. The prevalence and incidence of CSP varied across regions, with Yorkshire and Humber having the highest, and Northern Ireland having the lowest (Figure 2).

Conclusion: About one in fifty adults have chronic shoulder pain in the UK. The risk increases with age and women are at higher risk than men. While the prevalence increased gradually, the incidence increased until 2011, then decreased in the past 20 years. Some regional variations have been observed but the reason needs further investigation. This study provides insight into the burden of CSP in the UK which may inform primary health-care utilisation.

REFERENCES:

[1] Noten, S., Struyf, F., Lluch, E., D'Hoore, M., Van Looveren, E. & Meeus, M. 2017. Central Pain Processing in Patients with Shoulder Pain: A Review of the Literature. Pain Pract, 17, 267-280.

[2] jade, C. D., Porgo, T. V., Zomahoun, H. T. V., Perrault-Sullivan, G. & Dionne, C. E. 2020. Incidence of shoulder pain in 40 years old and over and associated factors: A systematic review. Eur J Pain, 24, 39-50.

Acknowledgements: This study was sponsored by the University of Nottingham and the Kuwait Cultural Office. We thank all the people who participated in this work.

Disclosure of Interests: None declared.

DOI: 10.1136/annrheumdis-2024-eular.1411

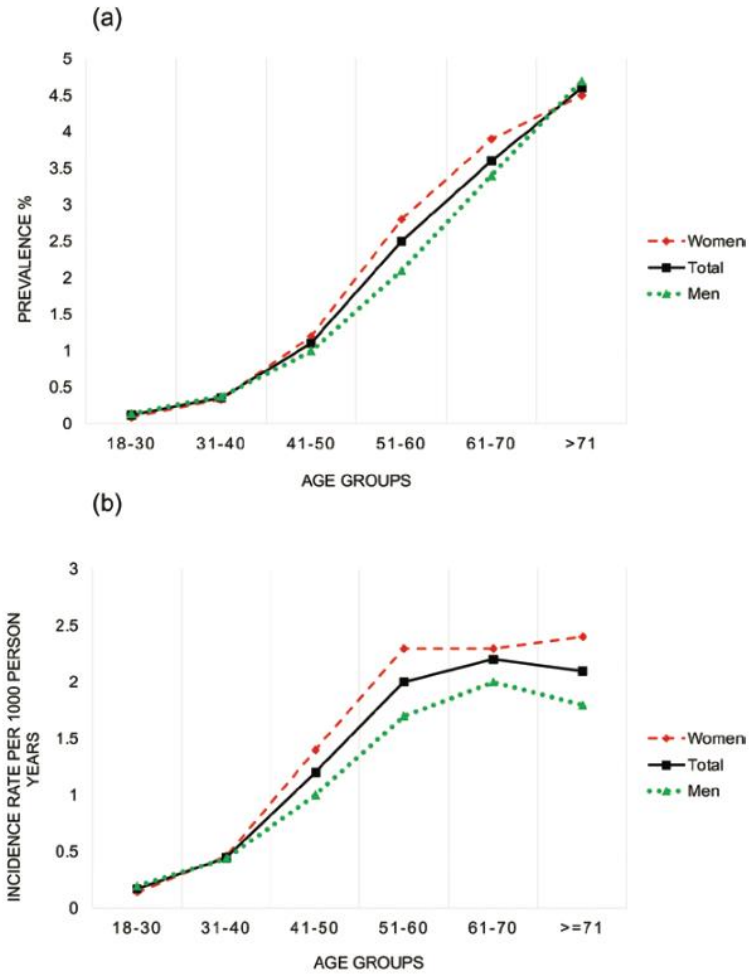


Figure 1. Age-specific (a) prevalence and (b) incidence of CSP in the year 2019 (Red - Women; green - Men; Black - Total)

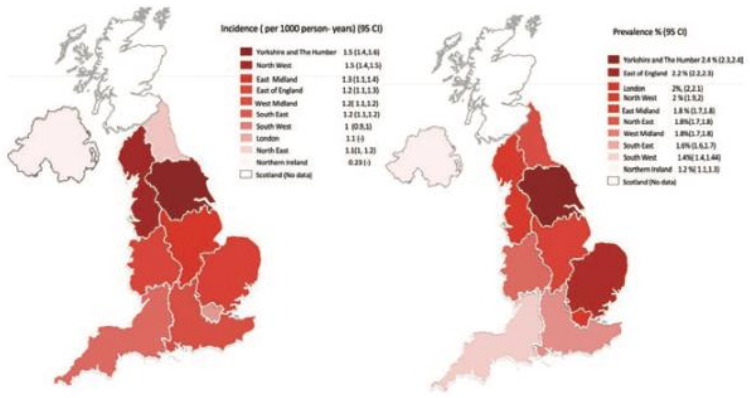


Figure 2. Age and sex standardised prevalence and incidence of CSP for the year 2019 across UK regions

9.2 Appendix 2. Search strategy for systematic literature review

Table 9-1 Search strategy for the systematic review

P	I	C	O	S’
Shoulder			Incidence	Cohort
OR			OR	Or
glenohumeral			Prevalence	Case-control
OR			OR	Or
acromioclavicular			Risk factors	Cross-sectional
AND			OR	
Chronic pain			epidemiology	
OR				
Pain$				
OR				
Bursitis				
OR				
Osteoarthritis				
OR				
Periarthritis				
OR				
Subacromial impingement syndrome				
OR				
Subacromial pain				
OR				
Shoulder impingement				
OR				
Shoulder impingement syndrome				
OR				
Tendinopathy				
OR				
Tendinosis				
OR				
Tendinitis				
OR				
RC tear				
OR				
Frozen shoulder				
OR				
Adhesive capsulitis				

These terms combined with (AND)

Table 9-2 Detailed search strategy for the systematic review

Database	Search strategy	Articles identified
Medline (Ovid)	1. Shoulder/ or shoulder.mp. 2. glenohumeral.mp. 3. Acromioclavicular Joint/ or acromioclavicular.mp. 4. chronic pain.mp. or Chronic Pain/ 5. Pain/ or Shoulder Pain/ or Chronic Pain/ 6. Osteoarthritis.mp. or Osteoarthritis/ 7. periarthritis.mp. or Periarthritis/ 8. dysfunction.mp. 9. subacromial pain.mp. 10. Shoulder Impingement Syndrome/ or impingement.mp. 11. Tendinopathy/ or tendinopathy.mp. 12. RC tear.mp. or RC Injuries/ 13. adhesive capsulitis.mp. or Bursitis/ 14. frozen.mp. 15. syndrom.mp. 16. Prevalence/ or prevalence.mp. 17. incidence.mp. or Incidence/ 18. Epidemiology/ or epidemiology.mp. 19. risk factors.mp. or Risk Factors/ 20. 1 or 2 or 3 21. 16 or 17 or 18 or 19 22. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 23. 20 and 21 and 22 24. case-control.mp. 25. cohort.mp. 26. cross-sectional.mp. 27. 24 or 25 or 26 28. 23 and 27	1010
CINHAL (EBSCO)	S32 (((S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28) AND (S16 OR S22)) AND (S17 AND S29 AND S30)) AND (S21 AND S31) S31 ((S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28) AND (S16 OR S22)) AND (S17 AND S29 AND S30) S30 (S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28) AND (S16 OR S22) S29 S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 S28 "Bursitis" S27 "Tendinitis" S26 "Tendinosis" S25 "Shoulder impingement syndrome" S24 "Shoulder impingement" S23 "Subacromial impingement syndrome" S22 "RC" S21 S18 OR S19 OR S20 S20 "case control" S19 "cross sectional" S18 "cohort" S17 S12 OR S13 OR S14 OR S15 S16 S1 OR S2 OR S3 S15 "epidemiology" S14 "risk factors" S13 "incidence" S12 "prevalence" S11 "periarthritis" S10 "subacromial pain"	643

	S9	"tendinopathy"	
	S8	"RC tear"	
	S7	"osteoarthritis"	
	S6	"adhesive capsulitis"	
	S5	(MH "Chronic Pain") OR (MH "Pain") OR "pain*"	
	S4	"chronic pain"	
	S3	"acromioclavicular"	
	S2	"glenohumeral"	
	S1	"shoulder"	
Scopus	Shoulder OR glenohumeral OR acromioclavicular AND chronic AND pain OR shoulder AND pain OR pain$ OR osteoarthritis ORperiarthitis OR frozen AND shoulder OR adhesive AND capsulitis OR rotator AND cuff AND tear OR subacromial AND pain OR shoulder AND impingement AND syndrome OR shoulder AND impingement OR subacromial AND impingement AND syndromeOR tendinopathy OR tendinitis OR tendinosis OR bursitis AND incidence OR prevalence OR risk AND factors OR epidemiology AND case- AND control OR cross-sectional OR cohort		1649
EMBASE	1.	shoulder.mp. or shoulder/	1915
	2.	glenohumeral.mp.	
	3.	acromioclavicular.mp.	
	4.	chronic pain.mp. or chronic pain/	
	5.	pain/ or chronic pain/ or pain$.mp.	
	6.	osteoarthritis.mp. or osteoarthritis/	
	7.	RC tear.mp. or RC rupture/	
	8.	tendinopathy.mp.	
	9.	subacromial pain.mp.	
	10.	prevalence.mp. or prevalence/	
	11.	incidence.mp. or incidence/	
	12.	risk factors.mp. or risk factor/	
	13.	epidemiology.mp. or epidemiology/	
	14.	periarthritis/ or Periarthritis.mp.	
	15.	cohort.mp.	
	16.	case-control.mp.	
	17.	cross-sectional.mp.	
	18.	1 or 2 or 3	
	19.	10 or 11 or 12 or 13	
	20.	15 or 16 or 17	
	21.	adhesive capsulitis.mp.	
	22.	frozen shoulder.mp. or frozen shoulder/	
	23.	tendinitis/ or tendinitis.mp.	
	24.	Tendinosis.mp. or tendinitis/	
	25.	subacromial impingement syndrome.mp. or shoulder impingement syndrome/	
	26.	shoulder impingement.mp. or shoulder impingement syndrome/	
	27.	Shoulder impingement syndrome.mp. or shoulder impingement syndrome/	
	28.	4 or 5 or 6 or 7 or 8 or 9 or 14 or 21 or 22 or 23 or 24 or 25 or 26 or 27	
	29.	18 and 28	
	30.	19 and 29	
	31.	20 and 30	
	32.	Bursitis.mp. or bursitis/	
	33.	4 or 5 or 6 or 7 or 8 or 9 or 14 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 32	
	34.	18 and 19 and 33	

9.3 Appendix 3. R codes for meta-analysis

R package was used for data analysis.

```
Library (meta)
Library (metafor)
Library (metadat)
```

Inverse variance meta-analytical methods involve computing an intervention effect estimate and its standard error was calculated for each study.

Meta-analysis for prevalence

```
metaprop_results <- metaprop(event=n, n= Total,studlab = Author, data =Total_prevalence)

metaforest<-forest(metaprop_results, xlim=c(0,1))

forest(metaprop_results, xlim=c(0,1),leftlabs = c("Author", "cases", "Total"),Rightlabs = c("prevalence"))

pdf (file = "prevalnecforest.pdf", width = 8, height = 7)
forest.meta(metaprop_results,  leftlabs = c("Author", "cases", "Total"),xlim=c(0,1),Rightlabs = c("prevalence"))

dev.off()
```

Meta-analysis for risk factors and comorbidities

To calculate SE for log odds ratio:

```
female_sex_unadjusted$seTE <- (log(female_sex_unadjusted$Upper) - log(female_sex_unadjusted$OR))/1.96
```

To perfom the meta-analysis for odds ratio:

```
result <- metagen(TE = female_sex_unadjusted$TE,seTE = female_sex_unadjusted$seTE,sm = "OR", method.tau = "PM", studlab = female_sex_unadjusted$Author,fixed = FALSE,random = TRUE,  title = "Female sex")

forest.meta(result, leftlabs = c("Author", "log OR", "SE(log OR)"))
pdf (file = "female_forest.pdf",width = 8, height = 7)
forest.meta(result)
```

dev.off()

Met-analysis for odds ratio if the n. of events in cases and control are present

test_result3 <- metabin(event.e = 43,event.c = 20,n.e = 66,n.c = 49,sm = "OR")
forest.meta(test_result3)

Arguments:
event.e: Number of events in experimental group or true positives in diagnostic study.
n.e: Number of observations in experimental group or number of ill participants in diagnostic study.
event.c: Number of events in control group or false positives in diagnostic study.
n.c: Number of observations in control group or number of healthy participants in : diagnostic study.

To conduct the funnel plot:

funnel. meta(result, xlim = c(0.1, 10), studlab = TRUE)

pdf(file = "funnelplot.pdf",width = 8, height = 7)
funnel. meta(result, xlim = c(0.1, 10),studlab = TRUE)
dev.off()

Testing for publication biasusing Egger's test

metabias(result, method.bias = "linreg")

Begg's test
ranktest(OR, TE, seTE, data= female_sex_unadjusted)
metabias(ma.binary, method. Bias = "rank")

Guide for help
https://cjvanlissa.github.io/Doing-Meta-Analysis-in-R/
https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/effects.html
https://www.metafor-project.org/doku.php/tips:assembling_data_or
https://stackoverflow.com/questions/35636805/meta-analysis-in-r-with-adjusted-ors
https://cjvanlissa.github.io/Doing-Meta-Analysis-in-R/smallstudyeffects.html
meta: General Package for Meta-Analysis (r-project.org)

9.4 Appendix 4. Individual study characteristics

Table 9-3 Individual study characteristics

Study ID	Author	Year	Country	Study design	Participants (sample size, population, sex, age)	Shoulder pain definition
1	Ahmad et al.	2020	Pakistan	Cross-sectional	General population n (190) n. of patients with SP (115) n. of patients without SP (75) Female (99) Male (91) mean age = 50.54 ±12.126	Painful and restricted movement of shoulder joint upon lateral rotation, abduction, and medial rotation. (Questionnaire based interview and clinical assessment)
2	Burner et al.	2014	USA	Cross-sectional	General population n (93) n. of patients with SP (29) n. of patients without SP (64) Female (9) Male (84) mean age = 74.7 ±10	Shoulder pain for more than 3 months in the last year (Questionnaire and clinical assessment)
3	Ding et al.	2014	China	Cross-sectional	General population n (254) n. of patients with SP (124)	Insidious onset of shoulder pain and last for at least three months / night pain / tenderness around the joint capsule/

					n. of patients without SP (130) Female (150) Male (104) mean age for patients with SP= 52.16 ± 6.16 mean age for patients without SP= 51.86 ± 6.87	external rotation is the most restricted motion (Questionnaire and clinical assessment)
4	Kiani et al.	2014	Iran	Cross- sectional	Diabetic population n (432) n. of patients with SP (38) n. of patients without SP (394) Female (298) Male (134) mean age for patients with SP= 59.6 ± 6.9 mean age for patients without SP= 52.5 ± 15.3	Shoulder capsulitis: shoulder pain for no less than one month with difficulty in laying on the affected shoulder and limited active and passive shoulder joint movements in at least three planes (Questionnaire and clinical assessment).
5	Kobayashi et al.	2014	Japan	Cross- sectional	General population n (541) n. of patients with SP (94) n. of patients without SP (447) Female (341) Male (200) mean age = 55.6 ±11	Shoulder OA was classified according to the Samilson-Prieto classification14 (S-P classification) for glenohumeral OA. (Questionnaire and clinical assessment + radiography)
6	Loew et al.	2019	Germany	Cross- sectional	Working population (painters) n (200) n. of patients with SP (82) n. of patients without SP (118) Female (0) Male (200)	RC lesions: Movement above shoulder level were painful and if there was pain under loading or motion, analysed on MRI and classified as intact, partial tear or complete tear. (Clinical assessment and MRI)

					mean age = 64 ± 9	
7	Milogram et al.	2008	Israel	Case-control	General population n (226) n. of patients with SP (126) n. of patients without SP (98) Female (140) Male (84) mean age for patients with SP= 55 ± 8.4 mean age for patients without SP= 56 ± 5.5	Frozen shoulder: the presence of both active and passive restriction of the glenohumeral joint in flexion, abduction, and internal rotation, with external rotation restricted to less than 50% of the normal side with the arm at the side, and a normal radiograph of the joint/ Idiopathic frozen shoulder: was defined as if there was no history of trauma and an ultrasound study showed no evidence of a RC tear (Clinical assessment).
8	Morse et al.	2007	USA	Cross-sectional	Working population (dental hygienists) n (94) n. of patients with SP (33) n. of patients without SP (61) Female (92) Male (2) mean age = 45.6 ± 8.8	Shoulder diagnoses including impingement syndrome, RC tendonitis, range of motion abnormalities, scapular winging, superior trapezius pain and trigger points, and findings for the Adson's, Roos, and Spurling tests. (Questionnaire and clinical assessment)
9	Otoshi et al.	2014	Japan	Cross-sectional	General population n (2144) n. of patients with SP (95) n. of patients without SP (2049) Female (1285) Male (859)	Diagnostic criteria for SIS: shoulder pain during shoulder elevation and a positive Neer or Hawkins impingement test result. (Clinical assessment).

					mean age = 67.9 ± 9	
10	Posch et al.	2019	Austria	Cross-sectional	Working population (pilots and crewmembers) n (221) n. of patients with SP (164) n. of patients without SP (57) Female () did not report Male () did not report mean age = 44.7 ± 8.4	Any reported pain experience, ache, or discomfort in shoulder area (in the previous 12 months) (Questionnaire).
11	Rodriguez Diez-Caballero et al.	2020	Spain	Case-control	Working population (automotive manufacturing sector) n (167) n. of patients with SP (73) n. of patients without SP (94) Female (16) Male (151) mean age = 47	Shoulder disorders are included into the same 2D0101 diagnosis code as tendinous chronic pathology of the RC (subacromial impingement syndrome, calcifying and chronic tendinitis and RC tears) (database).
12	Tekavec et al.	2012	Sweden	Retrospective Cohort	General population n (1,169,464) n. of patients with SP (6268) n. of patients without SP (1,163,196) n. of patients with SP female (3295) n. of patients with SP male (2973) Female (593,569) Male (575,895)	Shoulder pain diagnoses were collapsed into three major classes based on the ICD-10 coding: 1; Adhesive capsulitis (M75.0), 2; Tendinitis, bursitis, and impingement of the shoulder (M75.1-5) and 3; Unspecified shoulder pain diagnoses (M75.8, M75.9 and M75.9 P) (database).

					mean age (male) = 56 mean age (female) = 58	
13	Thomas et al.	2007	Scotland	Case-control	Diabetic population n (1067) n. of patients in diabetic group (865) n. of patients in non-diabetic group (202) n. of patients with SP in diabetic group (222) n. of patients without SP in diabetic group (643) n. of patients with SP in non-diabetic group (10) n. of patients without SP in non-diabetic group (192) Female (550) Male (517) mean age = 58.6	Frozen shoulder, defined as pain for more than 3 months and both shoulders restricted to less than 30 degrees external rotation (Questionnaire and clinical assessment).
14	White et al.	2011	USA	Retrospective cohort	General population n (2,188,958) n. of patients with SP (41,391) n. of patients without SP (2,147,567)	Read codes for adhesive capsulitis. 2 diagnostic Read codes, i.e., N210.00 and N210.12, which represent adhesive capsulitis and frozen shoulder, respectively. (Database)

					n. of patients with SP female (24,505) n. of patients with SP male (16,886) Female (1,094,479) Male (1,094,479) Min age = 40 Max age = 79	
15	Wright et al.	2015	USA	Cross-sectional	General population n (1672) n. of patients with SP (419) n. of patients without SP (1253) Female (1129) Male (543) mean age = 68.2 ± 9	"On most days do you have pain, aching, or stiffness of your left or right shoulders" (Questionnaire, Interview, clinical assessment, and radiography)
16	Wu et al.	2021	Taiwan	Cross-sectional	General population n (112) n. of patients with SP in sarcopenic group (28) n. of patients with SP in non-sarcopenic group (12) n. of patients with sarcopenia (56) n. of patients without sarcopenia (56) Female (86) Male (26) Patients with sarcopenia mean age = 75.12 ± 5.91 Patients without sarcopenia mean age = 75.12 ± 5.54	Intra-tendinous calcification: the presence of hyperechoic plaques with acoustic shadows underneath. Subluxation of the long head of the biceps tendon: when more than 50% of the tendon's cross-section was outside the bicipital groove. Subdeltoid bursitis: when the bursa was thicker than 2 mm. RC tendon tears: the existence of visible gaps or total absence of tendon tissue in the subacromial space. (Questionnaire, clinical assessment, and ultrasound scanning)

17	Cho et al.	2015	Korea	Cross-sectional	General population n (696) n. of patients with SP (36) n. of patients without SP (660) Female (398) Male (298) mean age = 72 ± 5	Radiographic glenohumeral OA: according to knee K/L grades, the presence of osteophytes plus narrowing of the glenohumeral articulation. If the K/L grade in one or both joints was Grade 2 or higher, the subject was considered to have radiographic shoulder OA. (Radiography)
18	Baumgarten et al.	2010	USA	Case-control	General population n (584) n. of patients with SP (375) n. of patients without SP (209) Female () not reported Male () not reported mean age = 57.8	Ultrasonography findings. Full-thickness RC tear: when the RC could not be visualized because of complete avulsion and retraction under the acromion or when there was a focal defect in the RC created by a variable degree of retraction of the torn tendon ends. Partial-thickness tear: minimal flattening of the bursal side of the RC (a bursal-side partial-thickness tear) or a distinct hypoechoic or mixed hyperechoic and hypoechoic defect visualized in both the longitudinal and the transverse plane at the deep articular side of the RC (an articular-side partial-thickness tear) (Questionnaire and diagnostic ultrasound).
19	Vogt et al.	2003	USA	Cross-sectional	General population n (3046) n. of patients with SP (575) n. of patients without SP (2471)	Shoulder pain lasting at least 1 month during the previous year (Home interview, questionnaire, and clinical assessment).

					Female (1569) Male (1477) mean age for patients with SP= 73.4 ± 2.9 mean age for patients without SP= 73.6 ± 2.9	
20	Ostergren et al.	2005	Sweden	Prospective cohort	Working population (different jobs) n (4919) n. of patients with SP (359) n. of patients without SP (4560) n. of patients with SP female (202) n. of patients with SP male (157) Female (2270) Male (2649) Min age = 45, Max age= 65	Shoulder pain during the past 12 months (Questionnaire).
21	Hill et al.	2010	Australia	Cross-sectional	General population n (3448) n of population > = 40 years old (1782) n. of patients with SP (487) n. of patients without SP (1295) Female (1776) Male (1712) mean age = not reported	Pain or aching in their shoulder at rest or when moving, on most days for at least a month and if they had ever had stiffness in their shoulder when getting out of bed in the morning on most days for at least a month (Questionnaire).
22	Alrowayeh et al.	2010	Kuwait	Cross-sectional	Working population (physiotherapists) n (212) n of population > = 40 years old (55) n. of patients with SP (4) n. of patients without SP (51)	Pain in the shoulder during the preceding 12 months (Questionnaire).

					Female (99) Male (113) mean age = 36.5 ± 9.1	
23	Haukka et al.	2006	Finland	Cross-sectional	Working population (kitchen workers) n (495) n of population > = 40 years old (347) n. of patients with SP (134) n. of patients without SP (213) Female (504) Male (19) mean age = 45 ± 10	Pain during the past 3 months in the shoulder (Questionnaire).
24	Kaliniene et al.	2016	Lithuania	Cross-sectional	Working population (computer workers) n (513) n of population > = 40 years old (367) n. of patients with SP (198) n. of patients without SP (169) Female (486) Male (27) mean age = 45.9 ± 11.1	Pain in the shoulder during the preceding 12 months (Questionnaire).
25	Janwantanakul et al.	2008	Thailand	Cross-sectional	Working population (Office workers) n (1185) n of population > = 40 years old (345) n. of patients with SP (61) n. of patients without SP (284) Female (807) Male (378) mean age = 35.2 ± 8.4	Pain in the shoulder during the preceding 12 months (Questionnaire).

26	Lecrac et al.	2004	France	Prospective Cohort study	Working population (repetitive work) n (598) n of population > = 40 years old (256) n. of patients with SP (163) n. of patients without SP (120) Female (420) Male (178) mean age = not reported	Shoulder incidence: Subjects free from SP at base line were those who did not report SP in the six months preceding the first questionnaire (1993–94). Incident cases were defined as the subjects free from SP at baseline who reported experiencing it at least one day in the six months preceding the second questionnaire (1996–97). Shoulder prevalence: period prevalence, for the six months preceding the questionnaire (Questionnaire).
27	Hinsley et al.	2022	UK	Cross-sectional	General population n (464,928 shoulders) n. of patients with SP (103) median age = 71	Full-thickness tears was defined as having at least one unilateral full-thickness tear. Tendon abnormalities was defined as having at least a unilateral tendon abnormality ranging from abnormal enthesis to a full-thickness tear.
28	Fehringer et al.	2008	USA	Cross-sectional	General population n (104) n. of shoulders total (200) n. of shoulders with tear (44) n. of shoulders without tear (156) Age 65 years or older	Full thickness tear : only full thickness tears, which were measured from anterior to posterior at their footprint. The first author, an orthopaedist trained and experienced in RC ultrasonography, performed all functional testing and ultrasounds. Shoulders were divided into 4 groups, depending on whether the subject had previously presented to a physician for their respective shoulder based on Milgrom et al's definition of asymptomatic

						cuff tears; ie, ‘‘.no history of shoulder problems in the past severe enough to have required medical attention. These 4 groups included: 1) those subjects without RC tears who had not seen a physician for their respective shoulders (control); 2) those without RC tears who had seen a physician for their respective shoulders; 3) those with RC tears who had not seen a physician for their respective shoulders, and 4) those with RC tears who had seen a physician for their respective shoulders.
29	Niedhammer et al.	1998	France	Cross-sectional	Working population n (210) n. of people aged 40 and more (38)	Shoulder pain during the preceding six months, they had suffered pain, stiffness, or discomfort in any of the four hatched areas of the shoulders on the diagram (left, right, front, or back). The following six variables relating to shoulder disorders were investigated according to the location of pain (right or left side), and the chronicity of pain: 1) shoulder disorders on whichever side; 2) right shoulder disorders; 3) left shoulder disorders; 4) chronic shoulder disorders (symptoms lasting more than 30 days) on whichever side; 5) chronic right-shoulder

	disorders; and 6) chronic left-shoulder disorders.

9.5 Appendix 5. Validation of the quality assessment

Table 9-4 Validation results for the quality assessment

Study ID	Item	Reviewer discussion	Agreement
2	Sample size	NA: B MS: A Overall: A	Resolved by discussion
2	Non respondents	NA: A MS: C Overall: A	Resolved by discussion
8	Sample size	NA: B MS: A Overall: B	Resolved by discussion
13	Non-response rate	NA: C MS: A Overall: A	Resolved by discussion
15	Representativeness of the sample	NA: B MS: A Overall: A	Resolved by discussion
22	Ascertainment of the exposure (risk factor)	NA: B MS: A Overall: A	Resolved by discussion
23	Sample size	NA : B	Resolved by discussion

MS: A Overall: B

9.6 Appendix 6. Quality assessment risk of bias aspects

A: Quality assessment risk of bias aspects of cross-sectional studies using the Newcastle-Ottawa Scale

Author, year	Score	Risk of bias aspect
Ahmad, 2020	50	There is no description of the tool if it is validated or not / no description of the response rate / it relies only on self-report / the study did not control for the most important factors
Burner, 2014	60	The non-random sampling: Its restriction to a Veteran affairs population which included few women.
Ding, 2014	60	No description if confounding factors were controlled
Kiani, 2014	80	-
Kobayashi, 2014	80	-
Loew, 2019	80	The recruitment method may not yield a true-cross-sectional representation of the general population and may result in a selection bias towards a better educated and healthier volunteers
Morse, 2007	90	-
Otoshi, 2014	70	No description of the response rate
Posch, 2019	70	The response rate of 69.8% has been achieved. They did not achieve a higher response rate. Unfortunately, only a small number of military pilots could be acquired, presenting a potential limitation.
Wright, 2015	80	The age of the cohort may limit generalizability to younger individuals.
Wu, 2015	80	-
Cho, 2015	80	The selection bias related to the recruitment of participants might exist. Respondents were younger than nonrespondents. Furthermore, individuals with symptoms and disability might have been more likely to volunteer to get radiographic examination and a diagnosis. These sampling errors might induce under or overestimation of the actual prevalence of OA in Koreans. the population studied is not truly representative of the Asian population because epidemiologic characteristics may vary by ethnicities and geographic region.
Vogt, 2003	60	The health ABC cohort specifically excluded younger individuals and those who were frail. Thus, the results are not generalizable to the entire US population of similar age
Hill, 2010	80	There is no description if the assessment was blind or not

Alrowayeh, 2010	50	There is no description of the tool if it is validated or not / non-random sampling / the sample size not justified / the study didn't control for the most important factor
Haukka, 2006	70	There is no description of the tool if it is validated, or not / it relies only on self-report
Kaliniene, 2016	80	There is no description if the assessment was blind or not
Janwantanakul, 2008	70	There is no description of confounding factors controlled
Lecrac, 2004	70	There is no description of the tool if it is validated, or not / it relies only on self-report / the sample size is not justified / The target population were selected according to occupational criteria and were required to be exposed to repetitive work.
Hinsley, 2022	90	

B: Quality assessment risk of bias aspects of case-control studies using the Newcastle-Ottawa Scale

Author, year	Score	Risk of bias aspect
Milogram 2008	70	small sample size
Rodriguez Diez-Caballero 2020	70	Data were retrieved from clinical records. The case definition was based on records only
Thomas 2007	60	the definition should have included a criteria for normal radiographic appearance to differentiate between osteoarthritis, primary degenerative arthritis and frozen shoulder
Baumgarten 2010	60	no description of non-respondents / recall bias: Data were collected for patients who were unavailable for telephone interview by chart review. However, chart reviews did contain information on history of smoking, dates of cessation, and amount of tobacco use as determined by mean packs per day. Recall bias was a potential confounder of the data because patients were asked to recall dates of initiation and cessation and average amounts of tobacco use.

C: Quality assessment risk of bias aspects of cohort studies using the Newcastle-Ottawa Scale

Author, year	Score	Risk of bias aspect
Tekavec, 2012	50	They only access diagnostic codes from public healthcare. They needed to adjust their estimates for the missing data which may introduce bias. No statement about the adequacy of follow up
White, 2011	50	The diagnosis of AC in our sample could not be validated beyond being diagnosed by a general practitioner. / They did not report any statement about the adequacy of follow up for the cohorts
Ostergren, 2005	50	The assessment of shoulder pain was based on questionnaires only (self-report) which might affect the results / Possible selection bias of the MSNS sample was estimated by comparing sociodemographic data from the municipal statistics office regarding the complete age cohort in February 1994.
Lecrac, 2004	40	No description about the adequacy of follow up for outcome to occur/ it relies only on self-report / The sample size is not justified / The target population were selected according to occupational criteria and were required to be exposed to repetitive work

9.7 Appendix 7. Forest plots and funnel plots

Figure 9.1 Forest plot showing the prevalence of chronic shoulder pain in diabetic population

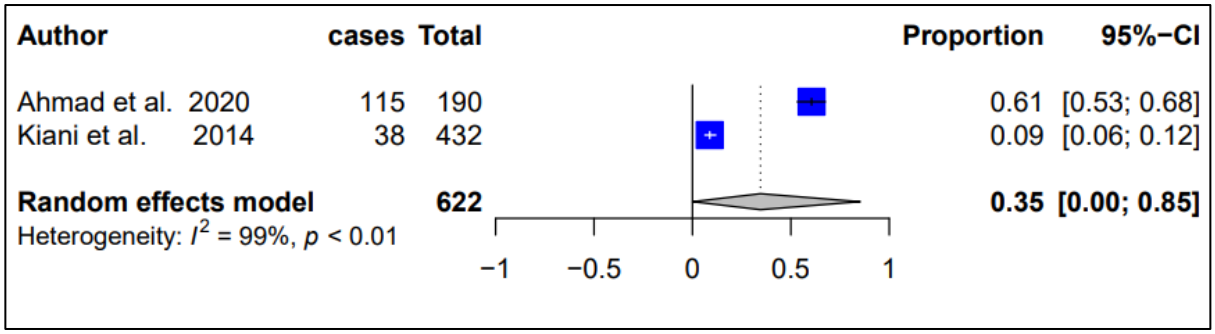


Figure 9.2 Forest plot showing the prevalence of chronic shoulder pain in workers

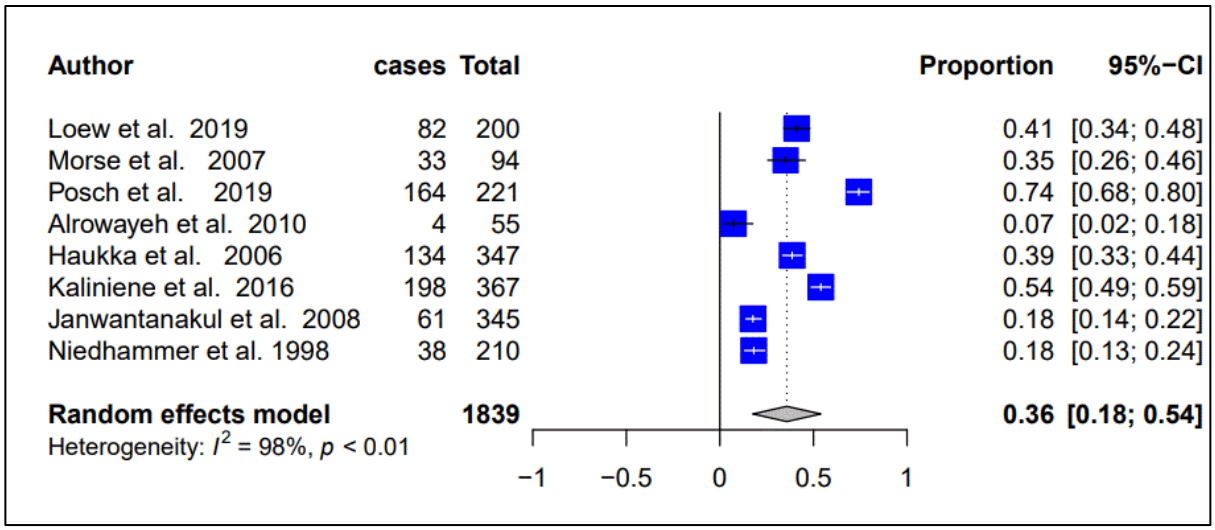


Figure 9.3 Funnel plot showing the prevalence of chronic shoulder pain in workers

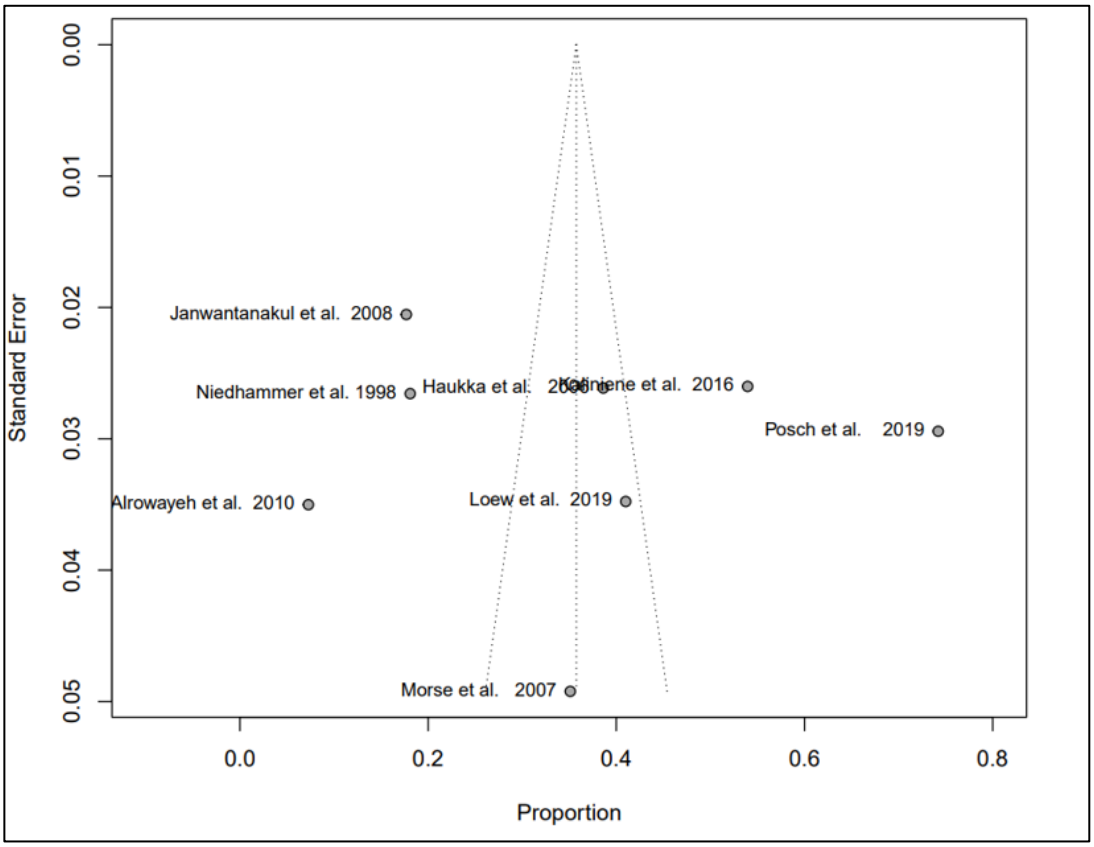


Figure 9.4 Funnel plot showing the association between the prevalence of chronic shoulder pain according to different diagnosis

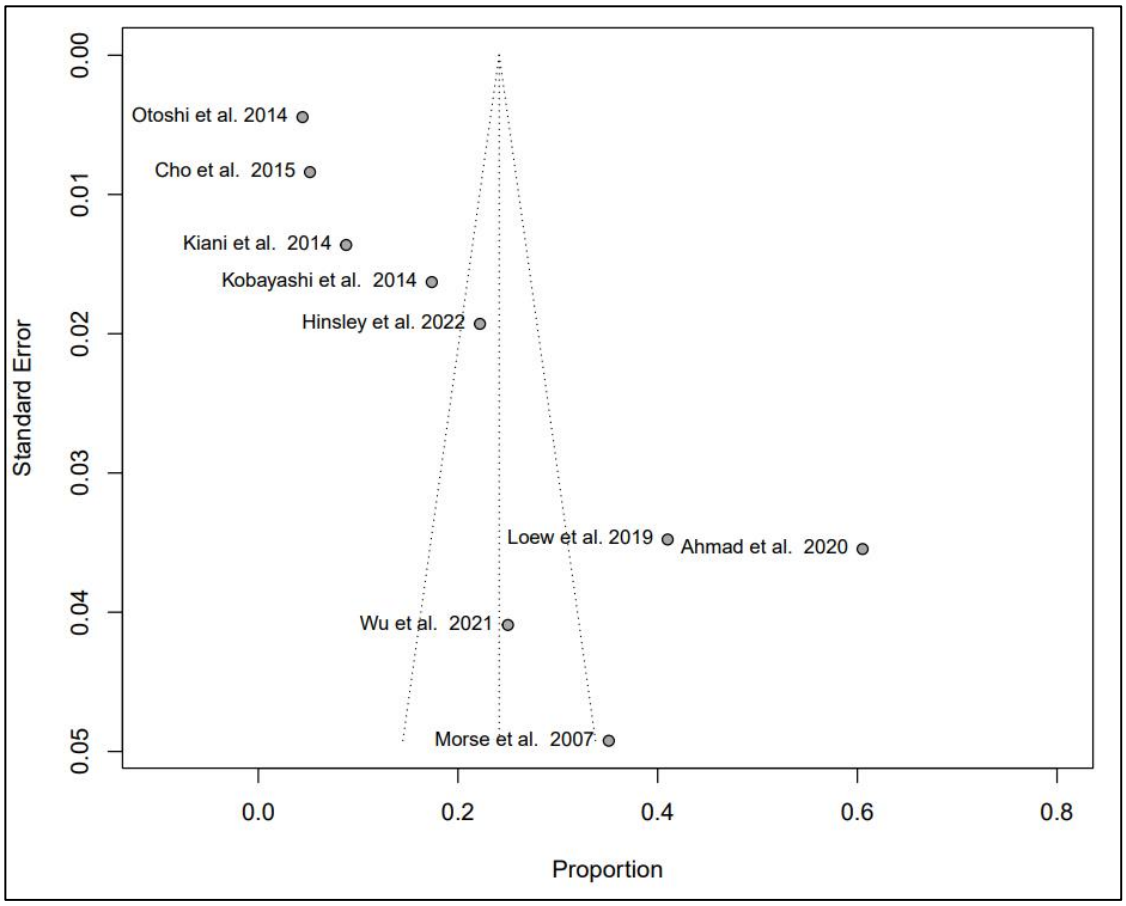
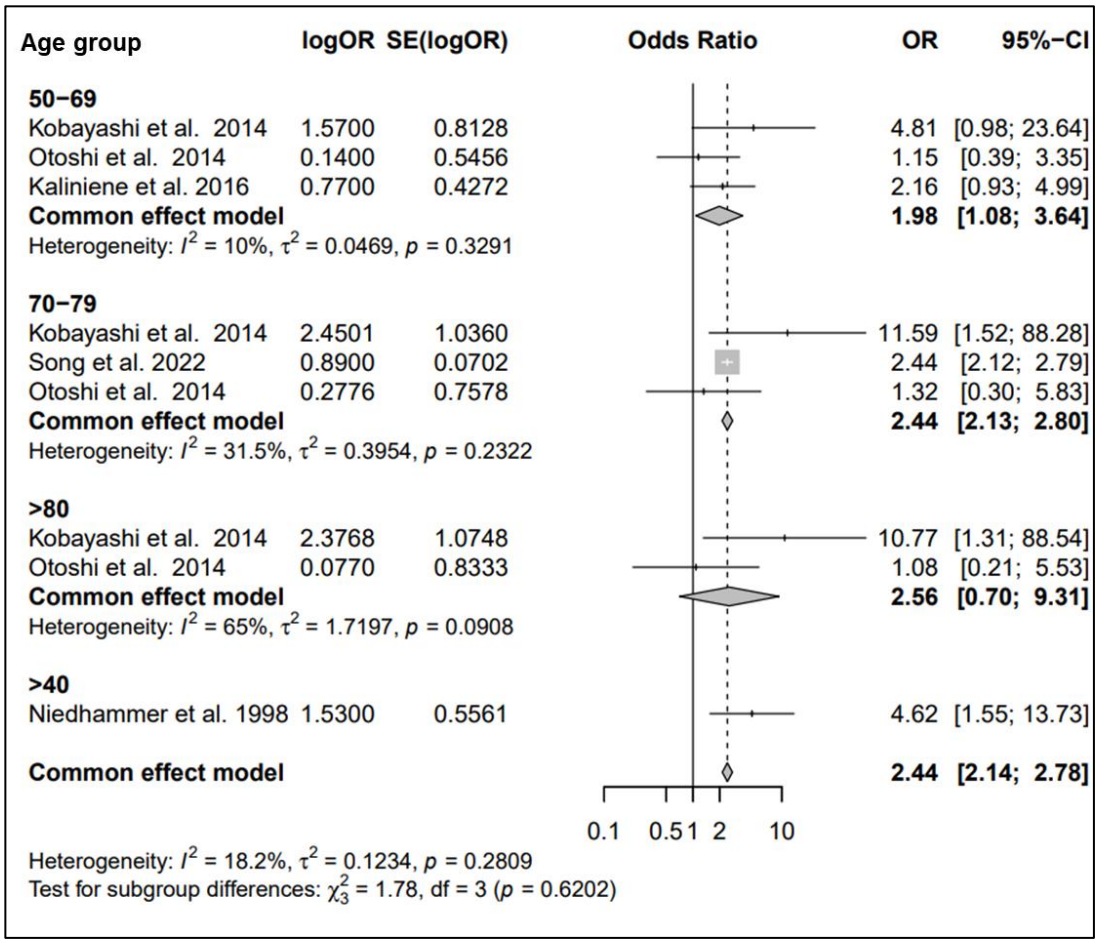


Figure 9.5 Forest plot showing the association between chronic shoulder pain and age groups



TE= log odds ratio, seTE=standard error of odds ratio, CI= confidence interval

Figure 9.6 Funnel plot showing the association between chronic shoulder pain and age groups

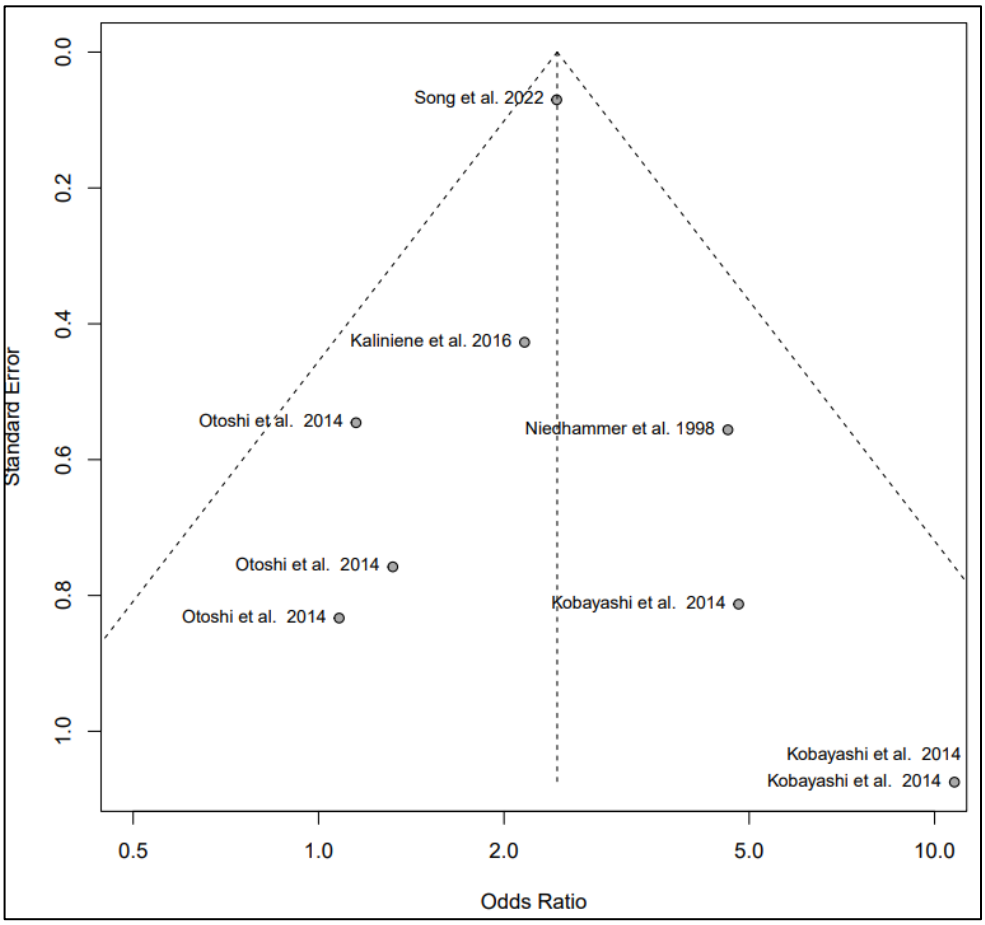
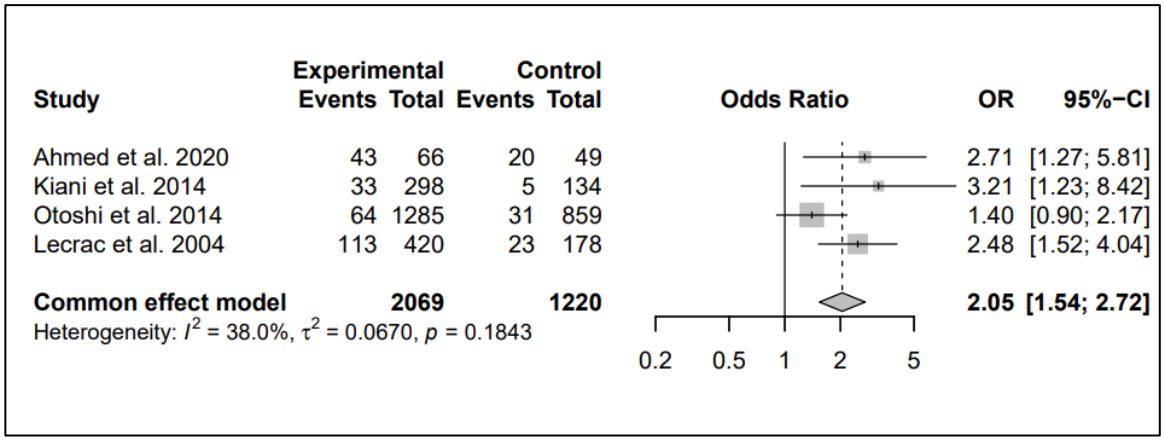
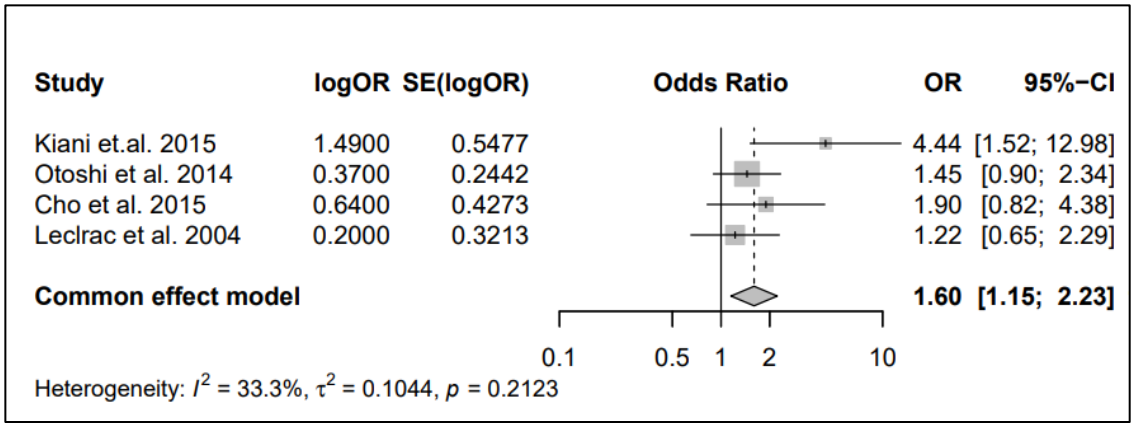


Figure 9.7 Forest plot showing the association between female sex and shoulder pain (crude)



TE= log odds ratio, seTE=standard error of odds ratio, CI= confidence interval

Figure 9.8 Forest plot showing the association between female sex and shoulder pain (adjusted)



TE= log odds ratio, seTE=standard error of odds ratio, CI= confidence interval

Figure 9.9 Funnel plot showing the association between female sex and chronic shoulder pain (crude)

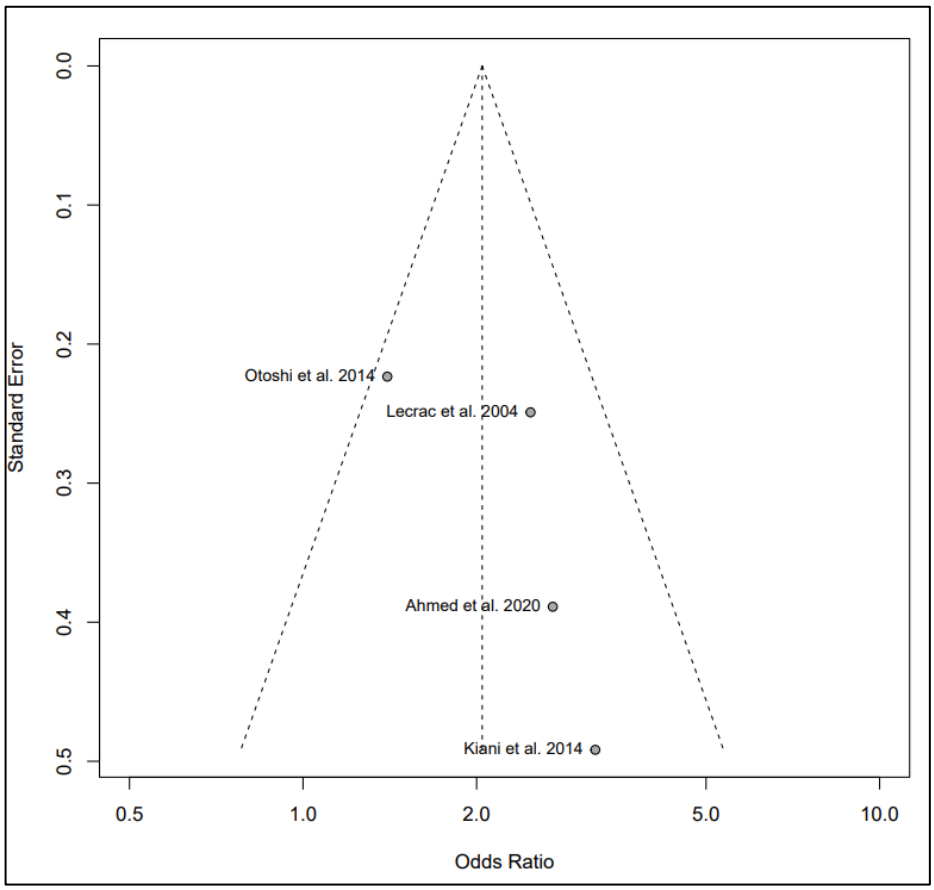


Figure 9.10 Funnel plot showing the association between female sex and shoulder pain (adjusted)

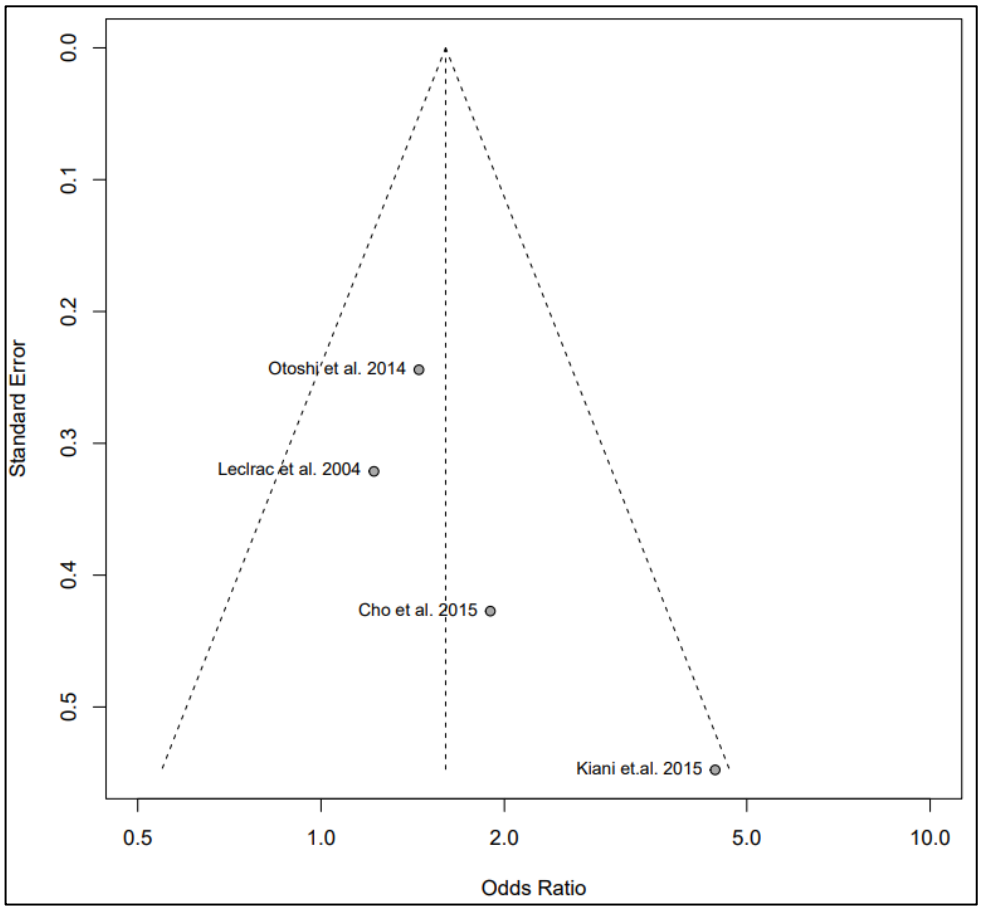
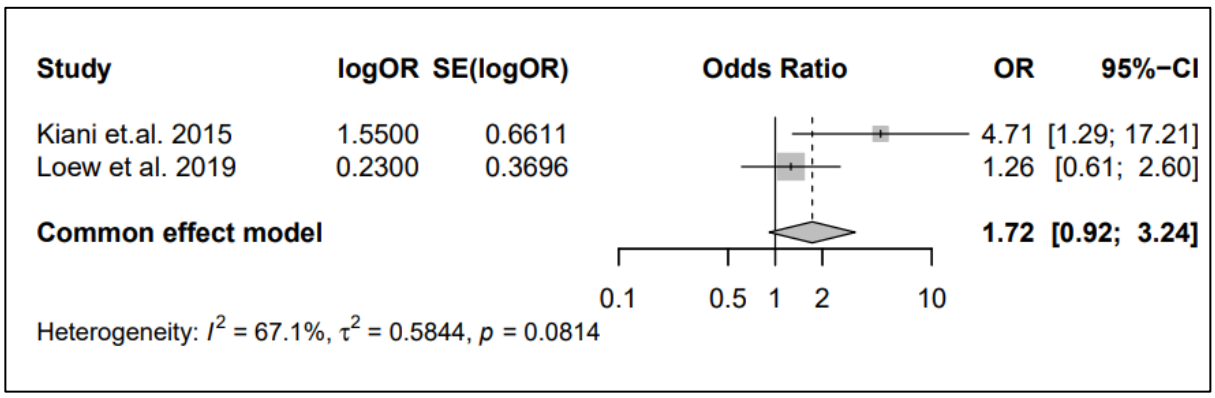


Figure 9.11 Forest plot showing the association between smoking and shoulder pain

(Multivariable odds ratio)



TE= log odds ratio, seTE=standard error of odds ratio, CI= confidence interval

Figure 9.12 Forest plot showing the association between smoking and chronic shoulder pain (subgroup based on analysis)

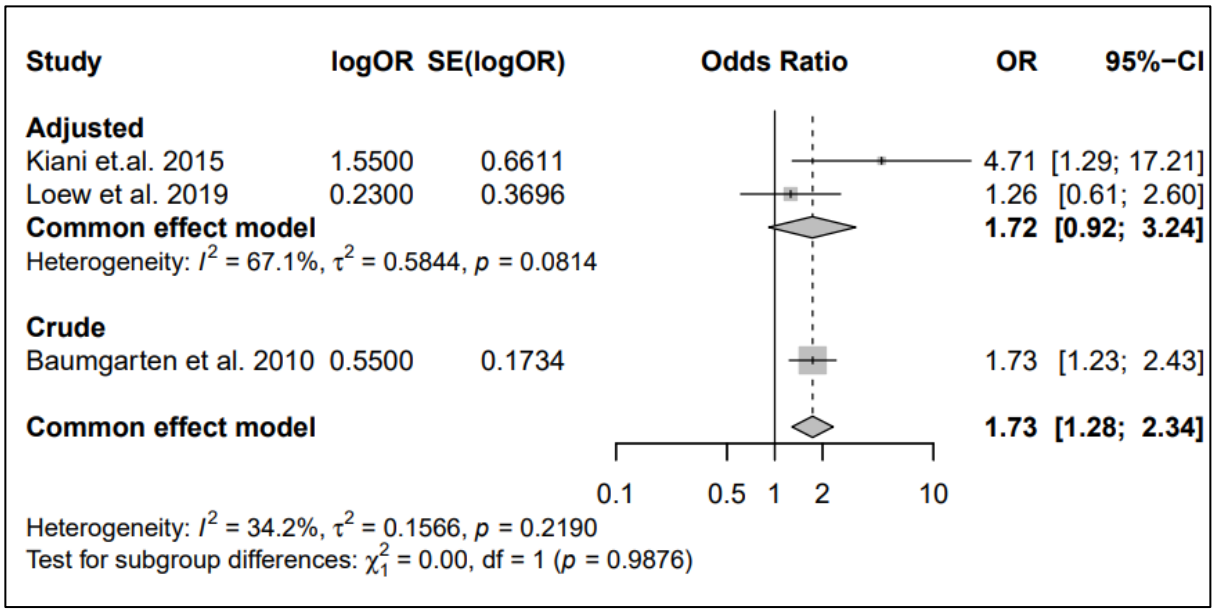


Figure 9.13 Funnel plot showing the association between smoking and shoulder pain

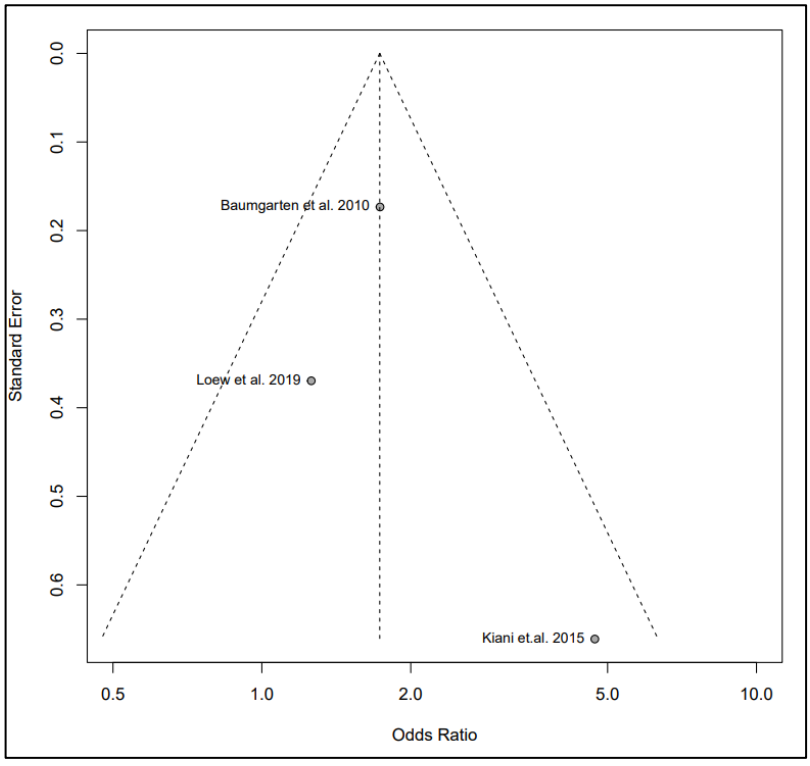


Figure 9.14 . Forest plot showing the association between manual work and chronic shoulder pain

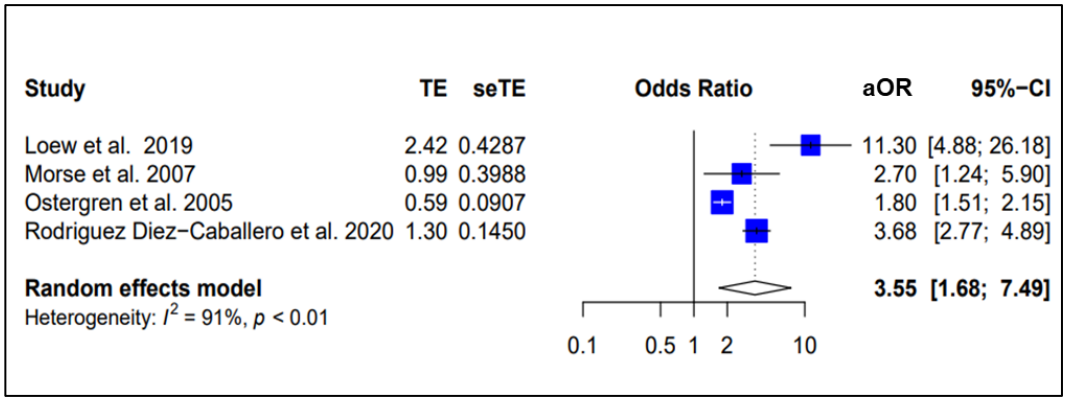
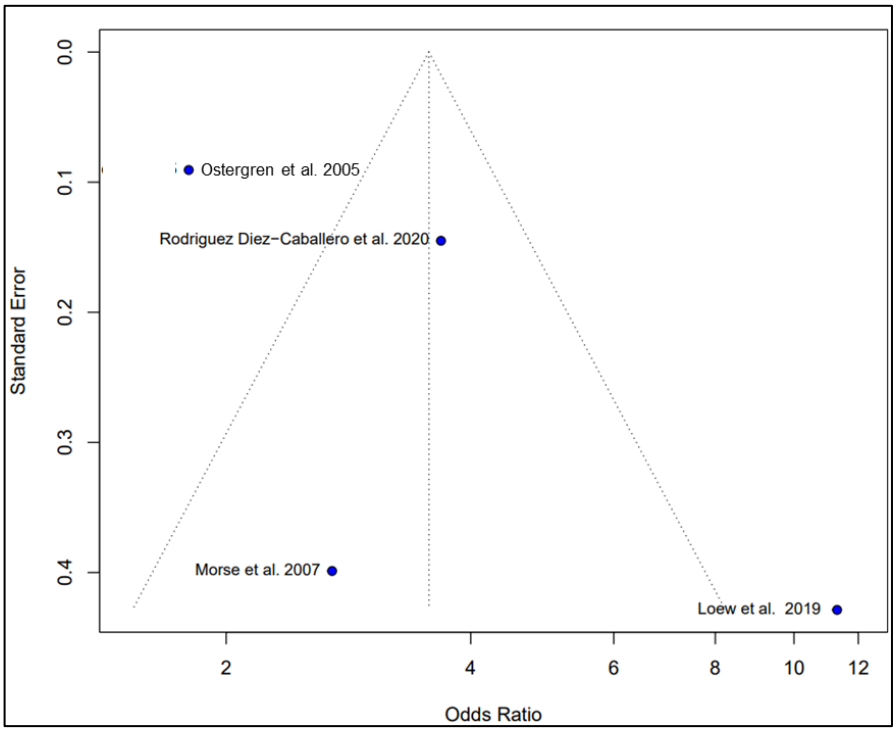


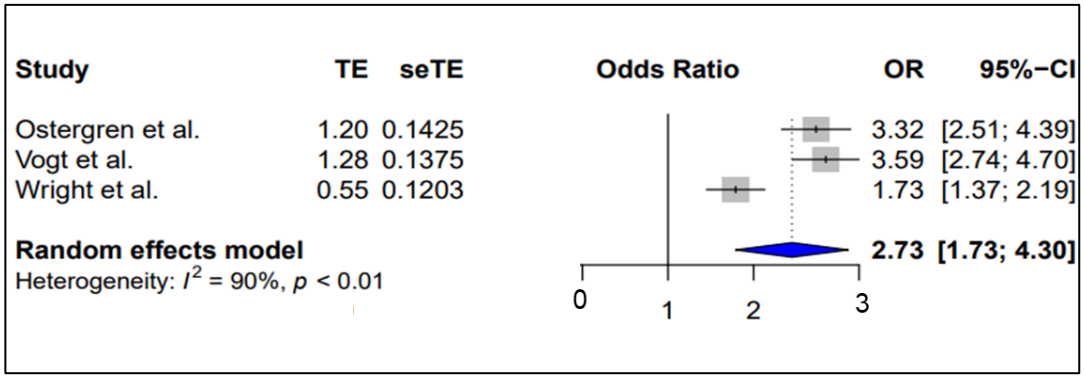
Figure 9.15 Funnel plot showing the association between manual work and chronic shoulder pain



Forst plots and funnel plots for comorbidities

Figure 9.16 Forest plot showing the association between pain in other joints and shoulder pain

(Adjusted odds ratio)



TE= log odds ratio, seTE=standard error of odds ratio, CI= confidence interval

Figure 9.17 Funnel plot showing the association between pain in other joint and shoulder pain

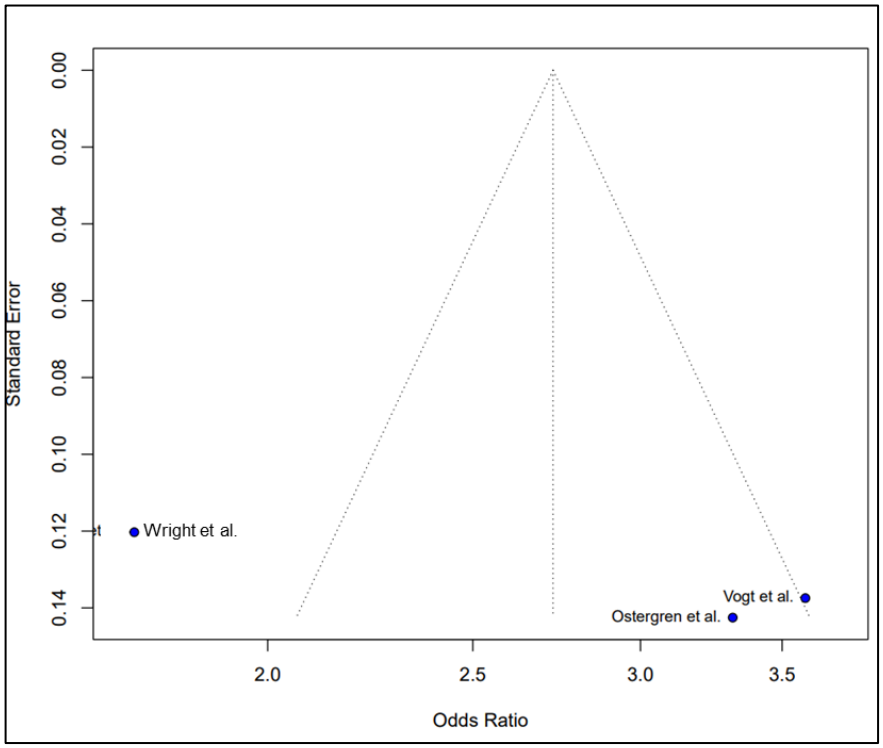
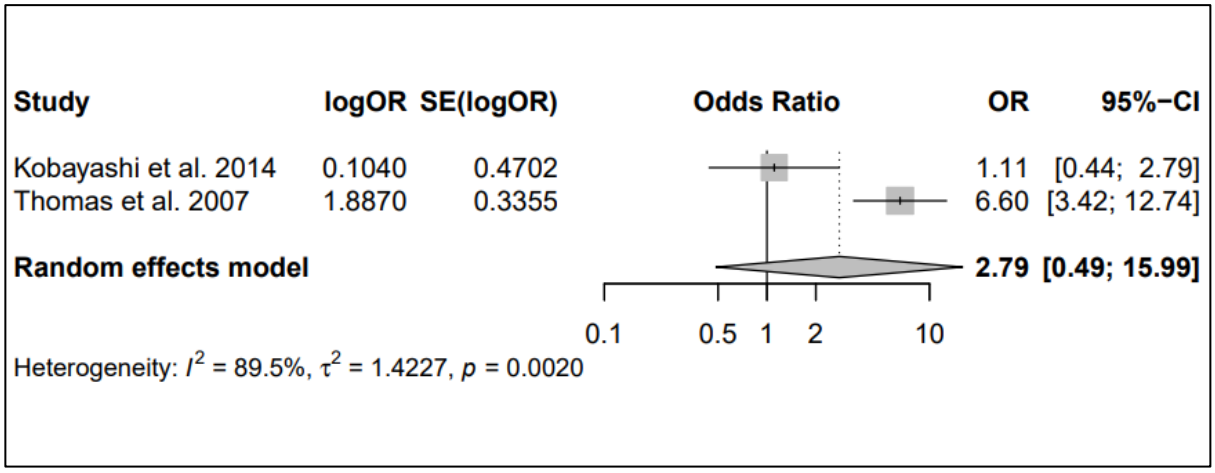


Figure 9.18 Forest plot showing the association between diabetes and chronic shoulder pain (crude odds ratio)



TE= log odds ratio, seTE=standard error of odds ratio, CI= confidence interval

Figure 9.19 Forest plot showing the association between diabetes and chronic shoulder pain (subgroup based on analysis)

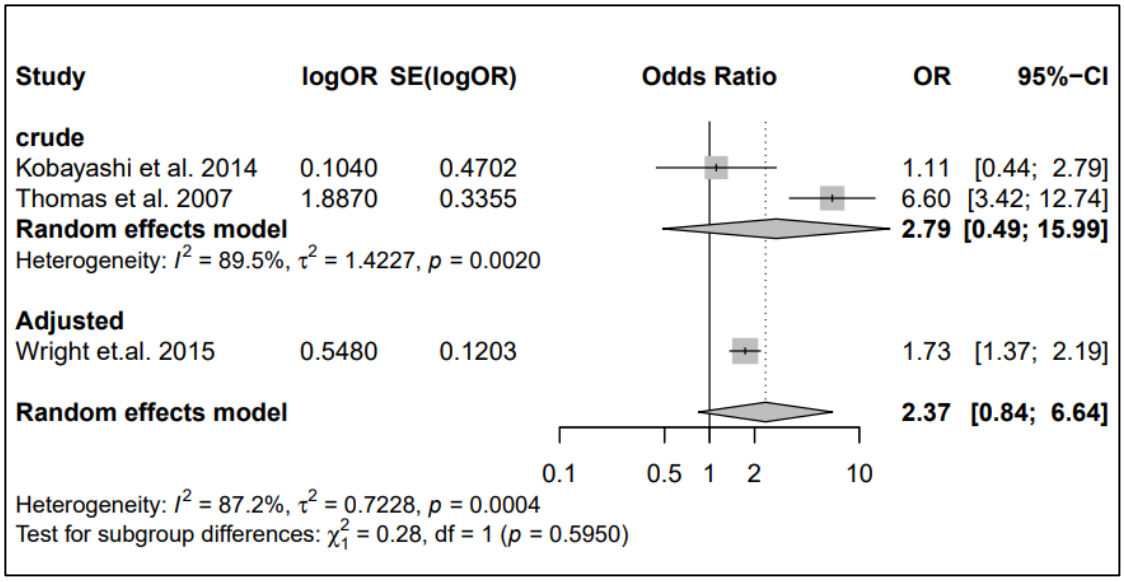


Figure 9.20 Funnel plot showing the association between diabetes and shoulder pain

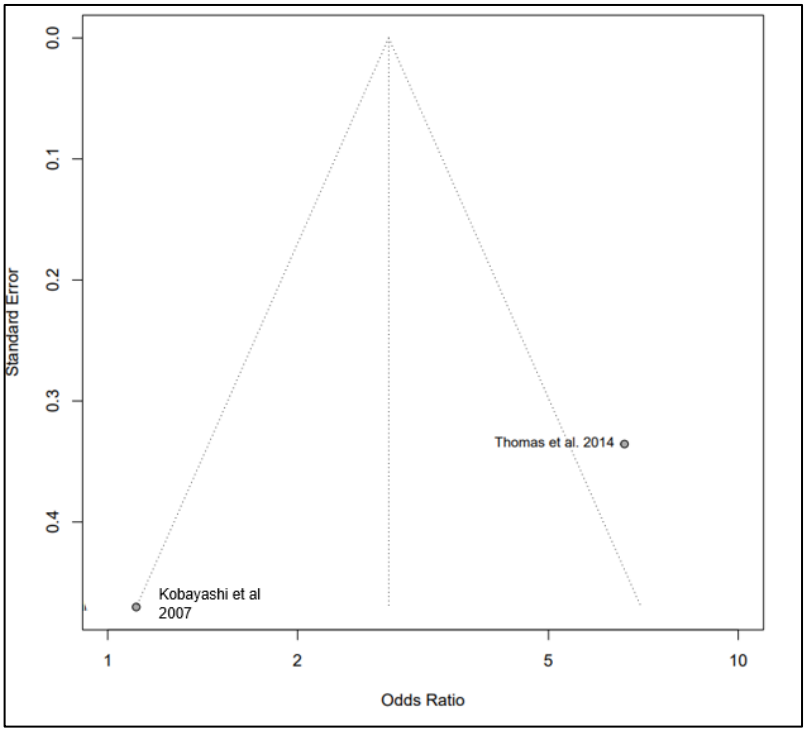


Figure 9.21 Forest plot showing the association between chronic shoulder pain and depression (adjusted odds ratio)

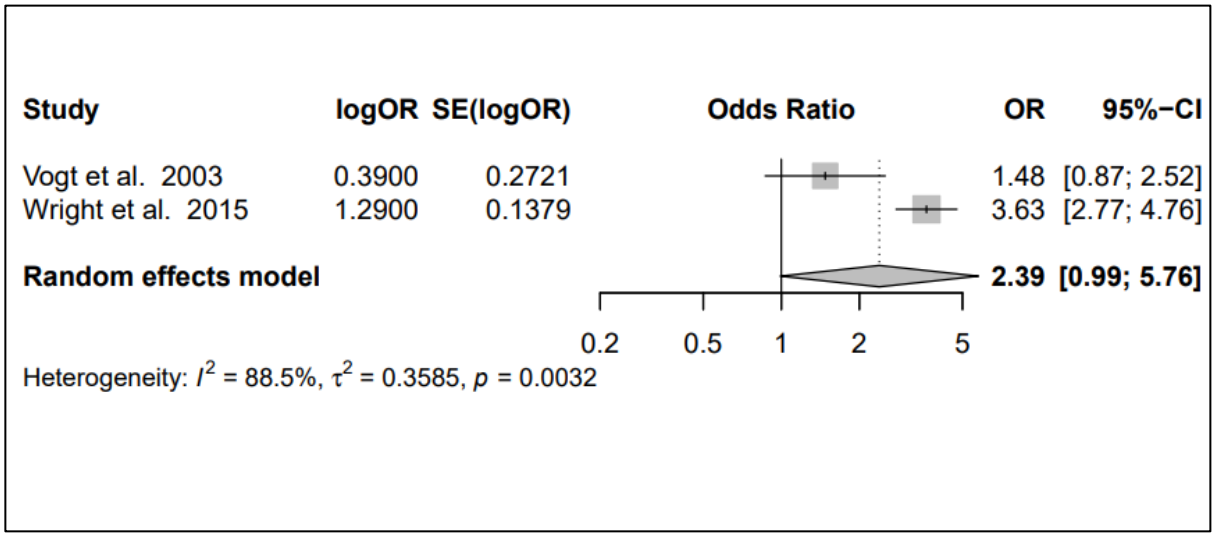
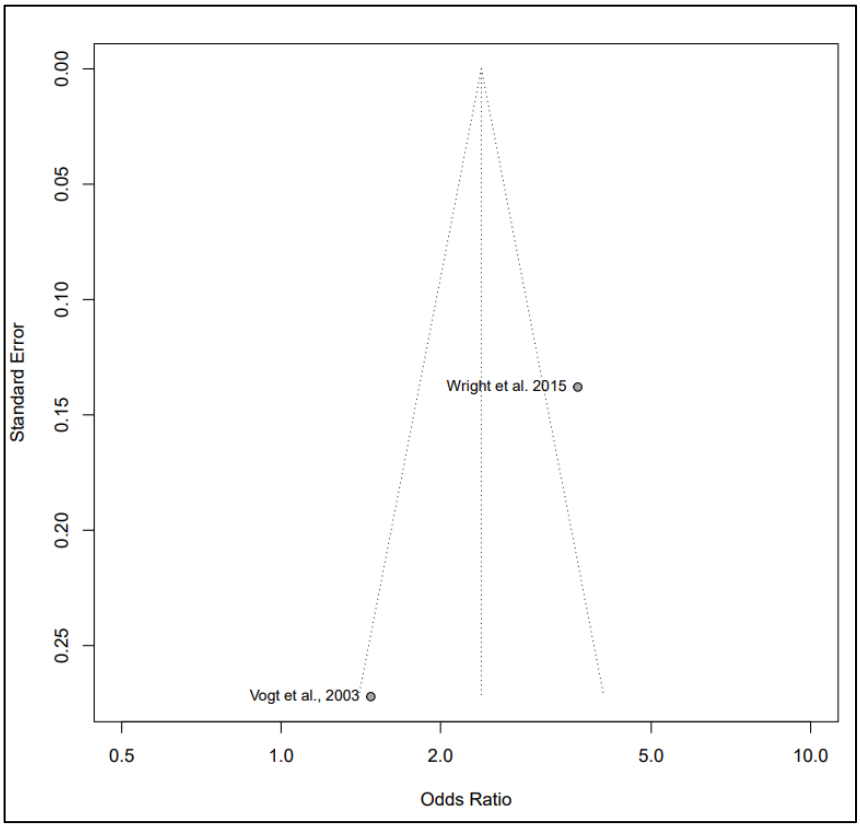


Figure 9.22 Funnel plot showing the association between chronic shoulder pain and depression



9.8 Appendix 8. Study outcomes

Table 9-5 Included studies outcomes

Study ID	Study	Prevalence/ incidence	Reported as significant risk factor(s) and reported statistics
1	Ahmad et al. 2020	Overall prevalence = 60.52 %	Female Vs. male (OR 2.7, 95% CI 1.265,5.809) Duration of DM (OR 3.11,95% CI 1,005,9.637) Family history of DM (yes / No) (OR 3 ,95% CI 1,51,6.32)
2	Burner et al. 2014	Overall prevalence = 31 %	Not reported
3	Ding et al. 2014	Not reported	Depression (OR 1.98, 95% CI 1.041,3.78) Anxiety (OR 1.9 ,95% CI 1, 3.7)
4	Kiani et al. 2014	Overall prevalence = 8.79 %	Female sex (OR 4.4, 95% CI 1.53,12.85) Age (OR 1.03,95% CI 1 ,1.06) Smoking (OR 4.72, 95% CI 1.29 ,17.24) Duration of DM (OR 1.04,95% CI 1,1.09)
5	Kobayashi et al. 2014	Overall prevalence primary OA = 17.4 % S-P grade 1 = 11.1% S-P grade 2 = 4.8% S-P grade 3 = 1.5% prevalence of B/L OA = 3.1% prevalence of secondary OA = 1.7%	OR for age (50-59) univariate (OR 5.77,95% CI 0.73,45.86) OR for age (60-69) univariate (OR 9.78,95% CI 1.29, 74.26) OR for age (70-79) univariate (OR 19.29 ,95% CI 2.59, 143.52) OR for age (>80) univariate (OR 20.43, 95% CI 2.58,162.16) OR for age (50-59) multivariate (OR 3.99, 95% CI 0.72,43.67) OR for age (60-69) multivariate (OR 5.59, 95% CI 1.29, 74.26) OR for age (70-79) multivariate (OR 11.59 ,95% CI 1.52, 88.29) OR for age (>80) multivariate (OR 10.77, 95% CI 1.31,88.54) DM (OR 1.11, 95% CI 0.44, 2.79) Hypertension (OR 1.69, 95% CI 1.03, 2.77) Hyperlipidaemia (OR 0.95,95% CI 0.59,1.55)
6	Loew et al. 2019	Overall prevalence = 52 %	Age (OR 1.052,95% CI 1.007 ,1.00)

			Smoking (OR 1.257, 95% CI 0.608, 2.59)
7	Milgrom et al. 2008	Not reported	DM female (case) (RR 5 ,95% CI (3.3,7.5) DM male (case) (RR 5.9 ,95% CI 4.1,8.4) DM female (control) (RR 2.8, 95% CI 1.4, 5.1) DM male (control) (RR 1.5,95% CI 0.5,4.3) Hypothyroidism female (case) (RR 7.3 , 95% CI 4.8, 11.1) Hypothyroidism male (case) (RR 2.6, 95% CI 0.4,17) Hypothyroidism female (control) (RR 3.8, 95% CI 1.9, 7.5) Hypothyroidism male (control) (RR 3.8, 95% CI 0.6, 23.4)
8	Morse et al. 2007	Overall prevalence = 35.1%	Occupation (OR 2.7, 95% CI 1.2, 5.9) Use of hand tool (OR 2.5, 95% CI 1.4, 4.5) Arm above shoulder level (OR 1.5, 95% CI 1, 2.4)
9	Otoshi et al. 2014	Overall prevalence = 4.4%	Female sex (OR 1.46, 95% CI 0.92, 2.36) OR for age (50-59) multivariate (OR 1.36, 95% CI 0.4, 6.23) OR for age (60-69) multivariate (OR 1.04,95% CI 0.34, 4.54) OR for age (70-79) multivariate (OR 1.32 ,95% CI 0.43, 5.83) OR for age (>80) multivariate (OR 1.08,95% CI 0.26, 5.53) Lumber kyphosis age and sex adjusted (OR 1.06, 95% CI 0.68, 1.67) Lumber kyphosis multivariable (OR 0.91, 95% CI 0.56,1.47) Thoracic kyphosis age and sex adjusted (OR 1.65, 95% CI 1.02, 2.64) Thoracic kyphosis multivariable (OR 1.27, 95% CI 0.75,2.11) Reduction in shoulder elevation (OR 6.31,95% CI 3.83,10.30).
10	Posch et al. 2019	Overall prevalence = 74% Prevalence in pilots = 34.3% Prevalence in crewmembers = 30.8%	Not reported
11	Rodriguez Diez-Caballero et al. 2020	Not reported	Age (OR 1.13, 95% CI 1.07, 1.2)
12	Tekavec et al. 2012	Incidence rate for females = 80 per 10 000 person years Incidence rate for males = 74 per 10 000 person years	Not reported

		Incidence rate for females aged 50 to 59 years = 129 per 10, 000 person years Incidence rate for males aged 60 to 69 years = 116 per 10,000 person years	
13	Thomas et al. 2007	Overall prevalence = 25.7%	DM (OR 6.6, 95% CI 3.448,12.746)
14	White et al. 2011	Incidence rate for females = 2.36 per 1000 person years Incidence rate for males= 3.38 per 1000 person years	Female sex (age adjusted) (HR 1.4, 95% CI 1.38, 1.43)
15	Wright et al. 2015	Overall prevalence = 12.8 %	DM (mild SP) * = (OR 1.9, 95% CI 1.3, 2.7) DM (mild SP) # = (OR 1.7, 95% CI 1.2, 2.5) DM (moderate/severe SP) * = (OR 1.6, 95% CI 1.1, 2.2) DM (moderate/severe SP) # = (OR 1.2, 95% CI 0.9, 1.8) CVD (mild SP) * = (OR 1.2, 95% CI 0.9, 1.7) CVD (mild SP) # = (OR 1, 95% CI 0.7, 1.4) CVD (moderate/severe SP) * = (OR 2.2, 95% CI 1.6, 3) CVD (moderate/severe SP) # = (OR 1.8, 95% CI 1.3, 2.5) Pain in other joints (mild SP) * = (OR 1.2, 95% CI 0.9, 1.7) Pain in other joints (mild SP) # = (OR 1.8, 95% CI 1.3, 2.5) Pain in other joints (moderate/severe SP) * = (OR 2.2, 95% CI 1.6, 3) Pain in other joints (moderate/severe SP) # = (OR 2.5, 95% CI 1.8, 3.3) Depression (mild SP) * = (OR 3.2, 95% CI 2.1, 4.9) Depression (mild SP) # = (OR 2.8, 95% CI 1.8, 4.3) Depression (moderate/severe SP) * = (OR 4, 95% CI 2.7, 5.8) Depression (moderate/severe SP) # = (OR 3.3, 95% CI 2.2, 4.9) Lung problems (mild SP) * = (OR 1.3, 95% CI 0.9, 2.0) Lung problems (mild SP) # = (OR 1.1, 95% CI 0.7, 1.6) Lung problems (moderate/severe SP) * = (OR 2.9, 95% CI 2.1, 3.9) Lung problems (moderate/severe SP) # = (OR 2.1, 95% CI 1.5, 3.0) Cancer (mild SP) * = (OR 1.1, 95% CI 0.8, 1.7)

			Cancer (mild SP) # = (OR 1.2, 95% CI 0.8, 1.7) Cancer (moderate/severe SP) * = (OR 1.4, 95% CI 1, 2) Cancer (moderate/severe SP) # = (OR 1.3, 95% CI 0.9, 1.9)
16	Wu et al. 2021	Prevalence of SP in sarcopenic group = 25% Prevalence of SP in non-sarcopenic group = 10.71%	Sarcopenia (OR 2.7, 95% CI 1.331, 5.798)
17	Cho et al. 2015	Overall prevalence = 5 %	Female sex (OR 1.9, 95% CI 0.8, 4.4) Age (OR 1.1, 95% CI 0.7, 1.6) BMI (OR 1.7, 95% CI 0.8, 3.8)
18	Baumgarten et al. 2010	Not reported	Smoking (OR 1.74, 95% CI 1.23, 2.44)
19	Vogt et al. 2003	Overall prevalence = 18.9 %	Female sex (OR 1.39, 95% CI 1.205, 1.618) Hypertension** (mild) (OR 1, 95% CI 0.8, 1.4) Hypertension** (moderate) (OR 1.3, 95% CI 1, 1.7) Hypertension** (severe) (OR 2.1, 95% CI 1.4, 3) Angina** (mild) (OR 1.3, 95% CI 0.8, 2) Angina** (moderate) (OR 1.5, 95% CI 1, 2.2) Angina** (severe) (OR 2.1, 95% CI 1.4, 3) Heart attack ** (mild) (OR 1, 95% CI 0.6, 1.6) Heart attack** (moderate) (OR 1.3, 95% CI 0.8, 1.9) Heart attack** (severe) (OR 1.9, 95% CI 1.2, 3) Arthritis ** (mild) (OR 2.5, 95% CI 1.8, 3.4) Arthritis** (moderate) (OR 3.2, 95% CI 2.3, 4.4) Arthritis** (severe) (OR 5.1, 95% CI 3.2, 8.2) Pain in other joints ** (mild) (OR 2.8, 95% CI 1.9, 4.1) Pain in other joints** (moderate) (OR 4.2, 95% CI 2.9, 6.1) Pain in other joints** (severe) (OR 4.1, 95% CI 2.5, 6.6) Depression ** (mild) (OR 1, 95% CI 0.6, 1.7) Depression** (moderate) (OR 1.3, 95% CI 0.8, 2) Depression** (severe) (OR 2.5, 95% CI 1.6, 3.9)
20	Ostergren et al. 2005	One-year Cumulative incidence in females (adjusted for age) = 8.9 %	OR for age 50-54 (female) (OR 0.9, 95% CI 0.61, 1.31) OR for age 50-54 (male) (OR 1.09, 95% CI 0.69, 1.74)

		One-year Cumulative incidence in males(adjusted for age) = 5.9% One-year Cumulative incidence in females age (45-49) = 10.3% One-year Cumulative incidence in females age (50-54) = 9.3% One-year Cumulative incidence in females age (55-59) = 8.9 % One-year Cumulative incidence in females age (60-64) = 5.8% One-year Cumulative incidence in males age (45-49) = 5.5% One-year Cumulative incidence in males age (50-54) = 6% One-year Cumulative incidence in males age (55-59) = 6.8 % One-year Cumulative incidence in males age (60-64) = 4.6%	OR for age 55-59 (female) (OR 0.85, 95% CI 0.75, 1.28) OR for age 55-59 (male) (OR 1.24, 95% CI 0.78, 1.99) OR for age 60-64 (female) (OR 0.54, 95% CI 0.31, 0.95) OR for age 60-64 (male) (OR 0.82, 95% CI 0.45, 1.49) Educational level 10-12 (male) (OR 1.18, 95% CI 0.74, 1.87) Educational level 10-12 (female) (OR 1.02, 95% CI 0.70, 1.48) Educational level < 9 (male) (OR 1.86, 95% CI 1.21, 2.86) Educational level <9 (female) (OR 1.75, 95% CI 1.21, 1.48) Pain in other joints (male) (OR 3.88, 95% CI 2.74, 5.49) Pain in other joints (female) (OR 2.92, 95% CI 2.14, 3.97)
21	Hill et al., 2010	Overall prevalence = 27.3 %	OR for age 50-54 (OR 2.2, 95% CI 1.7, 2.8) OR for age 55-64 (OR 2.6, 95% CI 2, 3.3) OR for age 65-74 (OR 1.8, 95% CI 1.3, 2.4) OR for age 65-74 (OR 2.1, 95% CI 1.5, 2.8)
22	Alrowayeh et al. 2010	Overall prevalence = 7.27 %	Not reported
23	Haukka et al. 2006	Overall prevalence = 38.6 % Prevalence of SP in 41-50 age group = 34% Prevalence of SP in > 50 age group = 44%	Not reported
24	Kaliniene et al. 2016	Overall prevalence = 53.9 % Prevalence of SP in 40-49 age group = 50.3% Prevalence of SP in 50-75 age group = 56.4%	OR for age 40-49 (OR 1.89, 95% CI 0.65, 3.53) OR for age 50-70 (OR 2.16, 95% CI 1.02, 4.99)
25	Janwantanakul et al. 2008	Overall prevalence = 17.68 % Prevalence of SP in 40-49 age group = 19%	Not reported

		Prevalence of SP in 50-75 age group = 14%	
26	Lecrac et al. 2004	Overall period prevalence = 53% Period prevalence of SP in 40-49 age group = 50.2% Period prevalence of SP in >50 age group = 64.1% Period prevalence of SP in male (40-49) age group = 46% Period prevalence of SP in male (>50) age group = 60% Period prevalence of SP in female (40-49) age group = 51% Period prevalence of SP in female (>50) age group = 65% Incidence was 29 among males , 21 among females Incidence % male (40-49) age group =25 Incidence % male (>50) age group = 25 Incidence % female (40-49) age group = 20 Incidence %female (>50) age group = 13	Female sex (OR 1.228, 95% CI 0.65, 2.31)
27	Hinsley et al. 2022	Prevalence = 22.2%	-
28	Fehringer et al. 2008	Prevalence = 22%	-
29	Niedhammer et al.	Prevalence of shoulder disorders = 65% Prevalence of CSP = 29%	Age >40 OR 4.64 (95% CI 1.56,13.8)

9.9 Appendix 9. ISAC approval

Medicines & Healthcare products Regulatory Agency

CPRD

1 General information

Protocol reference Id
21_000633

Study title
Epidemiology of shoulder pain and associated risk factors in the United Kingdom: a population-based study of UK primary care data using clinical practice research datalink (CPRD).

Research Area

Disease Epidemiology

Health Services Delivery

Does this protocol describe an observational study using purely CPRD data?
Yes

Does this protocol involve requesting any additional information from GPs, or contact with patients?
No

2 Research team

Role	Chief Investigator
Title	Assistant Professor
Full name	Michelle Hall
Affiliation/organisation	University of Nottingham
Email	michelle.hall@nottingham.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Role	Corresponding Applicant
Title	PhD student
Full name	Nouf Alotaibi
Affiliation/organisation	University of Nottingham
Email	msxna20@nottingham.ac.uk
Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Emeritus Professor
Full name	Michael Doherty
Affiliation/organisation	University of Nottingham
Email	Michael.Doherty@nottingham.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Role	Collaborator
Title	Clinical Assistant Professor
Full name	Barbara Iyen
Affiliation/organisation	University of Nottingham
Email	Barbara.iyen@nottingham.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

Role	Collaborator
Title	Quantitative Researcher
Full name	Subhashisa Swain
Affiliation/organisation	University of Oxford
Email	Subhashisa.Swain@phc.ox.ac.uk
Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Senior Research Fellow
Full name	Yana Vinogradova
Affiliation/organisation	University of Nottingham
Email	yana.vinogradova@nottingham.ac.uk
Will this person be analysing the data?	Yes
Status	Confirmed

Role	Collaborator
Title	Professor of Epidemiology
Full name	Weiya Zhang
Affiliation/organisation	University of Nottingham
Email	weiya.zhang@nottingham.ac.uk
Will this person be analysing the data?	No
Status	Confirmed

3

Access to data

Sponsor

University of Nottingham

Funding source for the study

Is the funding source for the study the same as Chief Investigator's affiliation?
Yes
Funding source for the study
University of Nottingham

Institution conducting the research

Is the institution conducting the research the same as Chief Investigator's affiliation?
Yes
Institution conducting the research
University of Nottingham

Method to access the data

Indicate the method that will be used to access the data
Institutional multi-study licence
Is the institution the same as Chief Investigator's affiliation?
Yes
Institution name
University of Nottingham

Extraction by CPRD

Will the dataset be extracted by CPRD
No

Multiple data delivery

This study requires multiple data extractions over its lifespan
No

Data processors

Data processor is	Same as the chief investigator's affiliation
Processing	Yes
Accessing	Yes
Storing	Yes
Processing area	UK

4

Information on data

Primary care data

CPRD Aurum

Do you require data linkages

Yes

Patient level data

HES Admitted Patient Care

ONS Death Registration Data

NCRAS data

Covid 19 linkages

Area level data

Do you require area level data?

Yes

Practice level (UK)

Practice Level Index of Multiple Deprivation

Patient level (England only)

Patient Level Index of Multiple Deprivation

Withheld concepts

Are withheld concepts required?
No

Linkage to a dataset not listed

Are you requesting a linkage to a dataset not listed?
No

Patient data privacy

Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?
No

5

Protocol information

Lay Summary

Shoulder pain is a common complaint that can lead to sleeping difficulties, work disability and functional limitations in daily activities such as dressing and driving. It affects between 5% and 47% of the adult population annually worldwide. In the United Kingdom (UK), about 2.4% of people aged between 18 and 60 years old annually consult their general practitioners (GPs) for shoulder pain and the number of consultations in primary care for shoulder pain appears to be increasing. Shoulder pain increases with age and is higher in women than in men. However, whether the occurrence of shoulder pain has changed in the past 21 years in the UK, its variations between regions and its major consequences remain largely unknown.
From a population health perspective, having insight into the frequency of shoulder pain in the UK will help to understand the disease burden and the population at risk, and provide effective management for patients in primary care. Therefore, this research aims to investigate the current frequency of shoulder pain, the trend in the past 21 years, variation between different areas and related risk factors in the UK population.

Technical Summary

This project aims to determine the prevalence and incidence, risk factors, and outcomes of shoulder pain from 2000 to 2020.
Prevalence and incidence rates in 2019 will be used to present the current disease burden as 2020 estimates may be unrepresentative due to the COVID pandemic. Age, sex and geographic distribution, and trends in prevalence and incidence from 2000-2020 will be examined. We will undertake a case-control study to examine risk factors. Incident cases of shoulder pain will be identified between 2000 and 2020 (first diagnosis date as index date). Each will be matched with a control without shoulder pain by age, sex, and practice at the index date. We will compare risk factors such as alcohol, smoking, body mass index (BMI), ethnicity and socioeconomic status between cases and controls by the index date retrospectively. A logistic regression model will be used to estimate odds ratios.
We will then undertake a cohort study to follow up the cases and controls from the index date for the outcomes of interest including number of general practitioner (GP) consultations and hospitalisations per year, comorbidities, and all-cause mortality. For comorbidity, people at risk of a specific comorbidity of interest will be followed up. For example, diabetes at the index date will be excluded in order to capture incident diabetes. The Cox regression model will be used for this analysis. Hospital episode statistics (HES) will be used to determine hospitalisations. Office for National Statistics (ONS) death registration data will be used for estimating all-cause mortality.

This research will increase understanding of the burden of shoulder pain in the UK, potential use of health resources because of shoulder pain and its comorbidities. It will also inform early intervention strategies for people at higher risk of comorbidity.

Outcomes to be measured

Primary outcomes :

1- The current prevalence and incidence of shoulder pain in the UK, overall, by age, sex, and regions. We will use 2019 data to present the current prevalence and incidence to avoid the bias due to the COVID-19 pandemic.

2- The risk factors associated with shoulder pain.

Secondary outcomes:

3- The outcomes of shoulder pain.

We will determine the number of GP consultations per year, the frequency of hospitalisations per year and all-cause mortality. We will also examine the incidence of comorbidities and their relative risk in people with shoulder pain versus those without.

4- Types of shoulder pain and their prevalence and incidence in 2019.
The prevalence of different diagnostic codes for shoulder pain in the year 2019 will be examined.

- The following pathoanatomical classification system of shoulder disorders has been widely used in clinical practice (1): rotator cuff; biceps tendon; adhesive capsulitis; glenohumeral arthritis; acromioclavicular joint abnormalities.
- A non–specific shoulder pain category is also frequently found in the general population and clinical practice due to the lack of a consistent standardised diagnostic approach for the shoulder (1).
- The diagnosis of shoulder disorders in the primary care (the Guidelines on referral and treatment) in the NHS is described in Appendix 1

5- The trends of shoulder pain in the past 21 years (2000 – 2020)
We will report the prevalence and incidence each year and examine the trend from 2000 to 2020. We will include 2020 data to examine the impact of the pandemic/lockdown on shoulder pain.

Objectives, specific aims & rationale

Aims :

The main aim of this study is to examine the prevalence, incidence, risk factors and outcomes of shoulder pain in the UK population.

The specific objectives :
• To determine the current prevalence and incidence of shoulder pain in the UK.
• To determine the trends of shoulder pain in the past 21 years (2000 – 2020)
• To examine the risk factors and comorbidities associated with shoulder pain
• To examine consultation rates, rates of hospitalisation, morbidity and mortality outcomes associated with shoulder pain

Rationale:
The most recent study on prevalence and incidence of shoulder pain in the UK primary care was undertaken in 2000 (2). It found that the overall annual adult prevalence of patients consulting GPs for shoulder pain was 2.4%, and that prevalence increased with age and was higher in women compared to men (2). However, this study has several limitations. First, the Mediplus general practice database used in that study has limited regional coverage of Scottish and Northern Irish general practices, whereas the CPRD data that will be used in our study is comprehensive and includes more regions in the UK and a much larger number of patients (3). Second, only two risk factors, age and sex, were explored, whereas we will additionally examine other possible risk factors associated with shoulder pain such as smoking, socioeconomic status, body mass index (BMI), ethnicity, and alcohol. We will also examine outcomes of shoulder pain in the UK such as number of hospitalisations per year, number of consultations, associated comorbidities and mortality rate.
Additionally, although shoulder pain has been reported to be associated with some conditions such as diabetes, few studies have investigated other possible associated comorbidities such as lung disease, cardiovascular disease and widespread chronic pain (4-6), and none have been conducted in the UK. Furthermore, the trend, geographic distribution and outcomes of shoulder pain have not been examined in the UK.
Therefore, this study aims to address this gap and understand the burden of shoulder pain conditions, and the population at risk, in order to inform the planning of effective management of shoulder pain in primary care in the UK.

Study background

Shoulder pain is a common musculoskeletal complaint affecting up to 47% of the adult population worldwide (7). Shoulder pain can cause movement restriction, sleeping disorders and working difficulties and can lead to functional limitations in daily activities (7-9). The overall prevalence of shoulder pain in the United Kingdom (UK) is approximately 7% (10) , but this increases with age to affect 26% of older people aged 60 or more (11). Shoulder pain is associated with several risk factors such as smoking, BMI and certain occupations such as heavy manual work (7, 9, 12). Current UK data exploring the prevalence and incidence of shoulder pain and the risk factors associated with this condition are sparse. In 1997, a cross-sectional study by Pope et al.(13) compared the estimates of the occurrence of shoulder pain according to two aspects: first, different definitions of the shoulder; and second, by restricting the definition to include only those with associated disability. A postal questionnaire was sent to 500 patients registered in a general practice in south Manchester. Of the 312 people who completed the questionnaires, 173 were women and 139 were men. In total, 160 (51%) people reported shoulder pain, giving a one month period prevalence ranging from 31% to 48% across the four definitions of the shoulder (13). Limiting the definition to include patients with shoulder pain with associated disability restricted the point prevalence to 20% (13).

A prospective cohort study by Linsell et al.(2) assessed the incidence and prevalence of consultations for shoulder complaints in UK primary health care in 2000. They used the Mediplus database, which contains anonymised medical records of approximately 1,700,000 patients from 211 general practices in the UK. The overall annual prevalence of adult patients consulting GPs for shoulder pain was 2.4%. There was a significant increase in rates from 1% in the population aged 18–29 years old to 4% in those aged > 80 years old and the prevalence was higher in women aged 40 than in men aged 40 (X^2; $P<0.001$) (2). Additionally, they reported that a limited number of codes were used for reporting the diagnosis, with just five out of 426 Read codes related to shoulder conditions accounting for 75% of the diagnoses recorded by GPs. These five codes were; sprained shoulder, shoulder joint pain, dislocated shoulder, rotator cuff shoulder syndrome and shoulder syndrome. Further limitations of this study include the use of the Mediplus database which has limited regional coverage of Scottish and Northern Irish general practices, whereas the CPRD data includes more regions in the UK and a much larger number of patients (3). Patients with shoulder pain were followed up for just three years, and include the exploration of only two risk factors, age and sex.

Shoulder complaints have also been associated with several comorbidities such as diabetes, lung diseases, cardiovascular diseases and other musculoskeletal problems, However, few studies have examined this and only one study, in the United States, has used a cohort design (5, 14). A longitudinal cohort study by Vogt et al (2003), reported associations between shoulder pain and cardiovascular and neurological conditions in the older population (70 to 79 years old) (5). People with a history of heart attack or depression were more likely to have severe shoulder pain (OR= 1.9 95% CI 1.2-3.0; and OR= 2.5, 95%CI 1.3-3.9) respectively (5). In Finland, a large cross-sectional study reported an association between shoulder pain and other chronic musculoskeletal conditions such as low back pain (OR 2.9, 95%CI 2.4-3.5) and osteoarthritis of the knee and hip (OR 3.2, 95%CI 2.6-3.9, OR 3.7, 95%CI 2.9-4.8) respectively (14). There is limited evidence available for the UK on whether people with shoulder pain are more likely to have other long-term health conditions.

The burden of shoulder pain in the UK is likely to be high. It is estimated that there are around 1.5 million shoulder consultations in the UK with an annual total cost of £100 million (16). Data from 2003, indicated that around 22% of patients with shoulder pain were referred to secondary care, 31% were prescribed non-steroidal anti-inflammatory medications and 11% were treated by injections by their GP (2).

Study type

This is a population-based observational study to determine the incidence and prevalence of shoulder pain in the UK and its associated risk factors. It is a combination of descriptive, exploratory and hypothesis testing.

Descriptive and exploratory: To describe the incidence and prevalence of shoulder pain overall and by age, sex and geography. To explore the associated risk factors and the outcomes of shoulder pain (number of consultations/ comorbidities/ hospitalisation/ mortalities).

Hypothesis testing : We hypothesise that shoulder pain varies between UK regions and is associated with BMI, ethnicity, socio-economic status, smoking, alcohol consumption, comorbidities (eg, diabetes and chronic widespread pain/fibromyalgia), mortality rate and health care services utilisation.

Study design

We will use a combination of cross-sectional study, case control study and cohort study design to answer the different questions, specifically:
• cross-sectional studies to examine the prevalence of shoulder pain each year from 2000 to 2020 in the UK.
• A case-control study to examine risk factors associated with shoulder pain
• A cohort study to determine the annual incidence of shoulder pain in the UK and the outcomes associated with shoulder pain.

Feasibility counts

The expected number of patients available in the CPRD are approximately 21,000,000. An initial check with CPRD data using the Read codes (appendix 3) reveals that there are 1,280,484 incident shoulder pain related cases in up-to-standard (UTS) practices between 1st January 2000 and 31st December 2020. In the year 2019, 29,114 incident cases were recorded in CPRD GOLD database between (1stJan to 31st Dec).

Sample size considerations

We calculated sample size based on the primary outcomes: Sample size for prevalence Previous studies reported that the prevalence of shoulder pain in adults was approximately 26% (2, 12, 15). The sample size based on prevalence was calculated using the equation below (17). The sample size needed is 295 patients according to the following. n= (z2p(1-p))/d2 = (3.84 ·0.26(1-0.26))/0.0025 = 295 where Z is the statistic corresponding to level of confidence = 1.96, p is expected prevalence = 26%, d is precision = 0.05. Sample size for risk factors Assuming the expected proportion exposed in controls is 9% for smoking exposure, assumed odds ratio 2 and the power 90% (2, 17, 18), p=0.09, alpha=0.05, correlation coefficient among multiple factors (R2) is 0.5 (R2 ranges from 0-1, the larger the R2 is, the bigger the sample size) (19). G power was used to calculate the sample size for logistic regression (19). The total sample size needed for both groups is 507 to give 90% power at 5% significant level. More details of the sample size calculation and the power plot is provided in Appendix 2. Sample size for cohort study The sample size calculation for cohort study was based on a COX regression model where shoulder pain was used as a primary exposure and diabetes was used as an incident outcome. Given a background incident risk of 4% for diabetes in the UK population (9), a minimum hazard ratio (HR) of 1.2 (7,8) in people with shoulder pain (standard deviation of ln HR=0.5), and a multiple correlation coefficient (R2) of 0.2 among covariates in the model, the sample size needed is 46485. This will give a power of 90% at a significant level of 0.05 for the study and allow drop-outs of 15%. Similar calculation was repeated according to other HRs, e.g., for a more clinically meaningful hazard ratio of 2, the sample size needed 3271 (figure below). Details of the sample size calculation using STATA are provided below. - Sample size calculation for cohort study : Significance level (alpha) = 0.05 Power =0.9 Hazard ratio (HR) = 1.2 Standard deviation (SD) of ln HR= 0.5 Correlation (R2) = 0.2 Proportion of withdrawal (Pr_W) = 0.15 Probability of event (Pr_E) = 0.04 References for cohort sample size 7. StataCorp LP. Stata power and sample-size reference manual. Texas: A Stata Press Publication StataCorp LP Retreived October. 2013;12:2018. 8. Cleves M, Gould W, Gould WW, Gutierrez R, Marchenko Y. An introduction to survival analysis using Stata: Stata press; 2008. 9. González EL, Johansson S, Wallander MA, Rodríguez LA. Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. J Epidemiol Community Health. 2009;63(4):332-6.

Planned use of linked data and benefit to patients in England and Wales

We will use Hospital Episode Statistics (HES) to determine hospitalisation and ethnicity, and the Office for National Statistics (ONS) death registration data to estimate all-cause mortality. We will use practice and patient level index of multiple deprivation (standard) for descriptive purposes and to examine any differences across the socio-economic status. As there is more complete and robust availability of practice level IMD-linkage than patient level IMD-linkage, this measure of deprivation will complement the patient level IMD-linkage and will be used to assess whether shoulder pain incidence, prevalence and outcomes, differ by level of practice and socio-economic deprivation.

The use of these linked data will enable us to determine the health care utilisation by people with shoulder pain. This will inform the development of clinical practice guidelines and strategies for early intervention for people at risk of shoulder pain outcomes.

HES Outpatient data will not be used because of cost

Definition of the study population

Study population : The CPRD contains approximately 21,000,000 individuals (3). For our study, the data available between 2000 to 2020 will be used.

General inclusion criteria:
1- Age 18 or over
2- Registered for at least one year after the earliest date that the practice started contributing quality-assured (the up-to-standard) data to CPRD.
3- Minimum of 2 consultations to GP within 6 months for the same problem/complaint. The reason for choosing more than one consultation is to include patients with chronic shoulder pain and to exclude acute self-limiting cases. The first consultation date will be used as the index date.

Case definition of shoulder pain:

We will use Read codes to identify people with a diagnosis of shoulder pain from the CPRD between 1st January 2000 to 31st December 2020. But we will extract the SNOMED codes (for AURUM database) for our study. The Read codes included are available in appendix 3 (https://www.keele.ac.uk/mrr/).
Shoulder pain cases in our study are defined as patients who complain of shoulder pain and have at least 2 consultations of shoulder pain in primary care within the last 6 months and with no history of severe acute shoulder trauma or fracture in the past 6 months prior to the first consultation of shoulder pain. The first consultation date will be used as the index date.

Exclusion criteria :
1- Severe acute trauma, including fracture, in the past 6 months
2- Postoperative cases in the past 3 months.
3- Cervical root entrapment and neuralgia within 3 months before or after incident shoulder pain to exclude patients with referred pain to the shoulder
4- Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis

Selection of comparison groups/controls

Controls are participants registered in the CPRD who have no record of the above defined shoulder pain since registration. One control will be selected per shoulder pain case and will be matched in a 1:1 ratio to shoulder pain cases by year of birth, sex, and practice. The same index date will be assigned to the matched control for analysis.

Exposures, outcomes and covariates

Exposures:

- For the case control study the exposures are the risk factors associated with shoulder pain (e.g. smoking, ethnicity, socioeconomic status, BMI and alcohol) and comorbidities prior to shoulder pain (e.g. diabetes, cardiovascular conditions, sarcopenia, arthritis, pain in other joints, and hypothyroidism)
- For the cohort study the exposure is shoulder pain.

Outcomes
Primary outcomes :

1- Prevalence and incidence of shoulder pain in the UK

The prevalence and incidence by age, sex and UK region (choropleth)

2- Risk factors and comorbidities associated with shoulder pain

Secondary outcomes:

1- Number of GPs consultations, hospitalisations, comorbidities and mortalities
2- Prevalence and incidence of different types of shoulder pain
3- Trend of shoulder pain in the past 21 years (2000 – 2020)

Covariates
Age, sex and practice will be the major covariates for this project. They will be matched in both case control and cohort studies. Other covariates may be included such as BMI, social class, ethnicity, smoking and alcohol to examine the independent effect of an exposure, e.g., the association between shoulder pain and diabetes.

Code list :

• The available Read code list for shoulder musculoskeletal conditions (https://www.keele.ac.uk/mrr/) have been updated and adapted according to the inclusion and exclusion criteria to identify people with a diagnosis of shoulder pain (Appendix 3) But we will extract the SNOMED codes for our study.
• For comorbidities, the codes will be obtained from the primary care unit, the University of Cambridge (https://www.phpc.cam.ac.uk/pcu/research/research-groups/crmh/cprd_cam/codelists/v11/).
• Ethnicity will be identified using Read codes, the codes will be obtained from Fairhurst et al.(2016) study (20) (https://clinicalcodes.rss.mhs.man.ac.uk/medcodes/article/47/codelist/res47-ethnicity/). Ethnicity will be categorised as White, Mixed, Asian, or Asian British, Black or Black British, other and unknown.

Comorbidity list :

We will use an extensive list of comorbidities, chronic conditions listed in the US Department of Health and human services Initiative on Multiple chronic conditions (21) and the Charlson comorbidity index (22) (appendix 4)
There are several key comorbidities that we will primarily aim to explore, including: diabetes; lung (asthma and chronic obstructive pulmonary disease (COPD)) and cardiovascular diseases; neurological conditions (stroke and other neurologic); other musculoskeletal conditions such as fibromyalgia and gout); osteoarthritis; ; arthritis; hypertension; depression and dementia. The rest of other comorbidities will be examined as appropriate. The list of comorbidities is provided in Appendix 4

Data/statistical analysis

All data analysis will be done using R (3.4.1) and STATA SE v 15 software.

1- To determine the current prevalence and incidence of shoulder pain in the UK in the year 2019.

Prevalence will be calculated by dividing the number of people diagnosed with shoulder pain at 1st July 2019 by the total number of people in the sample at that time point of the calendar year. Incidence rate for shoulder pain will be calculated by the number of new cases of shoulder pain divided by the number of person- years at risk in the year 2019. Eligible population for incidence rate calculations should have a first time recording of shoulder pain during the study period. We will identify people at risk (i.e., no previous diagnosis of shoulder pain) at 1st January of 2019 and follow them until 31st December of 2019 to identify incident cases with shoulder pain (i.e. the first diagnosis of shoulder pain) to estimate the incidence rate of shoulder pain. Person-years of follow up will be calculated by number of persons multiplied by the number of years.
The prevalence and incidence will be reported overall and by age, sex, and UK regions (choropleth) and the prevalence of different types of shoulder pain in 2019 will also be examined. The 95% confidence interval (CI) will be calculated for the prevalence and incidence.

2- To determine the trends of shoulder pain in the past 21 years (2000 – 2020).

We will examine the trend of prevalence and incidence of shoulder pain in the UK over the past 21 years (2000-2020). We will follow a similar approach as mentioned in objective 1 but for each year starting from 2000 to 2020. The 95% confidence interval (CI) will be calculated for the prevalence and incidence for the 21 years (2000-2020).

Prevalence and incidence for each year from 2000 until 2020 will be standardised according to the age and sex structure of the 2019 CPRD population. We will use joinpoint analysis to determine the trend/changes of shoulder pain in the UK over the past 21 years (23). The joinpoint model analysis constitutes of linear trends, which help to report the changes in trend (24).

3- To examine the risk factors and comorbidities associated with shoulder pain

We will identify incident shoulder pain cases diagnosed between 2000 and 2020 (first diagnosis date as index date). A control group without shoulder pain will be identified throughout the study period with the same year of birth, sex and in the same practice at the index date (matching). We will compare the risk factors/exposures that are recorded prior to incident shoulder pain such as alcohol, ethnicity, smoking, socioeconomic status and BMI between cases and controls by the index date retrospectively using a case control study design.We will compare comorbidities that are recorded prior to incident shoulder pain such as diabetes, cardiovascular conditions, hypothyroidism, and arthritis between cases and controls by the index date retrospectively.The patient characteristics will be presented using descriptive statistics (frequency, range and median). Mean and standard deviation will be used for continuous variables and number and percentage for categorical variables. Chi squared X2 test will be used to assess the association between each risk factors such as smoking, ethnicity, alcohol consumption, socioeconomic status, and shoulder pain.

Odds ratio (OR) and 95% confidence interval (CI) will be calculated using the logistic regression for association. Independent effect of each risk factors and their interaction will be examined as appropriate. Adjusted ORs will be estimated after adjusting for the following covariates age, sex and practice.

4- To examine outcomes of the shoulder pain

To examine the outcomes of shoulder pain such as number of consultations per year, number of hospitalisations per year, associated comorbidities and mortality, the identified cases and controls from the case control study described above will be followed up. Patient characteristics will be

presented using descriptive statistics (mean/median/frequency).

General practitioners (GP)-consultations in terms of the total number of consultations/ visits for any reasons including shoulder pain per year will be extracted. The number of hospital admissions for shoulder reasons or shoulder complaints per year including day case and in-patient admission will be extracted from HES data. The average consultations/admissions per year will be calculated by dividing the total number of consultations/admissions after the index date by the total active registration period in year after the index date. All-cause mortality will be calculated as the total number of deaths from all causes of death for a population during the period (1st Jan 2000- 31st Dec 2020) using Office for National Statistics death registration data.

Participants at risk for a specific comorbidity will be followed up from the index date for new cases of the comorbidity. Cumulative probability of having the comorbidity will be calculated for each group. Kaplan-Meier curve will be used to illustrate the difference between cases and controls. Proportional hazard assumption will be tested using Schoenfeld residual plots and PH test. The COX regression model will be used to estimate the hazard ratio (HR) and 95%CI between two

groups, adjusted for confounding factors such as age, sex, BMI, smoking, alcohol. For associated comorbidities, the survival analysis and the landmark analysis will be used.
Same analysis will be applied for all caused mortality.

Plan for addressing confounding

The matching of the case with controls will allow us to control bias and to deal with important confounders such as age, sex, and practice. In the cohort study, as we will be reselecting people at risk for an event, the previous matching may have been affected. We will therefore include age, sex, practice together with other potential confounding factors in the COX model for further adjustment for the association between shoulder pain and a specific comorbidity/all-cause mortality.
Furthermore, we will use the Bonferroni method to control the false discovery rate (FDR)(25) due to the multiple testing. Additionally, the landmark analysis will be used to minimise immortal time bias when examining the outcomes (e.g comorbidities) in the cohort study (26). We will use the date 12 month after the index date as the landmark date to start the follow-up. Any outcome that occurs prior to the landmark date will not be counted for both exposure and non-exposure groups. This is because only events that occur after the qualification of the exposure (two consultations within 6 months) should be counted. The additional 6 months will ensure some period to measure exposure more quantitatively, e.g., number of consultations for shoulder pain in the first year of the diagnosis as a surrogate marker of the severity of shoulder pain for dose response analysis. For this purpose, we may undertake a sensitivity analysis for different landmark dates, e.g., 6, 12, 24, and 36 months after the index date, as appropriate (27).

Plans for addressing missing data

Multiple Imputations by chained equations will be used to address missing continuous data when assumed to be missing at random (28). All other patient variables with no missing records/values will be included as auxiliary variables in the imputation models to improve prediction. Ten imputed datasets will be created.

Patient or user group involvement

This study does not involve direct patients contact or involvement. However, the Arthritis Research UK Pain Centre has a Public and Patient Involvement (PPI) group,the findings will be shared with the group for dissemination to patients.

Plans for disseminating & communicating

The findings from this study will be presented at primary care, orthopaedic and shoulder conferences and published in peer reviewed journals. The summary of the study findings will be shared with GPs, stakeholders, the social media, and through the Pain Centre Versus Arthritis and NIHR BRC Nottingham (Musculoskeletal theme). The CPRD will also be informed about the results of the study for dissemination on the CPRD website.

Conflict of interest statement

We declare no conflict of interest

Limitations of study design

Observational studies using primary care databases have some limitations. Firstly, in this study the case definition of shoulder pain is based on diagnosis by the General Practitioners (GPs) and therefore may be subject to misclassification bias or misdiagnosis. Secondly, errors in shoulder pain coding may affect the data quality. Thirdly, there may be missing data with respect to recording of BMI, alcohol intake etc. and occupational activity is not recorded in CPRD. Fourthly, not all people with shoulder pain may consult their GP so prevalence may be underestimated.

References

1. Linaker CH, Walker-Bone K. Shoulder disorders and occupation. Best Pract Res Clin Rheumatol. 2015;29(3):405-23.
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. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. Int J Epidemiol. 2019;48(6):1740-g.
4. Wright AR, Shi XA, Busby-Whitehead J, Jordan JM, Nelson AE. The Prevalence of Neck and Shoulder Symptoms and Associations with Comorbidities and Disability: The Johnston County Osteoarthritis Project. Myopain. 2015;23(1-2):34-44.
5. 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.
6. Luime JJ, Koes BW, Hendriksen IJ, Burdorf A, Verhagen AP, Miedema HS, et al. Prevalence and incidence of shoulder pain in the general population; a systematic review. Scand J Rheumatol. 2004;33(2):73-81.
7. 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.
8. 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.
9. Pribicevic M. The epidemiology of shoulder pain: A narrative review of the literature. Pain in perspective. 2012.
10. 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.
11. Chard MD, Hazleman BL. Shoulder disorders in the elderly (a hospital study). Ann Rheum Dis. 1987;46(9):684-7.
12. Woolf AD. Bone and Joint Decade report: moving together beyond the decade. Preface. Best Pract Res Clin Rheumatol. 2012;26(2):167-8.
13. 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.
14. Mäkelä M, Heliövaara 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.
15. van der Windt DA, Burke DL, Babatunde O, Hattle M, McRobert C, Littlewood C, et al. Predictors of the effects of treatment for shoulder pain: protocol of an individual participant data meta-analysis. Diagn Progn Res. 2019;3:15.
16. Watson J, Helliwell P, Morton V, Adebajo A, Dickson J, Russell I, et al. Shoulder acute pain in primary healthcare: is retraining effective for GP principals? SAPPHIRE--a randomized controlled trial. Rheumatology (Oxford). 2008;47(12):1795-802.
17. Pourhoseingholi MA, Vahedi M, Rahimzadeh M. Sample size calculation in medical studies. Gastroenterol Hepatol Bed Bench. 2013;6(1):14-7.
18. Wang K, Ho V, Hunter-Smith DJ, Beh PS, Smith KM, Weber AB. Risk factors in idiopathic adhesive capsulitis: a case control study. J Shoulder Elbow Surg. 2013;22(7):e24-9.
19. Hsieh FY, Bloch DA, Larsen MD. A simple method of sample size calculation for linear and logistic regression. Stat Med. 1998;17(14):1623-34.
20. Fairhurst C, Martin F, Watt I, Doran T, Bland M, Brackenbury WJ. Sodium channel-inhibiting drugs and cancer survival: protocol for a cohort study using the CPRD primary care database. BMJ Open. 2016;6(9):e011661.
21. Medicine C for : Baltimore MS 7500 BS UMC. chronic conditions US2017 [
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
23. Martinez-Beneito MA, García-Donato G, Salmerón D. A Bayesian joinpoint regression model with an unknown number of break-points. The Annals of applied statistics. 2011;5(3):2150-68.
24. Yu B, Barrett MJ, Kim H-J, Feuer EJ. Estimating joinpoints in continuous time scale for multiple change-point models. Computational statistics & data analysis. 2007;51(5):2420-7.
25. Rice TK, Schork NJ, Rao DC. Methods for handling multiple testing. Advances in genetics.

2008 Jan 1;60:293-308.
26. Morgan CJ. Landmark analysis: A primer. J Nucl Cardiol. 26. United States2019. p. 391-3.
27. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Effect of allopurinol on all-cause mortality in adults with incident gout: propensity score-matched landmark analysis. Rheumatology (Oxford). 2015;54(12):2145-50.
28. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338:b2393.
29. Cagliero E, Apruzzese W, Perlmutter GS, Nathan DM. Musculoskeletal disorders of the hand and shoulder in patients with diabetes mellitus. Am J Med. 2002;112(6):487-90.
30. Thomas SJ, McDougall C, Brown ID, Jaberoo MC, Stearns A, Ashraf R, et al. Prevalence of symptoms and signs of shoulder problems in people with diabetes mellitus. J Shoulder Elbow Surg. 2007;16(6):748-51
31. Cole A, Gill TK, Shanahan EM, Phillips P, Taylor AW, Hill CL. Is diabetes associated with shoulder pain or stiffness? Results from a population based study. J Rheumatol. 2009;36(2):371-7.
32. Laslett LL, Burnet SP, Jones JA, Redmond CL, McNeil JD. Musculoskeletal morbidity: the growing burden of shoulder pain and disability and poor quality of life in diabetic outpatients. Clin Exp Rheumatol. 2007;25(3):422-9.
33. Gill TK, Shanahan EM, Taylor AW, Buchbinder R, Hill CL. Shoulder pain in the community: an examination of associative factors using a longitudinal cohort study. Arthritis Care Res (Hoboken). 2013;65(12):2000-7.
34. Rauoof MA, Lone NA, Bhat BA, Habib S. Etiological factors and clinical profile of adhesive capsulitis in patients seen at the rheumatology clinic of a tertiary care hospital in India. Saudi Med J. 2004;25(3):359-62.
35. Struyf F, Lluch E, Falla D, Meeus M, Noten S, Nijs J. Influence of shoulder pain on muscle function: implications for the assessment and therapy of shoulder disorders. Eur J Appl Physiol. 2015;115(2):225-34.
36. Gerdle B, Björk J, Cöster L, Henriksson K, Henriksson C, Bengtsson A. Prevalence of widespread pain and associations with work status: a population study. BMC Musculoskelet Disord. 2008;9:102.
37. Coronado RA, Simon CB, Valencia C, George SZ. Experimental pain responses support peripheral and central sensitization in patients with unilateral shoulder pain. Clin J Pain. 2014;30(2):143-51.
38. Leijon O, Wahlström J, Mulder M. Prevalence of self-reported neck-shoulder-arm pain and concurrent low back pain or psychological distress: time-trends in a general population, 1990-2006. Spine (Phila Pa 1976). 2009;34(17):1863-8.
39. Huang SW, Wang WT, Chou LC, Liao CD, Liou TH, Lin HW. Osteoarthritis increases the risk of dementia: a nationwide cohort study in Taiwan. Sci Rep. 2015;5:10145.

40. Weber A, Mak SH, Berenbaum F, Sellam J, Zheng YP, Han Y, et al. Association between osteoarthritis and increased risk of dementia: A systemic review and meta-analysis. Medicine (Baltimore). 2019;98(10):e14355.

Appendices

appendix-1-diagnosis-of-shoulder-problems-in-primary-care.pdf

appendix-2---sample-size-calculations.pdf

appendix-3-shoulder-musculoskeletal-conditions-code-list.pdf

appendix-4-list-of-comorbidities.pdf

Grant ID

Sample size calculation for the cross-sectional study

Based on a 7% prevalence of shoulder pain in the general population (Urwin et al., 1998), the sample size needed was calculated using the equation below (Pourhoseingholi et al., 2013). To provide 4% level of precision (d), with Z, which is the statistic corresponding to level of confidence (1.96), the sample size required was 150 participants.

$$N = \frac{z2p(1-p)}{d2}$$

For incidence, same formula above was used. Incidence for shoulder pain in previous research were approximately 7.7 per 1000 person years (Lucas et al., 2022). To provide 4% level of precision (d), with Z, which is the statistic corresponding to level of confidence (1.96), the sample size required was 419 participants.

9.10 Appendix 10. Medical code list for chronic shoulder pain

Table 9-6 Medical code list for chronic shoulder pain

Shoulder Diagnosis	Medical Code
Internal impingement of left shoulder	84496310000061
Internal impingement of right shoulder	84496510000061
Subacromial bursitis of right shoulder	84511610000061
Subacromial bursitis of left shoulder	84512910000061
Sub coracoid impingement of right shoulder	3528468013
Subdeltoid bursitis of right shoulder	3528473019
Subdeltoid bursitis of left shoulder	3528471017
Scapulothoracic bursitis of left shoulder	3528231013
Non-traumatic complete rupture of RC of bilateral shoulders	94796210000061
Derangement of shoulder	310585011
Osteoarthritis of shoulder joint	35949510000061
Osteoarthritis of shoulder region	35949710000061
Frozen shoulder	1786699016
Bursitis of shoulder	359546010
Tendon rupture - shoulder	89147100000611
Shoulder tendon rupture	57306210000061
Tendon rupture - shoulder	57306310000061
Tendinitis of bilateral RCs	98730410000061
Tendinitis of left RC	98730510000061
RC arthropathy of right shoulder	98730710000061
RC arthropathy of left shoulder	98730910000061
RC arthropathy of bilateral shoulders	98731110000061
Bilateral RC arthropathy of shoulder	98731010000061
Tendinosis of right shoulder	98785610000061
Tendinosis of left shoulder	98786410000061
Shoulder joint pain	400244011
Chondrocalcinosis due to dicalcium phosphate crystals, of the shoulder region	55217100000611
Chondrocalcinosis due to pyrophosphate crystals, of the shoulder region	55228100000611
Chondrocalcinosis – pyrophosphate, of the upper arm	55232100000611
Localized, primary osteoarthritis of the shoulder region	309885015
Localized, secondary osteoarthritis of the shoulder region	309918012
Localized osteoarthritis, unspecified, of the shoulder region	73671100000611
Other specified arthropathy of shoulder region	310183014
Loose body in joint of shoulder region	310309019

Detachment of the glenoid labrum and/or capsule of the shoulder joint	48128010000061
Glenoid labrum detachment	310569018
Acromioclavicular joint pain	48140510000061
Arthralgia of acromioclavicular joint	310819018
Stiff acromioclavicular joint NEC	310883011
Other joint symptoms of the shoulder region	310911019
Painful shoulder	89066100000611
Other specified joint disorders of the shoulder region	311013011
Joint disorder NOS of shoulder region	311025014
Shoulder syndrome	89103100000611
Shoulder syndrome	55604710000061
Supraspinatus tendinitis	311325017
Painful arch syndrome	359542012
Supraspinatus syndrome	1778711014
Supraspinatus tendonitis	22164100000011
Partial thickness RC tear	311326016
Full thickness RC tear	311327013
RC complete rupture	16482100000611
Complete rupture of RC	48161410000061
Subacromial impingement	311336012
Coracoid impingement	311337015
Clavicle pain	312238013
Complete tear, shoulder joint	320320015
Complete tear, shoulder joint NOS	320324012
Rupture infraspinatus tendon	320507019
Rupture of infraspinatus tendon	48532210000061
Rupture subscapularis tendon	320508012
Osteoarthritis of shoulder region	35949510000061
Osteoarthritis of shoulder	310011016
Osteoarthritis of acromioclavicular joint	310013018
Infraspinatus tendinitis	51419310000061
Shoulder impingement syndrome	51419610000061
Impingement syndrome of shoulder region	78457100000611
Impingement syndrome of shoulder	51419710000061
Subscapularis tendinitis	55604810000061
Calcific tendinitis of shoulder	29452510000061
Calcific tendinitis of the shoulder	483645017
Calcific tendonitis of shoulder	29452810000061
Shoulder joint painful on movement	439693015
Shoulder joint painful on movement	18927610000061

Shoulder joint - painful arc	58597510000061
Impingement sign	30017810000061
Osteoarthritis of joint of left shoulder region	81020110000061
Osteoarthritis of joint of right shoulder region	11892541000006
Crystal arthropathy of shoulder region	309707019
Other Crystal arthropathy of the shoulder	309687013
Crystal arthropathy NOS, of shoulder region	309700017
Crystal arthropathy of NOS, of acromioclavicular joint	309710014
Periarthritis of shoulder	1786700015
Osteoarthritis of glenohumeral joint	63833910000061
Adhesive capsulitis of shoulder	21965100000011
Pericapsultis of shoulder	66175810000061
Rupture supraspinatus tendon	1786831018
Supraspinatus rupture	66214110000061
Supraspinatus tear	66214010000061
Tear of supraspinatus tendon	66214310000061
Subacromial bursitis	68050018
Subacromial bursitis	12268100000611
RC syndrome	311320010
RC syndrome, unspecified	400295013
RC syndrome NOS	400296014
RC rupture	25644310000061
RC tear	25644410000061
Rupture of RC of shoulder	25644510000061
RC tear arthropathy	68740510000061
Nontraumatic RC tear	70212610000061
Disorder of glenohumeral joint	71288210000061
Inflammation of RC tendon	72654910000061
Shoulder tendonitis	14083100000611
Tendinitis of RC	72654810000061
Chondrocalcinosis of shoulder region	309662018
Chondrocalcinosis of shoulder joint	72697810000061
Disorder of joint of shoulder region	310198011
Shoulder pain	14074100000611
Shoulder pain	75568012
Shoulder region pain	32312610000061
Disorder of acromioclavicular joint	310931015
Other symptoms of sternoclavicular joint	310930019

Stiff acromioclavicular joint NEC	310883011
Degenerative joint disease of shoulder region	309988017
Problem of shoulder	78586710000061
Subdeltoid bursitis	130615018
Osteoarthritis of sternoclavicular joint	310012011
Shoulder joint painful on external rotation	23645110000001
Shoulder joint painful on external rotation	18927710000061
Shoulder joint painful on movement	439693015
Shoulder joint painful on movement	18927610000061

9.11 Appendix 11. Methodological process of inclusion and exclusion criteria

Apply Inclusion Criteria:

1. **Filter people aged 18 and above**

People aged 18 and above were included to focus on adults, and this also ensures the relevance of the study to adult primary care patients.

2. **Ensure patients were registered ≥ 1 year before the index date and have data flagged as 'acceptable'.**

Patients were required to have been registered in the CPRD practice for at least 1 year before their first consultation for CSP. This criterion ensures that sufficient data for each patient is available to capture pre-existing conditions and prior medical history. It also minimises bias from newly registered patients whose medical history may be incomplete or unavailable. Only patients with acceptable data quality were included, ensuring the reliability of their information.

3. **Merge the SNOMED code list of CSP conditions with the dataset to identify CSP patients**

4. **Ensure there are at least two consultations for the same complaint (CSP) within 6 months (183 days).**

The rationale for this was to exclude self-limiting acute shoulder pain and focus on those with chronic symptoms, which often

require multiple consultations. The 6-months period was chosen to align with typical clinical practice for assessing chronicity in MSK conditions.

Apply Exclusion Criteria:

1. **Define the Exclusion Code Lists**
2. **Define the first consultation date**
3. **Exclude trauma/fracture within 6 months prior to the first consultation date**

   The rationale for this is that trauma can result in acute pain. Including these cases would lead to misclassification of the study cohort.

4. **Exclude shoulder surgery in the past 3 months before the first consultation**

   To ensure that only patients with chronic non-surgical shoulder pain are included, and not those recovering from recent procedures.

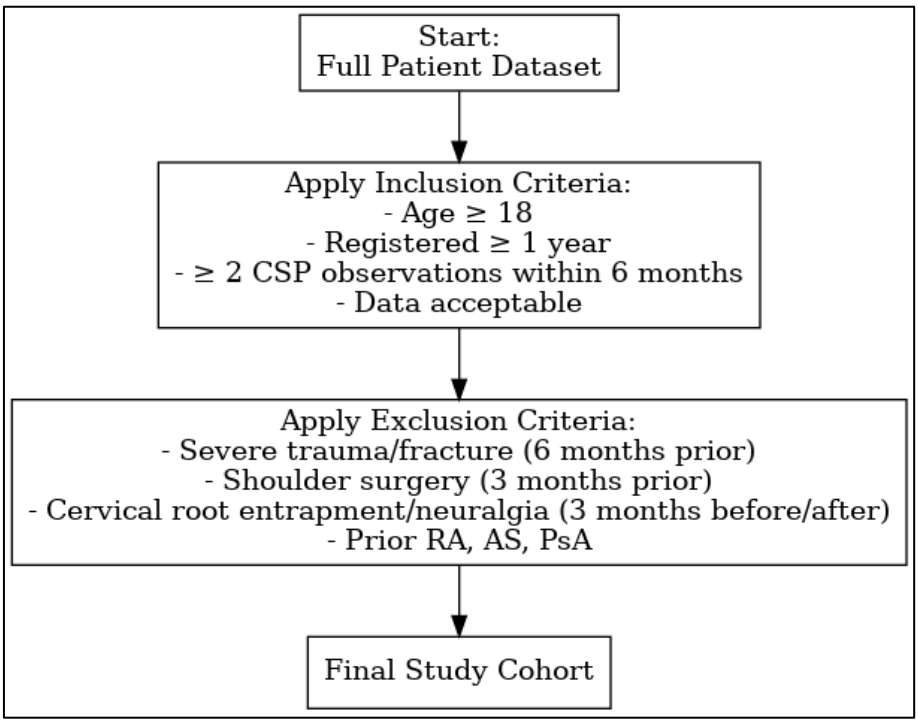
5. **Exclude cervical root entrapment/neuralgia 3 months before or after the incident of CSP.**

   People with cervical complaints often experience referred pain to the shoulder, which could confound the results of the study. Therefore, individuals with cervical root entrapment or neuralgia were excluded.

6. **Previous diagnosis of rheumatoid arthritis, ankylosing spondylitis, or psoriatic arthritis.**

   These conditions could lead to secondary shoulder pain due to joint involvement. By excluding patients with these conditions, the study focuses on primary CSP.

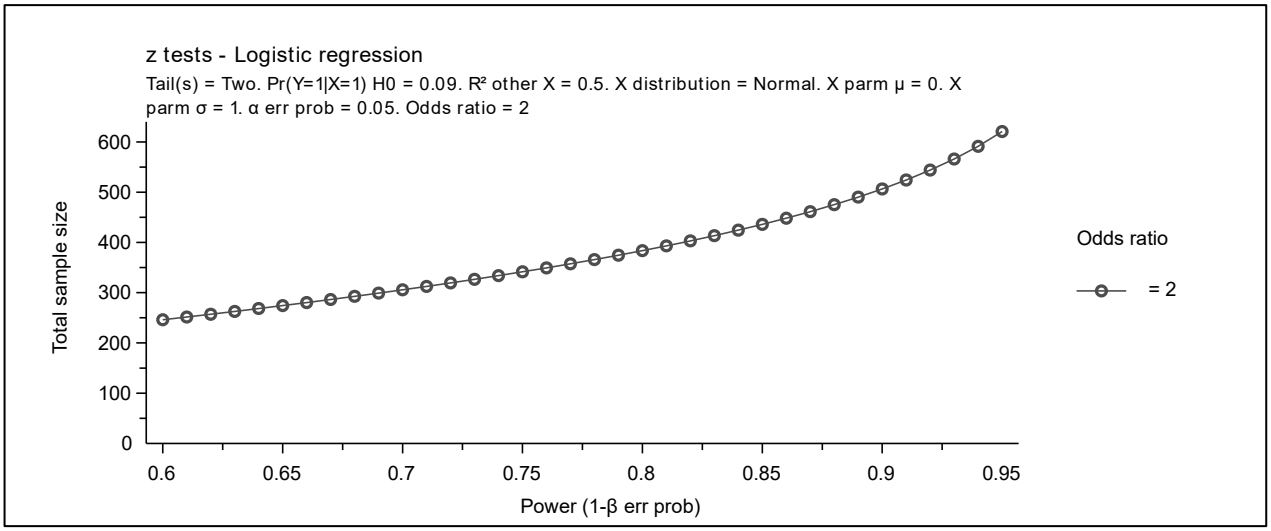
Figure 9.23 Process map of inclusion and exclusion criteria application



9.12 Appendix 12. Sample size calculation for the case-control study

The study was designed to have a sample size to detect an odds ratio (OR) of 1.5–2.0, with 90% power at the 5% significance level for a 1:1 matched case-control study. Assuming the expected proportion exposed in controls is 9% for smoking exposure, assumed odds ratio 2 and the power 90% (Mikkonen et al., 2008, Pourhoseingholi et al., 2013, Wang et al., 2013), p=0.09, alpha=0.05, correlation coefficient among multiple factors (R^2) is 0.5 (R^2 ranges from 0-1, the larger the R^2 is, the bigger the sample size (Hsieh et al., 1998). G power was used to calculate the sample size for logistic regression (Ngamjarus, 2016, Yenipınar et al., 2019). The total sample size needed for both groups is 507 to give 90% power at 5% significant level.

- The power plot



9.13 Appendix 13. Code lists of comorbidities

Diabetes

Medcodeid	Term
197761014	Type 2 DM
457954013	HbA1c level diabetes control and complications trial aligned
121589010	diabetes mellitus
197984010	Type 1 DM
280571000006116	non-insulin dependent DM
493774016	Type 2 DM
914391000006116	insulin treated type 2 DM
264693010	has seen dietician-DM
20191016	gestational diabetes mellitus
84471000006119	Type 2 DM
169731000006118	retinal abnormality-diabetes related
908831000006118	(RFC) DM
73466011	non-insulin dependent DM
251591016	H/O DM
47957100000110	DM type 2 review
772171000006114	Insulin dependent DM
194670100006110	provision of written information about DM and high haemoglobin A1c level
216195015	DM care by hospital only
456686014	Attending DM clinic
2549196011	patient offered DM structured education program
54706100000110	referral to XPERT DM structured education program
772161000006119	Insulin dependent DM
1946711000006113	provision of written information about DM and high cholesterol
2116661000000116	referral to community DM service
494564012	Type 1 DM
616511000006110	DM, adult onset, no mention complication
801901000006119	gestational diabetes mellitus
77727018	Insulin dependent DM
2533102013	Attending DM structured education programme
2533107019	patient DM education review

2622193012	DM with ketoacidosis
84841000006113	Type 2 DM
479981000000119	referral to community DM specialist nurse
532331000000119	DM structured education program
928561000006118	persistent microalbuminuria associated with type 2 DM
2182651000000118	referral to community DM clinic
457953019	HbA1 level (DM control and complications trial aligned)
459520010	DM resolved
493773010	NIDDM- non insulin dependent DM
2549069011	seen in community diabetes specialist clinic
616391000006114	nervous system disorder due to DM
840951000006119	insulin treated type 2 DM
84281000006115	Type 1 DM
881451000006113	DM adult onset
928541000006117	persistent proteinuria associated with type 2 DM
1946691000006110	provision of written information about DM and hypertension
2220161000000117	provision of written information about DM and driving
2586611000000113	seen by DM specialist nurse
26721014	DM insipidus
345487013	DM with neuropathy
2159956013	under care of DM specialist nurse
2474726011	pan retinal photocoagulation for DM
25261000000111	DM clinic administration
84651000006114	Type 1 DM
223291000000111	maturity onset DM
616421000006118	eye disorder due to DM
787111000006112	IDDM-insulin dependent DM
1713231000006118	Q DM (Score) type 2 DM10 year risk
2287971000000119	DM in remission
292466013	DM without complication
292590011	Type 2 DM poorly controlled
127041000006110	steroid induced DM
546871000000112	referral to DAFNE DM structured education program
616461000006112	DM with renal manifestation
616621000006115	Type 1 DM without complication

928501000006119	ketoacidosis in type1 DM
1694761000006113	Newly diagnosed DM
2288061000000111	Type 1 DM in remission
13949611000006116	no Maculopathy of LT eye with DM
13949641000006117	no Maculopathy of RT eye with DM
457329019	Type 2 DM without complication
259365016	Glucose tolerance test indicating DM
214921000006116	polyneuropathy in DM
281171000006119	Type 2 DM uncontrolled
764191000006112	foot abnormality- DM
1775381000006118	referred to DM services
2288071000000116	Type 2 DM in remission
546291000000112	XPERT DM structured program completed
8098931000006110	referral to DM education and self-management for ongoing and newly diagnosed DM structured education program
12623631000006115	referral to online DM structured education program
1230890017	Autonomic neuropathy due to DM
2674067015	latent autoimmune DM in adult
905621000006113	RFC DM
457328010	non-insulin dependent DM without complication
299601000000114	gastroparesis with type 1 DM
546001000000113	Attended XPERT DM structured education programme
616241000006112	DM induced by steroids
881441000006111	DM - juvenile
881501000006110	DM + neuropathy
914151000006112	retinopathy with type 2 DM
914261000006119	DM type 2 with nephropathy
1776581000006117	reason for referral- DM
1966441000006113	recommendation to self -refer for DM structured education
292475010	DM NOS with no mention of complication
2532967014	clinically significant macular oedema of RT eye due to DM
616191000006112	DM during pregnancy, child birth and the puerperium
616441000006113	peripheral vascular disorder due to DM
1957911000006111	H/O hypoglycaemic event in DM
411891014	unstable DM
483886014	maturity onset DM in youth

1230929011	secondary pancreatic DM
1780311019	Type 1 DM with persistent microalbuminuria
2159854012	DM key contact
299621000000117	gastroparesis with type 2 DM
622051000000118	h/o gestational DM
764201000006110	foot abnormality- DM related
914031000006118	renal disorder associated with type 2 DM
928461000006119	persistent proteinuria associated with type 1 DM
2586731000000110	under care of community-based DM specialist nurse
7480721000006111	h/o gestational DM
15518018	secondary DM
19931010	brittle DM
292512019	DM NOS with neurological manifestation
292577016	Type 2 DM with multiple complication
292617015	DM with other specified manifestation
1223147012	insulin treated type 2 DM
546151000000110	Attended DAFNE DM structured education programme
856771000006110	patient has been told has DM
913451000006117	Type 1 DM with renal complications
913661000006118	retinopathy with type 1 DM
928571000006113	Type 2 DM with persistent microalbuminuria
928581000006111	ketoacidosis in type 2 DM
2243331000000115	erectile dysfunction due to DM
4636471000006118	has seen dietician-DM
119846018	nephrogenic diabetes insipidus
292479016	DM NOS with ketoacidosis
292496015	DM with nephropathy NOS
292548017	Type1DM poorly controlled
292553010	Type 1 DM maturity onset
292579018	Type 2 DM with ulcer
1223148019	insulin treated non-insulin DM
1488898011	hyperosmolar ketonic state in type 2 DM
84481000006116	Type 2 DM poorly controlled
494831000000119	DM with cystic fibrosis
616481000006119	DM, adult onset, + neurological manifestation

616571000006118	DM, adult onset, + Other specified manifestation
616641000006110	DM, juvenile type, with ketoacidosis
841351000006110	insulin treated type 2 DM
881481000006117	DM+ nephropathy
881491000006119	DM+ eye manifestation
913841000006116	renal disorder associated with type 1 DM
914051000006113	disorder of eye with type 2 DM
914071000006115	neurological disorder associated with type 2 DM
938321000006116	exudative maculopathy associated with type 2 DM
2586691000000116	under care of hospital-based DM specialist nurse
7480661000006114	H/O DM type 2
13488541000006117	Non-proliferative retinopathy of left eye due to DM
13488551000006115	Non-proliferative retinopathy of right eye due to DM
14083811000006118	persistent microalbuminuria due to type 2 DM
457330012	Type 2 DM without complication
494186019	DM insipidus - pituitary
198461000000116	DM associated with pancreatic disease
913541000006118	Type 1 DM with multiple complication
1946681000006112	provision of written information about DM and hypertension
306112011	pre-existing DM, insulin -dependent
459313016	Type 2 DM with neuropathic arthropathy
616381000006111	DM with ketoacidosis coma
616491000006116	DM, adult onset, + Ophthalmic manifestation
914241000006118	polyneuropathy due to type 2 DM
14079681000006115	Non-proliferative retinopathy due to DM
292523015	DM NOS with peripheral circulatory disorder
303846016	nephrotic syndrome in DM
356085010	maturity onset DM in youth type 2
84661000006111	Type 1 DM poorly controlled
587521000006111	non-insulin dependent DM with renal complication
616531000006116	DM, adult onset, with ketoacidosis
772181000006112	Insulin dependent DM-poor control
881511000006113	DM+ peripheral circulatory disease
913711000006112	Insulin dependent DM-maturity onset
292622015	DM with unspecified complication

84291000006117	Type 1 DM poorly controlled
84551000006113	Type 2 DM with nephropathy
84851000006110	Type 2 DM poorly controlled
616501000006112	disorder due to type 2 DM
616551000006111	DM, adult onset, with renal manifestation
616581000006115	DM, adult onset, peripheral circulatory disorder
641581000006115	non-insulin dependent DM with retinopathy
840971000006112	DM autosomal dominant type 2
881461000006110	DM+ ketoacidosis-no coma
928511000006116	Type 1 DM with ketoacidosis
1823921000006119	DM confirmed
4636411000006110	Diet controlled DM
483882011	maturity onset DM in youth
2476117016	maturity onset DM in youth type 1
84921000006110	renal disorder due to type 2 DM
127051000006112	steroid induced DM without complication
377001000006117	DM
616831000006118	DM with gangrene
746791000006111	Insulin dependent DM without complication
772151000006116	Insulin dependent DM-maturity onset
928521000006112	ketoacidosis coma in type1 DM
928551000006115	Type 2 DM with persistent proteinuria
2686071000006114	gestational diabetes mellitus
292478012	other specified DM with ketoacidosis
429971019	unstable type 1 DM
457326014	Type 1 DM without complication
84741000006118	Type 1 DM with nephropathy
280591000006115	non-insulin dependent DM with neuro complication
616351000006115	DM with gangrene
674961000006118	Peripheral circulatory disorder associated with type 2 DM
850691000006118	hyperosmolar non ketonic state in type 2 DM
913481000006113	Type 1 DM with ophthalmic complication
938301000006114	exudative maculopathy associated with type 1 DM
292503016	DM NOS with ophthalmic manifestation
292583018	Type 2 DM with gangrene

354316011	kidney disorder due to DM
457327017	Insulin dependent DM without complication
13751000006117	other specified DM with multiple complications
84731000006111	multiple complications of type 1 DM
280551000006114	non-insulin dependent DM with ulcer
280581000006118	non-insulin dependent DM with multiple complication
771411000006117	Insulin dependent DM with retinopathy
881521000006117	DM+ other complications
913681000006111	Insulin dependent DM poor control
914301000006111	Type 2 DM with diabetic cataract
1667921000000117	Type 2 DM with gastroparesis
1667941000000112	Type 1 DM with gastroparesis
292540012	Type 1 DM with ulcer
292541011	Type 1 DM with gangrene
292589019	Type 2 DM poorly controlled
459161015	Type 1 DM with hypoglycaemic coma
459167016	Type 2 DM with hypoglycaemic coma
459296014	Type 1 DM with neuropathic arthropathy
459308015	Type 2 DM with peripheral angiopathy
459310018	Type 2 DM with arthropathy
2160090014	DM induced by non- steroid drugs
84371000006110	Type 1 DM with nephropathy
84541000006111	Type 2 DM with multiple complication
84581000006117	Type 2 DM with ophthalmic complications
84611000006113	Type 2 DM with renal complication
84671000006116	Type 1 DM maturity onset
616451000006110	DM with polyneuropathy
616561000006113	DM, adults with gangrene
616601000006113	DM, juvenile type+ ophthalmic manifestations
771361000006113	Insulin dependent DM with hypoglycaemic coma
771381000006115	Insulin dependent DM with multiple complication
771491000006110	Insulin dependent DM with ophthalmic comps
913441000006119	Insulin dependent DM with renal complication
913471000006110	Insulin dependent DM with ophthalmic complication
913651000006115	Insulin dependent DM with retinopathy

914221000006113	Type 2 DM with mononeuropathy
7480691000006118	h/O DM type 1
14072461000006116	Neuropathy due to DM
14072591000006111	disorder of macula due to DM
14092431000006119	disorder of right macula due to DM
14092441000006112	disorder of left macula due to DM
135166013	Acquired nephrogenic diabetes insipidus
292484010	hyperosmolar coma associated with DM
292489017	DM NOS with ketoacidosis coma
292495016	other specified DM with renal complications
292565014	DM with multiple complications
292606016	malnutrition -related DM with ketoacidosis
459162010	Insulin dependent DM with hypoglycaemic coma
2817479019	hyperglycaemic crisis in DM
13761000006115	other specified DM with neurological complications
72651000006114	unstable insulin dependent DM
84561000006110	Type 2 DM with neurological complication
84621000006117	Type 2 DM with retinopathy
84761000006119	Type1DM with neuropathic arthropathy
84871000006117	cataract due to DM 2
84991000006112	Type 2 DM with retinopathy
281161000006114	non-insulin dependent DM with diabetic cataract
616661000006114	DM, juvenile type, with renal manifestation
616671000006119	DM, adult onset, with neurological manifestation
616681000006116	DM, juvenile type + other specified manifestation
771391000006117	Insulin dependent DM with nephropathy
913501000006115	Insulin dependent DM with neurological complication
913511000006117	Type 1 DM with neurological complication
913531000006111	Insulin dependent DM with multiple complication
913591000006110	skin ulcer associated with DM
938331000006118	exudative maculopathy associated with type 2 DM
967701000006116	Lipoatrophic DM
3209441000006114	DM type 2
8012091000006113	type 2 DM on diet only
9986011	drug induced DM

13771000006110	other specified DM with ophthalmic complications
84401000006113	Type 1 DM with ophthalmic complication
84811000006114	Type 1 DM with retinopathy
281211000006117	gangrene associated with type 2 DM
913811000006115	Type 1 DM with polyneuropathy
9093013	diabetic retinopathy
914391000006116	insulin treated type 2 DM
264681018	diabetic on oral treatment
65526011	diabetic amyotrophy
345486016	diabetic neuropathy
297754014	Pre-proliferative diabetic retinopathy
264679015	diabetic on diet only
264682013	diabetic on insulin
13781000006113	other specified DM with other spec complications
297755010	advanced diabetic maculopathy
1484867016	Non-proliferative diabetic retinopathy
297758012	diabetic retinopathy NOS
264707013	diabetic good control
299261000000111	diabetic 6-month review
418920011	H/O DM in child of subject
84691000006115	cataract due to DM 1
264718013	diabetic - uncooperative patient
301641000000117	diabetes monitoring higher risk albumin excretion
84861000006112	type 2 DM with arthropathy
84391000006111	type 1DM with neuropathic arthropathy
459292011	type 1 DM with arthropathy
292480018	DM with hyperosmolar coma
84431000006117	Type 1 DM with renal complications
264716012	diabetic poor control
459309011	non-insulin dependent DM with arthropathy
771371000006118	Insulin dependent DM with mononeuropathy
458512016	diabetic on insulin and oral treatment
1785163015	high risk proliferative diabetic retinopathy
345492010	diabetic mononeuropathy
399419012	myasthenic syndrome due to diabetic amyotrophy

292482014	DM, juvenile type with hyperosmolar coma
281181000006116	non-insulin dependent DM with neuropathic arthropathy
84441000006110	type 1 DM with retinopathy
293756010	other specified DM
771401000006115	Insulin dependent DM with polyneuropathy
616651000006112	DM, juvenile type with ketoacidosis coma
84711000006117	Type 1 DM with hypoglycaemic coma
292483016	DM, adult onset, with hyperosmolar coma
292576013	Type 2 DM with multiple complication
280511000006113	non-insulin dependent DM with hypoglycaemia coma
264717015	diabetic - cooperative patient
301611000000118	diabetes monitoring lower risk albumin excretion
771341000006114	Insulin dependent DM with diabetic cataract
771421000006113	Insulin dependent DM with ulcer
84501000006114	Type 2 DM with cataract
280541000006112	non-insulin dependent DM with polyneuropathy
303847013	kimmelstiel- wison disease
84511000006112	Type 2 DM with gangrene
771501000006119	Insulin dependent DM with renal complication
84971000006111	Type 2 DM with polyneuropathy
913451000006117	Type 1 DM with renal complication
84941000006115	Type 2 DM with neuropathic arthropathy
914311000006114	Type 2 DM with diabetic cataract
84751000006116	Type 1 DM with neurological complication
913901000006112	Type 1 DM with diabetic cataract
914161000006114	Type 2 DM with retinopathy
84491000006118	type 2 DM with arthropathy
429970018	unstable type 1 DM
84981000006114	Type 2 DM with renal complication
914251000006116	Type 2 DM with polyneuropathy
306113018	pre-existing DM, non-insulin -dependent
84901000006117	mononeuropathy with type 2 DM
928601000006118	ketoacidosis coma in type2 DM
84821000006118	Type 1 DM with ulcer
719531000006118	malnutrition -related DM

771481000006112	Insulin dependent DM with neurological complication
429972014	unstable insulin dependent DM
84961000006116	Type 1 DM with peripheral angiopathy
85001000006117	Type 2 DM with ulcer
213141000006111	pre-existing DM, unspecified
84891000006116	Type 1 DM with hypoglycaemic coma
914041000006111	Type 2 DM with renal complications
292488013	coma associated with DM
84951000006118	disorder of eye with type 2 DM
616921000006113	diabetic amyotrophy
72721000006113	unstable type 1 DM
771351000006111	Insulin dependent DM with gangrene
84591000006119	Type 2 DM with peripheral angiopathy
84521000006116	Type 2 DM with hypoglycaemic coma
84801000006111	Type 1 DM with renal complication
84381000006113	Type 1 DM with neurological complication
84881000006119	Type 2 DM with gangrene
457325013	Type 1 DM without complication
13811000006110	other specified DM with unspecified complications
292626017	diabetic complications
841011000006112	severe non proliferative diabetic retinopathy
771331000006116	Insulin dependent DM with arthropathy
84631000006119	Type 2 DM with ulcer
928531000006110	Type 1 DM with ketoacidotic coma
719541000006111	malnutrition -related DM with coma
84571000006115	Type 2 DM with neuropathic arthropathy
84931000006113	neurological disorder with DM type 2
913781000006117	Type 2 DM with mononeuropathy
84451000006112	Type 1 DM with ulcer
616611000006111	disorder due to type 1 DM
616541000006114	DM, adult onset with ketoacidiotic coma
787101000006114	IDDM with peripheral circulatory disorder
616591000006117	DM, juvenile type with peripheral circulatory disorder
84341000006119	Type 1 DM with hypoglycaemic coma
292621010	DM NOS with other specified manifestation

280521000006117	non-insulin dependent DM with mononeuropathy
292581016	Type 2 DM with ulcer
913551000006116	Type 1 DM with multiple complications
913821000006111	Type 1 DM with polyneuropathy
913931000006116	Type 1 DM with peripheral angiopathy
292538019	Type1 DM with ulcer
189721000000113	secondary DM without complications
913671000006113	type 1 DM with retinopathy
914231000006111	Type 2 DM with mononeuropathy
622221000000118	maternally inherited DM
84831000006115	Type 1 DM without complication
292551012	Type 1 DM maturity onset
84301000006116	Type 1 DM maturity onset
72711000006117	unstable type 1 DM
938311000006112	Type 1 DM with exudative maculopathy
914081000006117	Type 2 DM with neurological complication
459169018	hypoglycaemic coma co current and due to DM
84721000006113	mononeuropathy with type 1 DM
913491000006111	Type 1 DM with ophthalmic complication
293759015	diabetic renal disease
719601000006110	malnutrition -related DM with peripheral circulatory disease
913891000006113	Insulin dependent DM with diabetic cataract
914061000006110	Type 2 DM with ophthalmic complication
913801000006118	Insulin dependent DM with polyneuropathy
26727014	diabetic annual review
1177721000000112	diabetic on subcutaneous treatment
292543014	Type 1 DM with gangrene
913831000006114	Insulin dependent DM with nephropathy
914271000006114	Type 2 DM with nephropathy
928491000006110	Type 1 DM with microalbuminuria
459311019	type 2 DM with arthropathy
292582011	Type 2 DM with gangrene
459306016	Type 2 DM with peripheral angiopathy
292550013	Type 1 DM - poor control
84641000006112	Type 2 DM without complication

928611000006115	ketoacidosis coma in type2 DM
928591000006114	Type 2 DM with ketoacidosis
913621000006112	Insulin dependent DM with gangrene
85011000006119	Type 2 DM without complication
306114012	pre-existing malnutrition related DM
459312014	type 1DM with neuropathic arthropathy

Hypothyroidism

Medcodeid	Term
68268011	hypothyroidism
178809013	acquired hypothyroidism
292408011	Other acquired hypothyroidism
398784019	hypothyroidism NOS
91116012	subclinical hypothyroidism
2533422017	hypothyroidism monitoring first letter
1780191013	congenital hypothyroidism
2536050019	post-surgical hypothyroidism
251589012	H/O: hypothyroidism
881391000006112	acquired hypothyroidism NOS
292373016	congenital hypothyroidism
2533534011	hypothyroidism monitoring second letter
637341000000118	hypothyroidism annual review
292395017	irradiation hypothyroidism
225971000000116	hypothyroidism monitoring administration
292397013	iodine hypothyroidism
2533420013	hypothyroidism monitoring third letter
881381000006114	hypothyroidism congenital +acquired
940101000006114	hypothyroidism monitoring invite 1
292404013	Iatrogenic hypothyroidism NOS
406721000000115	hypothyroidism monitoring telephone invitation
939981000006114	hypothyroidism medication review
2548835019	hypothyroidism monitoring verbal invite

123651000006111	subclinical iodine deficiency hypothyroidism
216181000006112	post ablative hypothyroidism
292396016	post ablative hypothyroidism NOS
292400016	Iatrogenic hypothyroidism
2474336017	hypothyroidism clinical management plan
1707531000000116	suspected hypothyroidism
292394018	other post ablative hypothyroidism
398783013	congenital hypothyroidism NOS
940111000006112	hypothyroidism monitoring invite 2
5108351000006116	Autoimmune hypothyroidism
3843671000006116	secondary hypothyroidism
413721000006119	other specified hypothyroidism
940121000006116	hypothyroidism monitoring invite 3
1539151000006110	secondary hypothyroidism
933261000006110	subclinical hypothyroidism
958231000006113	didn’t attend hypothyroidism clinic
2933341000006117	post-surgical hypothyroidism
2933321000006112	postoperative hypothyroidism
211321000006115	postinfectious hypothyroidism
8065681000006113	hypothyroidism review
355957018	congenital hypothyroidism without goitre
292376012	other specified congenital hypothyroidism
2693005013	suspected congenital hypothyroidism
5108391000006110	hypothyroidism due to Hashimoto’s thyroiditis
6858301000006118	hypothyroidism monitoring invitation
415432015	congenital hypothyroidism with diffuse goitre
316625012	Neonatal jaundice with congenital hypothyroidism
292417011	premature puberty due to hypothyroidism
988831000006119	acquired hypothyroidism NOS
3152641000006114	hypothyroidism following radioiodine therapy
292401017	hypothyroidism resulting from para-amino salicylic acid
297588017	myasthenic syndrome due to hypothyroidism
1823931000006116	hypothyroidism confirmed
5108441000006114	compensated hypothyroidism
988821000006117	subclinical hypothyroidism

1757291000006118	suspected hypothyroidism
5108381000006112	hypothyroidism with positive thyroid antibodies
5108431000006116	borderline hypothyroidism
4197341000006114	primary hypothyroidism
8118661000006116	drug-induced hypothyroidism
5721011000006111	hypothyroidism - congenital and acquired
8118651000006118	hypothyroidism caused by drug
292403019	hypothyroidism resulting from resorcinol
1877411000006112	hypothyroidism clinical management plan no longer in place
5108411000006110	hypothyroidism due to TSH receptor blocking antibody
940091000006115	hypothyroidism monitoring administration
7084321000006110	hypothyroidism in pregnancy
292402012	hypothyroidism resulting from phenylbutazone
7776171000006111	congenital hypothyroidism due to absence of thyroid gland
116846019	Pendred's syndrome
415431010	Goitrous cretin
600791000006112	Cretinism
588661000006115	congenital thyroid insufficiency
329968011	Cretinism
493538010	Myxoedema
101171000006116	thyroid deficiency
292403019	hypothyroidism resulting from resorcinol
356012016	acquired atrophy of thyroid
355964016	Autoimmune myxoedema
35727012	Myxoedema coma
208391000006113	Pretibial myxoedema - hypothyroid
101581000006112	Thyroid insufficiency
355961012	Hypothyroid goitre, acquired

Hyperlipidaemia

Medcodeid	Term
3406761000006110	hyperlipidaemia
5500491000006110	mixed hyperlipidaemia
5117271000006119	primary combined hyperlipidaemia
2716221000006111	high cholesterol
259229012	Serum cholesterol raised
259230019	Serum cholesterol very high
259258010	serum triglycerides raised
7261041000006112	serum triglycerides border line high
2716211000006115	hypercholesterolemia
5116951000006116	polygenic hypercholesterolemia
6596631000006112	familial hypercholesterolemia
5116911000006117	primary hypercholesterolemia
5500431000006111	pure hypercholesterolemia
475418015	hypercholesterolaemia
293267012	other specified pure hypercholesterolemia
5117071000006113	secondary hypercholesterolemia
5117091000006114	primary hypertriglyceridemia
5117131000006111	Fredrickson type IV hyperlipoproteinemia
5117221000006115	Secondary hypertriglyceridemia
398852019	Pure hypercholesterolemia
293270011	Pure hypercholesterolemia NOS
398855017	Pure hyperglyceridaemia
398856016	Mixed hyperlipidaemia
398868013	Familial hyperchylomicronaemia
5575101000006110	hyperlipoproteinemia, type1
444854010	Hypertriglyceridemia
794201000006112	Familial type 5 hyperlipoproteinemia
6594651000006110	Fredrickson type II hyperlipoproteinemia
17773186016	Familial hypercholesterolemia
666301000006115	Familial hypercholesterolemia
734191000006118	Familial hypercholesterolemia
794211000006110	Familial hypercholesterolemia
735661000006117	Familial hypercholesterolemia
794181000006111	Familial type 3 hyperlipoproteinemia

6687861000006113	Familial hypercholesterolemia due to heterozygous low density lipoprotein receptor mutation
7097901000006110	Dietary education for hyperlipidaemia
293299018	hyperlipidaemia
293821018	hyperlipidaemia
7966571000006116	Mixed hyperlipidaemia due to type 2 diabetes mellitus
2469357012	Hyperlipidaemia clinical management plan
5912411000006113	Hypertriglyceridemia
4428121000006110	mixed hypercholesterolaemia and hypertriglyceridemia
3281141000006116	disorder of lipid and lipoprotein metabolism
293823015	disorder of lipoprotein storage and metabolism
259215011	lipids abnormal
356800016	familial combined hyperlipidaemia
794171000006116	Fredrickson type lipidaemia
5116271000006116	familial hyperlipoproteinemia type
5116291000006115	Fredrickson type hyperproteinaemia
5116961000006119	familial hypercholesterolaemia - homozygous
5117001000006119	familial hypercholesterolaemia - heterozygous
356878012	familial defective apolipoprotein B-100
5117061000006118	familial hypercholesterolemia due to genetic defect
5867281000006112	familial multiple lipoprotein type- hyperlipidaemia
6594651000006110	familial type II hyperlipoproteinemia
1773186016	familial hypercholesterolaemia
666301000006115	familial hypercholesterolaemia
734191000006118	low density lipoprotein type
794161000006118	familial hypobetalipoproteinemia
794181000006111	Fredrickson type 3 lipidaemia
6611881000006114	Familial type 3 hyperlipoproteinemia
6611941000006113	Dysbetalipoproteinemia
6687861000006113	familial hypercholesterolaemia due to heterozygous
6687901000006118	familial hypercholesterolaemia due to homozygous
1659061000000112	possible familial hypercholesterolemia
8192861000006119	possible heterozygous familial hypercholesterolemia
6596631000006112	familial hypercholesterolaemia
12107611000006112	familial history of double heterozygous hypercholesterolaemia

Hypertension

Medcodeid	Term
99042012	Essential hypertension
790091000006115	hypertension monitoring
1780319017	hypertension annual review
790011000006113	hypertension monitoring first letter
411919011	hypertension monitoring
1780253016	hypertension six -month review
1131851000000118	lifestyle advice regarding hypertension
395751018	Essential hypertension NOS
790121000006116	hypertension
790141000006111	hypertension screening
789961000006118	hypertension monitoring second letter
790071000006116	hypertension monitoring check done
8093016	ocular hypertension
251674014	H/O: hypertension
931171000006114	expected from hypertension quality indicators-informed dissent
3135013	benign essential hypertension
15881000000111	hypertension screening administration
789971000006113	hypertension monitoring third letter
789991000006114	hypertension monitoring telephone invite
264471012	good hypertension control
285265015	Seen in in hypertension clinic
21601000000111	hypertension monitoring administration
931161000006119	expected from hypertension quality indicators-patient unsuitable
443764015	on treatment for hypertension
498791000006113	attends hypertension monitoring
790001000006110	hypertension monitoring verbal invite
264472017	poor hypertension control
940001000006110	hypertension medication review
405053013	hypertension monitored
1484957010	didn’t attend hypertension clinic

93494011	systolic hypertension
113392018	benign intracranial hypertension
790131000006118	hypertension resolved
43850011	pulmonary arterial hypertension
264467014	yearly observation of borderline hypertension
461309011	screening of hypertension
253532015	hypertension resolved
264485019	treatment for hypertension started
5999791000006119	hypertension monitoring invite
53452019	secondary hypertension
57989014	portal hypertension
264473010	hypertension follow-up default
2474335018	hypertension clinical management plan
138991000000110	expecting reporting -hypertension quality indicators
153941000006118	Seen in in hypertension clinic
790031000006119	hypertension annual review
1846991000006111	stage 2 hypertension NICE
1946691000006110	provision of written information about DM and hypertension
2117971000000119	hypertension self- management
8439991000006115	hypertension monitoring SMS
12626361000006113	QOF hypertension quality indicators-related care invitation
131046010	malignant essential hypertension
146259010	secondary pulmonary hypertension
284062018	referral to hypertension clinic
495022012	Gestational hypertension
15901000000114	hypertension screening administration, NOS
26091000000116	hypertension clinical administration
789951000006115	hypertension monitoring offer default
790051000006114	hypertension complicating pregnancy, child birth, and the puerperium
1846941000006119	Stage 1 hypertension (NICE)
1908711000006115	Stage 1 hypertension (NICE) without evidence of end organ damage
2193031000000112	Stage 1 hypertension
1706551000000114	hypertension nine- month review
7276911000006114	lifestyle education regarding hypertension
8439981000006118	hypertension monitoring invitation SMS

1780318013	moderate hypertension control
164121000006118	risk factors present at hypertension screening
2403141000000118	borderline hypertension monitoring first letter
47076011	renal hypertension
8440001000006117	hypertension monitoring SMS
179371000006114	hypertension monitoring refused
504831000006116	benign essential hypertension complicating pregnancy, childbirth, and the puerperium
3654631000006113	pulmonary hypertension
80224019	diastolic hypertension
1780252014	hypertension treatment refused
2645973019	chronic peripheral venous hypertension
909441000006118	hypertension
350517010	thromboembolic pulmonary hypertension
1855781000006115	hypertension monitoring in primary care
1908721000006111	Stage 1 hypertension (NICE) with evidence of end organ damage
2115801000000110	hypertension self-management plan review
2193021000000110	severe hypertension
2193971000000110	hypertension resistant to drug therapy
2403221000000116	borderline hypertension monitoring second letter
2403261000000112	borderline hypertension monitoring third letter
6516381000006117	didn’t attend hypertension clinic
262960017	hypertension induced by oral contraceptive pill
299681011	hypertension secondary to endocrine disorders
299683014	renovascular hypertension
158241000006117	secondary hypertension NOS
1846961000006115	severe hypertension NICE
2423811000000118	telehealth hypertension monitoring
3642801000006112	malignant hypertension
299682016	secondary hypertension NOS
351381000000114	primary pulmonary hypertension drugs band1
884121000006111	malignant hypertension
99047018	primary hypertension
305818015	pre-eclampsia or eclampsia with pre-existing hypertension
151161000006115	malignant secondary hypertension
299684015	hypertension secondary to drug

2478822013	secondary benign renovascular hypertension
8440011000006119	hypertension monitoring SMS
12734361000006112	QOF hypertension quality indicators-related care invitation using preferred method of communication
299678018	secondary benign hypertension
5978371000006116	hypertension screening recall
300871017	hypertension secondary to other renal disorders
905451000006118	pulmonary embolism/pulmonary hypertension
8459521000006112	hypertension monitoring invitation email
299677011	secondary malignant hypertension NOS
299680012	benign secondary hypertension
1488750011	hypertension monitoring not required
212981000006111	pre-eclampsia or eclampsia with pre-existing hypertension - delivered with postnatal complication
213001000006110	pre-eclampsia or eclampsia + pre-existing hypertension - not delivered
1823901000006112	hypertension confirmed
5979471000006115	hypertension monitoring call
300870016	Another secondary hypertension
19451000006111	Another pre-existing hypertension in pregnancy/childbirth/puerp, unspecified
212971000006113	pre-eclampsia or eclampsia + pre-existing hypertension with postnatal complication
1806071000006118	Stage 1 hypertension
213111000006112	pre-existing hypertension complicating pregnancy, childbirth and the puerperium
504781000006113	benign essential hypertension complicating pregnancy, childbirth and the puerperium with postnatal complication
504821000006119	benign essential hypertension complicating pregnancy, childbirth and the puerperium- not delivered
1806081000006115	stage 2 hypertension
19431000006116	Another pre-existing hypertension in pregnancy/childbirth/delivered
19441000006114	Other pre-existing hypertension in pregnancy/childbirth-NOS
504761000006115	benign essential hypertension complicating pregnancy, childbirth, and the puerperium- delivered with postnatal complication
3117481000006113	hypertension
5978381000006118	hypertension screening call
299676019	secondary malignant renovascular hypertension
213081000006118	pre-existing secondary hypertension complicating pregnancy, childbirth and the puerperium
3117511000006117	hypertension

19421000006119	Other pre-existing hypertension in pregnancy/childbirth/not delivered
351401000000114	primary pulmonary hypertension drugs band 2
1992471000006116	uncontrolled systolic hypertension
176951000006110	renal hypertension complicating pregnancy, childbirth and the puerperium-delivered
176981000006119	renal hypertension complicating pregnancy, childbirth and the puerperium, NOS
3898601000006112	pre-existing hypertension in obstetric context
4775831000006118	hypertension secondary to endocrine disorder
5979461000006110	hypertension monitoring status
176941000006113	renal hypertension complicating pregnancy, childbirth and the puerperium- not delivered
176961000006112	renal hypertension complicating pregnancy, childbirth and the puerperium unspecified
1855791000006117	hypertension monitoring in secondary care
6349461000006119	labile essential hypertension
7696031000006114	supine hypertension
64168014	Hypertensive disease
64172013	elevated blood pressure
299687010	Hypertensive disorder
53452019	secondary hypertension
299686018	Other specified hypertensive disease
300869017	Hypertensive diseases
790131000006118	hypertension resolved
264475015	O/E-initial high BP
1780253016	O/E-check high BP
264486018	hypertensive treatment changed
451424017	antihypertensive therapy
2159168015	patient on maximal tolerated antihypertensive therapy
12496011	hypertensive retinopathy
107545013	hypertensive heart disease
90135019	Malignant hypertensive heart disease
728681000006116	Malignant hypertensive heart disease without congestive heart failure
728671000006119	Malignant hypertensive heart disease with congestive heart failure
299650019	Malignant hypertensive heart disease NOS
523801000006119	BP - hypertensive disease
60444016	Benign hypertensive heart disease

504911000006115	Benign hypertensive heart disease without CCF
299654011	Benign hypertensive heart disease NOS
741691000006114	hypertensive heart disease NOS without CCF
411508017	Cardiomegaly - hypertensive
741681000006111	hypertensive heart disease NOS with CCF
299655012	hypertensive heart disease NOS
64282015	Hypertensive renal disease
108730018	Malignant hypertensive renal disease
1409014	Benign hypertensive renal disease
299665018	Hypertensive renal disease with renal failure
395753015	Hypertensive renal disease NOS
47076011	renal hypertension
143003017	hypertensive heart and renal disease
110659019	Malignant hypertensive heart disease and renal disease
109700019	Benign hypertensive heart and renal disease
741701000006114	hypertensive heart and renal disease with (congestive) heart failure
299673010	hypertensive heart and renal disease with renal failure
789941000006117	hypertensive heart and renal disease with renal failure with both (congestive) heart failure and renal failure
299675015	hypertensive heart and renal disease NOS
84111015	hypertensive encephalopathy
84112010	hypertensive crisis
3117461000006115	systemic arterial hypertension
3117451000006117	BP- high blood pressure
3117491000006111	High blood pressure
3784371000006115	accelerated essential hypertension
3117411000006118	High blood pressure
3468491000006113	idiopathic hypertension

Diverticular disease

Medcodeid	Term
1777478012	diverticular disease
1786077011	diverticular disease of colon
303132018	diverticular disease of large intestine
886341000006110	diverticular disease NOS
626571000006113	diverticular disease of both small and large intestine
626561000006118	diverticular disease of both small and large intestine
11823191000006119	haemorrhage of large intestine with diverticular disease
5689211000006119	diverticular disease of left side colon
5531971000006117	simple diverticular disease
6594231000006117	diverticular disease
5085401000006114	diverticular disease of right side of colon
11828731000006111	perforation with diverticular disease of colon
13950041000006115	diverticular disease of small bowel
7820861000006114	diverticular disease of small and large intestine
5531981000006119	uncomplicated diverticular disease
11823181000006117	haemorrhage of large intestine with diverticular disease
11851201000006116	perforation with diverticular disease of small and large intestine
1222658010	Appendicular diverticulum
105596011	diverticula of intestine
1786007012	diverticulosis
303123015	diverticulosis of the duodenum
303124014	diverticulosis of the jejunum
303126011	diverticulosis of the ileum
303127019	diverticulosis of small intestine unspecified
303128012	diverticulosis of small intestine
1786077011	diverticular disease of colon
303131013	diverticulosis of the large intestine
626561000006118	diverticular disease of both small and large intestine
303134017	bleeding diverticulosis
303135016	diverticulosis
303136015	diverticulosis NOS

450775010	diverticulitis
485644015	diverticulitis of the duodenum
626681000006110	diverticulitis of jejunum
500628015	diverticulitis of the ileum
303141011	diverticulitis of small intestine unspecified
303142016	diverticulitis of small intestine
626651000006119	diverticulitis of colon
303143014	diverticulitis of the large intestine unspecified
303144015	diverticulitis of large intestine
303145019	diverticulitis unspecified
303146018	diverticulitis NOS
303147010	perforated diverticulum
303148017	perforated diverticulum of duodenum
303149013	perforated diverticulum of jejunum
303150013	perforated diverticulum of ileum
303151012	perforated diverticulum of small intestine unspecified
303152017	perforated diverticulum of small intestine
503419012	perforated diverticulum of colon
303153010	perforated diverticulum of large intestine unspecified
303154016	perforated diverticulum of large intestine
303156019	perforated diverticulum of intestine
303157011	perforated diverticulum of intestine NOS
353440011	diverticular abscess
303159014	diverticula of the intestine NOS

Congestive heart failure

Medcodeid	Term
101281000119107	Congestive heart failure due to cardiomyopathy
14015051000006114	Acute on chronic right-sided congestive heart failure
504901000006118	Benign hypertensive heart disease with congestive cardiac failure
7056281000006118	Congestive heart failure due to left ventricular systolic dysfunction
2585431000006117	Chronic left-sided congestive heart failure
3489281000006119	Hypertensive heart disease without congestive heart failure
3589241000006116	Chronic right-sided congestive heart failure
18472010	Acute congestive heart failure
60444016	Benign hypertensive heart disease
82584011	Acute cor pulmonale
94251011	Acute heart failure
107545013	Hypertensive heart disease
132655012	Chronic cor pulmonale
139482012	Cardiac failure
141306010	Left ventricular failure
147247018	Chronic congestive heart failure
216207010	Left ventricular systolic dysfunction
216246012	Referral to heart failure clinic
299673010	Hypertensive heart and renal disease with renal failure
300179017	Decompensated cardiac failure
300180019	Compensated cardiac failure
300190010	Acute left ventricular failure
316833010	Congenital cardiac failure
350413012	Congestive obstructive cardiomyopathy
350484012	Heart failure as a complication of care
403107019	Cardiac insufficiency as a complication of care
411506018	Impaired left ventricular function
412678013	Neonatal cardiac failure
451426015	Cardiac failure therapy

453099015	H/O: Heart failure in last year
1484917012	Heart failure follow-up
1484918019	Heart failure annual review
1488804017	Heart failure confirmed
1778488011	Congestive cardiomyopathy
2159197017	Echocardiogram shows left ventricular systolic dysfunction
2159198010	Echocardiogram shows left ventricular diastolic dysfunction
2549243014	Seen in heart failure clinic
2616473014	New York Heart Association Classification - Class IV
2694523019	Left ventricular cardiac dysfunction
311561000000117	Referred to heart failure education group
790091000006115	Heart failure 6-month review
404741000000119	Heart failure 6-month review
864961000006117	Artificial heart implant
139482012	[RFC] Cardiac failure
1576321000006113	Cause of Death- Congestive Cardiac Failure
1647701000000118	Heart failure with normal ejection fraction
1734081000000112	Referral to heart failure exercise programme declined
1861731000006114	AURAS-AF - consider the patient to have heart failure
1991651000006115	Severe left ventricular systolic dysfunction
2256811000000114	Referral to rapid access heart failure clinic
270768010	Transplantation of heart and lung NOS
270777015	Other specified other transplantation of heart
299655012	Hypertensive heart disease NOS
299675015	Hypertensive heart and renal disease NOS
300217019	Post cardiac operation heart failure NOS
300910013	[X]Another hypertrophic cardiomyopathy
301694014	Pulmonary oedema NOS
301695010	Pulmonary congestion and hypostasis NOS
301741013	Acute pulmonary oedema unspecified
305601017	Cardiac failure following abortive pregnancy
395772015	Heart failure NOS
1495417010	Asthma - cardiac
55971000006117	Xenotransplantation of heart
213091000006115	Pre-exist hypertension heart

223981000000118	Cardiac failure NOS
728671000006119	Malignant hypertensive heart disease with CCF
728681000006116	Malignant hypertensive heart disease without CCF
741661000006118	Hypertensive heart disease NOS
741681000006111	Hypertensive heart disease NOS with CCF
741701000006114	Hypertensive heart& renal dis with (congestive) heart failure
789941000006117	Hypertension heart &renal both(congestive)heart and renal fail
404621000000115	Preferred place of care for next exacerbation heart failure
1784061000006118	Preferred place of care for next exacerbation heart failure
1816101000006113	Right ventricular failure
1490256017	Pulmonary oedema - acute
460645013	[V]Heart transplanted
2549208013	Admit heart failure emergency
299650019	Malignant hypertensive heart disease NOS
3182541000006117	CHF - Congestive heart failure
493287011	CHF - Congestive heart failure
70653017	CHF - Congestive heart failure
3182551000006115	CHF - Congestive heart failure
141306010	Left heart failure
3886041000006118	Left heart failure
299655012	HHD - Hypertensive heart disease
741661000006118	HHD - Hypertensive heart disease
741691000006114	HHD - Hypertensive heart disease
107545013	HHD - Hypertensive heart disease
3552501000006119	HHD - Hypertensive heart disease
132655012	COR - Chronic pulmonale
3800291000006115	COR - Chronic pulmonale
251680018	History of heart failure
4540521000006111	History of heart failure
411506018	Impaired left ventricular function
5573991000006118	Impaired left ventricular function
2549208013	Emergency hospital admission for heart failure
510016018	Biventricular failure
4005301000006110	Biventricular failure

3886071000006114	Left-sided heart failure
1734241000000113	Referral to cardiac rehabilitation program
7585711000006119	Referral to cardiac rehabilitation program
270777015	Heart transplant
270778013	Heart transplant
270769019	Heart transplant
7321121000006119	Heart failure with preserved ejection fraction
30038015	Hypertrophic cardiomyopathy without obstruction
4777091000006118	Hypertrophic cardiomyopathy without obstruction
3868341000006118	Weak heart
6615851000006116	CCM - Congestive cardiomyopathy
1778488011	COCM - Congestive cardiomyopathy
864951000006119	Heart transplant
1661371000000112	HFNEF - heart failure with normal ejection fraction
884131000006114	Hypertensive renal + heart dis
30336100000111	Referred by heart failure nurse specialist
283830011	Referral to heart failure exercise programme
308041000000118	Referral to heart failure exercise programme
2548316014	Seen by community heart failure nurse
2616472016	New York Heart Association Classification - Class III
498953012	Beriberi heart disease
301689014	Pulmonary congestion and hypostasis
251924010	H/O: heart recipient
72934016	Rheumatic left ventricular failure
110659019	Malignant hypertensive heart AND renal disease
112265015	Pulmonary congestion
270769019	Other transplantation of heart
270770018	Allotransplantation of heart NEC
270776012	Revision of transplantation of heart NEC
270778013	Other transplantation of heart NOS
301743011	Acute pulmonary oedema NOS
510016018	Biventricular failure
213101000006114	Pre-exist hypertension heart renal dis complication
784191000006110	Impaired left ventricular function
90421000006112	HLTx - Heart lung transplant

3023081000006113	HLTx - Heart lung transplant
1216090015	Pulmonary oedema - acute
301743011	Pulmonary oedema - acute
301741013	Pulmonary oedema - acute
1490256017	Pulmonary oedema - acute
3535951000006117	Heart lung bypass
878761000006116	Heart lung bypass
499653015	Heart lung bypass
270776012	HTx - Heart transplant
3022121000006117	HTx - Heart transplant
225671000006116	Piggyback transplantation of heart
299654011	Benign hypertensive heart disease NOS
317955011	[D]Cardiorespiratory failure
139481017	Weak heart
2352391000000117	On optimal heart failure therapy
2227501000000110	Heart failure with preserved ejection fraction
2378231000000112	Discharge from heart failure nurse service
1705341000000110	Discharge from heart failure nurse service
2549697018	Referral to heart failure nurse
2616470012	New York Heart Association Classification - Class I
2616471011	New York Heart Association Classification - Class II
2675255018	Congestive heart failure due to valvular disease
494669012	Chronic pulmonary oedema
1489358014	Left ventricular diastolic dysfunction
270766014	Revision of transplantation of heart and lung
253994013	O/E - pulmonary oedema
90135019	Malignant hypertensive heart disease
206703015	Right heart failure
251680018	H/O: heart failure
478111000006114	Allotransplantation of heart and lung
818821000006110	Heart transplant with complication, without blame
460657016	[V]Has artificial heart
833381000006119	New York Heart Assoc classification heart failure symptoms
300910013	HCM - Hypertrophic cardiomyopathy
5056831000006119	HCM - Hypertrophic cardiomyopathy

460657016	History of artificial heart
5043981000006115	Allotransplant of heart
270767017	Other specified transplantation of heart and lung
30826100000111	Heart failure review completed
490972013	Right ventricular failure
251940013	H/O: artificial heart
109700019	Benign hypertensive heart AND renal disease
139475013	Heart failure
143003017	Hypertensive heart AND renal disease
504901000006118	Benign hypertensive heart disease with CCF
498953012	Cardiac beriberi
395601017	Induced termination of pregnancy complicated by cardiac failure
1495417010	Asthma - cardiac
412678013	Cardiac failure developing in the perinatal period
504911000006115	Benign hypertensive heart disease without congestive heart failure
7119751000006110	Chronic left ventricular systolic dysfunction
6914191000006115	Systolic heart failure
3855401000006112	Cor pulmonale
7573211000006119	Heart failure with reduced ejection fraction due to heart valve disease
3283871000006117	Chronic heart failure
7475721000006114	Heart failure due to end stage congenital heart disease
6616021000006111	Left ventricular systolic area
2660881000006116	High output heart failure
6212521000006115	Acute cardiac pulmonary oedema
7964821000006113	Non-ischemic congestive cardiomyopathy
7573171000006116	Heart failure with reduced ejection fraction
7025691000006110	Decompensated chronic heart failure
8030311000006111	Exacerbation of congestive heart failure
7052811000006113	Right heart failure due to pulmonary hypertension
7484711000006114	Heart failure medication review
7517591000006114	Implantation of cardiac defibrillator lead
6919191000006119	Diastolic heart failure
8011111000006111	Congestive heart failure with right heart failure
8290471000006114	Heart failure initial assessment

Ischaemic heart diseases

Medcodeid	Term
258968018	Cardiac enzymes abnormal
258969014	Cardiac enzymes abnormal - first set
299758019	Stenocardia
299782012	Single coronary vessel disease
299796018	Ischaemic cardiomyopathy
350346019	Triple vessel disease of the heart
350350014	New onset angina
350354017	Silent myocardial ischaemia
350379019	Cardiac syndrome X
397829016	H/O: cardiovascular disease
411874010	H/O: myocardial problem
451372015	H/O: Treatment for ischaemic heart disease
494438016	Subendocardial ischaemia
1235573016	Ventricular cardiac aneurysm
1484833014	Coronary heart disease review
1488382011	Acute coronary syndrome
1489353017	Cardiac rehabilitation - phase 3
1489354011	Cardiac rehabilitation - phase 4
1786197015	Coronary thrombosis
2474304012	Radionuclide heart study abnormal
2534218019	Cardiac rehabilitation declined
2534664018	Ischaemic heart disease
2534674015	Chronic myocardial ischaemia
2537480011	IHD - Ischaemic heart disease
2619484018	MI - Myocardial infarction aborted
5957310000006114	Coronary atherosclerosis
856451000006113	Possible angina
3371421000006117	[RFC] coronary heart disease
457285013	[RFC] Cardiac rehabilitation
931961000006117	Acute coronary syndrome
1731551000000112	Angina self-management plan commenced
1734201000000110	Referral to cardiac rehabilitation programme not indicated

1752201000000116	Frequency of angina
1771631000006114	Attended cardiac rehabilitation
182391000006113	Coronary heart disease confirmed
1895641000006114	On coronary heart disease register
2115181000000110	Coronary microvascular disease
2173281000000112	H/O acute coronary syndrome
2609111000000119	Non-obstructive coronary atherosclerosis
251691013	H/O: heart disease NOS
395755010	Another cardiac wall aneurysm
2536393012	Arteriosclerotic heart disease
2536395017	Coronary artery disease
394541000006112	[X]Ischaemic heart diseases
283514010	Admit to cardiac ITU
411904010	Aspirin prophylaxis - IHD
2486801000000115	Cardiac rehabilitation programme offered
248907100000111	Cardiac rehabilitation initial assessment offered
216244010	Canadian Cardiovascular Society classification of angina
8439311000006114	Emergency department discharge to coronary care unit
2571561000006118	Intermediate coronary syndrome
3318871000006117	Aneurysmal lesion of coronary artery
84241012	Aneurysm of coronary vessels
4775931000006111	Aborted myocardial infarction
1489351015	Cardiac rehabilitation-phase 1
350346019	Triple vessel coronary artery disease
1489352010	Cardiac rehabilitation-phase 2
538131000006110	CVD - cardiovascular disease
300996015	CVD - cardiovascular disease
557611000006113	CVD - cardiovascular disease
2536395017	CAD - coronary artery disease
6546111000006118	ACS - Acute coronary syndrome
7585711000006119	Referral to cardiac rehabilitation program
300886011	Cardiac diseases
299871010	Cardiac diseases
223951000000112	Cardiac diseases
300238013	Cardiac diseases

300239017	Cardiac diseases
537341000006118	Cardiac diseases
39773018	Angina pectoris with documented spasm
460687010	History of coronary artery disease with stent placement
2536354015	Placement of stent in coronary artery
1786197015	Coronary artery thrombosis
2536393012	Atherosclerosis of coronary artery
89332015	Atherosclerosis of coronary artery
7278491000006111	Atherosclerosis of coronary artery
7789771000006114	Non-obstructive atherosclerosis of coronary artery
3371411000006113	Coronary arteriosclerosis
3371381000006110	Coronary arteriosclerosis
39111000006114	IHD - ischemic heart disease
6860261000006118	IHD - ischemic heart disease
4776051000006110	Single vessel coronary artery disease
299782012	Single vessel coronary artery disease
5887641000006118	Exertional angina
1489354011	Cardiac rehabilitation-phase 4
262247015	Coronary arteriography abnormal
6557571000006117	Cardiac rehabilitation-phase 2
1489353017	Cardiac rehabilitation-phase 3
457274011	Admit cardiology emergency
299757012	AP - Angina pectoris
283514010	Admit to cardiac ITU
6601131000006115	CT - Coronary thrombosis
6601121000006118	CT - Coronary thrombosis
1786198013	CT - Coronary thrombosis
7585731000006113	Referral to cardiac rehabilitation program declined
271136016	Other open operations on coronary artery
299723016	Other acute and subacute ischaemic heart disease
2537480011	Other acute and subacute ischaemic heart disease NOS
299750014	Other acute and subacute ischaemic heart disease NOS
300876010	[X]Other forms of acute ischaemic heart disease
300879015	[X]Other forms of chronic ischaemic heart disease
884171000006112	Chr. ischaemic heart dis. NOS

884161000006117	Acute/subacute IHD NOS
89332015	Atherosclerotic heart disease
1885981000006112	Referral to Angina Plan self-management programme declined
2210251000000115	Referral to Angina Plan self-management programme declined
1489351015	Cardiac rehabilitation - phase 1
459488019	Transient myocardial ischaemia
459859010	Asymptomatic coronary heart disease
1232666014	Cardiac aneurysm
1488440011	Coronary heart disease medication review
411503014	Mural cardiac aneurysm
449302011	Referral to cardiac rehabilitation nurse
338974012	Ischaemic chest pain
262243016	Angiocardiography abnormal
32122016	Status anginous
36036010	Syncope anginose
299741012	Periinfarction syndrome NOS
299776014	Other chronic ischaemic heart disease
299834013	Other specified ischaemic heart disease
5.3734E+14	Cardiac diseases
350608017	Coronary artery dissection
496991000006111	Atherosclerotic cardiovascular disease
262247015	Coronary arteriography abnormal
459505016	Euro score for angina
2878041000006119	Coronary spasm
299783019	Double vessel coronary artery disease
4776071000006117	Double vessel coronary artery disease
4776081000006119	Two coronary vessel disease
314321000000119	Suspected ischaemic heart disease
299790012	Aneurysm of heart NOS
144819018	Variant angina pectoris
84241012	Aneurysm of coronary vessels
2112641000000118	Cardiac rehabilitation programme completed
2193891000000115	Referral to cardiology multidisciplinary team
2210191000000118	Referral to Angina Plan self-management programme
406641000000119	Referral to community cardiology service

1757251000000117	Referral to community cardiology service
1539331000006118	H/O: coronary heart disease
2534218019	Cardiac rehabilitation declined
970861000006117	Cardiac rehabilitation declined
884141000006116	Coronary thrombosis
786071000006119	IHD annual review
1786198013	Thrombosis - coronary
457285013	Cardiac rehabilitation
299742017	Coronary thrombosis not resulting in myocardial infarction
299783019	Double coronary vessel disease
299723016	Other acute and subacute ischaemic heart disease
299804015	Other specified chronic ischaemic heart disease NOS
460925019	[V]Cardiac rehabilitation
7844010	Periinfarction syndrome
375751000006111	Adverse reaction caused by coronary vasodilator
451372015	History of treatment for ischaemic heart disease
411904010	Aspirin prophylaxis for ischaemic heart disease
299835014	Ischaemic heart disease NOS
229081000006112	Angina tonsillitis
1731571000000115	Angina self-management plan completed
173412000000110	Referral to cardiac rehabilitation programme declined
1734241000000113	Referral to cardiac rehabilitation programme
2839404013	Referral to cardiac rehabilitation service by secondary care
449050017	Referral to cardiac rehabilitation service by secondary care
1736191000000116	Referral to cardiac rehabilitation service by secondary care
1626531000006110	Emergency IHD admission since last appointment
1047381000006114	Adverse reaction to Trangia Xl
2537483013	Chronic coronary insufficiency
1489352010	Cardiac rehabilitation - phase 2
442204010	Angina on effort
460133017	Coronary heart disease annual review
299757012	Angina pectoris
256747018	Exercise tolerance test abnormal
264494013	Angina control - poor
585631000000113	Admit ischaemic heart disease emergency

457274011	Admit cardiology emergency
353061000006114	Adverse reaction to coronary vasodilators NOS
353051000006112	Adverse reaction to coronary vasodilators NOS
331272010	Adverse reaction to coronary vasodilators NOS
299800012	Other specified chronic ischaemic heart disease
3536581000006113	Coronary artery occluded
3536601000006115	Coronary artery occluded
3600701000006114	Coronary artery atheroma
5944391000006110	Seen by cardiac rehabilitation nurse
5941971000006112	Under care of cardiac rehabilitation nurse
6360361000006114	Left main coronary artery disease
7602891000006115	Drug-eluting coronary artery stent
2981141000006112	Coronary artery embolism
5056471000006118	Accelerated coronary artery disease in transplanted heart
5956981000006118	Discharge by cardiac rehabilitation nurse
6450471000006112	Stented coronary artery
3516223013	Angina self-management plan
8067801000006114	Stent in anterior descending branch of left coronary artery
5294561000006119	Coronary stent patent
6360351000006112	Multi vessel coronary artery disease
6841231000006113	Acute ischaemic heart disease
5294571000006114	Coronary stent stenosis
7602941000006119	Coronary artery stent
6361661000006114	Diffuse disease of coronary artery
5000291000006114	Cardiac rehabilitation class
5294531000006111	Coronary stent patency
8240941000006118	Angina self-management plan declined
8036721000006118	Chronic total occlusion of coronary artery
5997351000006115	Cardiac rehabilitation nurse
4354151000006115	Right coronary artery occlusion
299758019	Stenocardia
299765010	Angina pectoris NOS
300874013	another forma of angina pectoris
482941000006119	Angina pectoris NOS
4775971000006114	Angina

4775981000006112	cardiac angina
4776001000006111	Anginal syndrome
4776031000006115	Ischaemic heart disease - angina
2534664018	Ischaemic heart disease
299835014	Ischaemic heart disease NOS
251679016	H/O angina
350348018	stable angina
72571000006115	Unstable angina
855991000006115	Angina control -stable
264496010	Angina control -worsening
264495014	Angina control -improving
442204010	Angina on effort
494261017	Worsening angina
264497018	Angina control NOS
451370011	H/O angina last year
1235225010	Prinz metals angina
498328016	Angina at rest
286906018	herpangina
905381000006117	(RFC) angina
98087016	Angina decubitus
302275011	Ludwigs's angina
458410010	post infarct angina
459487012	refractory angina
960181000006111	anginal pain
5887611000006117	Exercise induced angina
352222018	angina bullosa haemorrhagic
59952018	Nocturnal angina
482801000006110	abdominal angina
395416013	Vincent's angina
299763015	Angina decubitus NOS
854491000006113	Unstable angina
6360391000006118	Atypical angina
3920021000006112	coronary artery spasm angina
5887631000006111	Exertional angina
7105241000006116	typical angina

73160011	streptococcal angina
3920011000006116	variant angina
3919991000006112	Prinz metal angina
3166141000006114	angina class II
3499001000006116	angina class I
3886751000006118	angina class III
1576311000006117	cause of death-angina pectoris
4776001000006111	anginal syndrome
9868461000006110	Unstable angina co-occurrent and due to coronary arteriosclerosis
12276271000006112	progressive angina
7966931000006114	angina associated with type 2 diabetes
3458791000006114	anginal chest pain at rest
3920001000006119	variant angina pectoris
4743831000006116	Vincent angina -pharyngitis
6360401000006116	recurrent angina after percutaneous transluminal coronary angioplasty
6360421000006114	recurrent angina after coronary stent placement
6360441000006119	recurrent angina after coronary artery bypass graft
264492012	angina control
264493019	angina control- poor
264494013	angina control- poor
451425016	antianginal therapy
682481000006118	Myocardial infarction aborted
7845011	unstable angina
7847015	crescendo angina
482811000006113	angina at rest
299745015	acute coronary insufficiency
148819018	variant angina pectoris

Myocardial infarction

Medcodeid	Term
4031011	Old myocardial infarction
94884017	Acute myocardial infarction
109916013	Dressler's syndrome
256452010	ECG: myocardial infarction
256454011	ECG: old myocardial infarction
256457016	ECG: posterior/inferior infarct
256458014	ECG: subendocardial infarct
299712015	True posterior myocardial infarction
299719012	Acute atrial infarction
299808017	Subsequent myocardial infarction
299811016	Subsequent myocardial infarction of anterior wall
299812011	Subsequent myocardial infarction of inferior wall
350376014	Silent myocardial infarction
447324018	Acute Q-wave infarct
450322013	Acute non-Q wave infarction
451369010	H/O: Myocardial infarction in last year
1229885017	Microinfarction of heart
1234005010	Acute infer posterior infarction
1235655012	Mural thrombosis
1786197015	Coronary thrombosis
2855301000006112	[RFC] Myocardial infarction (MI)
884151000006119	[RFC] Myocardial infarction (MI)
6546751000006118	First myocardial infarction
1576271000006117	Cause of Death- Myocardial Infarction
2436731000000112	Old cerebral infarction on imaging
37443015	Heart attack
256460011	ECG: myocardial infarct NOS
299707016	Other specified anterior myocardial infarction
299710011	Posterior myocardial infarction NOS
299718016	Other acute myocardial infarction
299720018	Other acute myocardial infarction NOS

299721019	Acute myocardial infarction NOS
299813018	Subsequent myocardial infarction of other sites
67081000006119	Ventricle septal defect/current comp follows acute myocardial infarction
300881018	Subsequent myocardial infarction of unspecified site
299813018	Subsequent myocardial infarction of unspecified site
299808017	Subsequent myocardial infarction of unspecified site
118831000006118	Subsequent myocardial infarction of unspecified site
158601000006116	Rupture cardiac wall without hemopericardia/cur comp following ac MI
158611000006118	Ruptured chordae follow acute myocardial infarct
159001000006119	Rupture papillary muscle/current complication follow acute myocardial infarct
212061000006119	Postoperative transmural myocardial infarction anterior wall
212071000006114	Postoperative transmural myocardial infarction inferior wall
455423016	Postoperative transmural myocardial infarction unspecified site
208365015	Postoperative transmural myocardial infarction unspecified site
212091000006110	Postoperative transmural myocardial infarction unspecified site
457531000006110	Acute inferolateral infarction
94884017	Acute transmural myocardial infarction of unspecified site
299721019	Acute transmural myocardial infarction of unspecified site
219531000000117	Acute transmural myocardial infarction of unspecified site
460681000006116	Acute transmural myocardial infarction of unspecified site
537751000006115	Cardiac rupture following myocardial infarction (MI)
616081000006113	Diab Mellit insulin-glucose acute myocardial infarct
810811000006116	H/O: myocardial infarct <60
813961000006116	Hemopericardium /current comp follow acute myocardial infarct
967931000006114	Acute posterolateral myocardial infarction
299709018	Anterior myocardial infarction NOS
299711010	Lateral myocardial infarction NOS
37443015	Attack - heart
219521000000119	Attack - heart
461192018	[V]Observation for suspected myocardial infarction
447324018	Acute Q wave myocardial infarction
5935321000006111	Acute Q wave myocardial infarction
299718016	AMI - Acute myocardial infarction
3427201000006111	AMI - Acute myocardial infarction

2855351000006111	Myocardial infarct
3565871000006113	Acute myocardial infarction of inferolateral wall
1780491019	STEMI - ST elevation myocardial infarction
6651221000006117	STEMI - ST elevation myocardial infarction
109916013	Post myocardial infarction pericarditis
109915012	Post myocardial infarction pericarditis
3576371000006117	Post myocardial infarction pericarditis
299708014	Acute Anteroapical myocardial infarction
25646001	Electrocardiographic myocardial infarction NOS
256452010	Electrocardiographic myocardial infarction
1786197015	Coronary artery thrombosis
1786198013	Coronary artery thrombosis
6601121000006118	Coronary artery thrombosis
256458014	Electrocardiographic subendocardial infarct
5056941000006119	Post-infarction pericarditis
1218860015	Acute infarction of papillary muscle
256455012	ECG: antero-septal infarct
4586111000006115	ECG: antero-septal infarct
158601000006116	Rupture of cardiac wall without hemopericardium as current complication following acute myocardial infarction
350376014	MI - Silent myocardial infarction
5056461000006113	MI - Silent myocardial infarction
498031000006112	Atrial septal defect due to and following acute myocardial infarction
1780501013	NSTEMI - non-ST segment elevation MI
6651391000006114	NSTEMI - non-ST segment elevation MI
5056501000006113	Defect of ventricular septum following myocardial infarction
67081000006113	Defect of ventricular septum following myocardial infarction
1234306015	Acute myocardial infarction of septum
299711010	Acute myocardial infarction of lateral wall
3452181000006112	Acute myocardial infarction of lateral wall
458611000006115	Anteroseptal infarction on electrocardiogram
37443015	Infarction of heart
299813018	Reinfarction of myocardium
299808017	Reinfarction of myocardium
1738171000006114	Previous myocardial infarction
230021000006115	Previous myocardial infarction

216351000006118	Pericarditis following myocardial infarction
5056941000006119	Pericarditis following myocardial infarction
299714019	Acute myocardial infarction of diaphragmatic wall
369921000006110	Acute myocardial infarction of diaphragmatic wall
6601131000006115	CT - Coronary thrombosis
94884017	Myocardial infarction
219531000000117	Myocardial Infarction
884151000006119	Myocardial Infarction
455422014	Postoperative subendocardial myocardial infarction
4032016	Healed myocardial infarction
116992017	Acute subendocardial infarction
299714019	Inferior myocardial infarction NOS
300881018	[X]Subsequent myocardial infarction of other sites
455423016	Postoperative myocardial infarction, unspecified
100681000006116	Thrombosis following acute MI
455641000006112	Acute anterolateral infarction
543291000006110	Certain current complication follows acute myocardial infarct
810821000006112	History of myocardial infarct at age greater than sixty
256454011	EKG: old myocardial infarction
299721019	Coronary thrombosis
1780491019	Acute ST segment elevation myocardial infarction
1786198013	Thrombosis - coronary
1218860015	Acute papillary muscle infarction
299708014	Acute Anteroapical infarction
256455012	ECG: antero-septal infarct.
208365015	Postoperative myocardial infarction
212081000006110	Postoperative transmural myocardial infarction other sites
256457016	EKG: posterior/inferior infarct
2855341000006114	MI - Myocardial infarction
3699921000006110	Acute inferior myocardial infarction
256459018	Electrocardiogram: lateral infarction
3641641000006116	Acute myocardial infarction of anterolateral wall
109916013	Post myocardial infarction syndrome
109915012	Post myocardial infarction syndrome
299719012	Acute myocardial infarction of atrium

109915012	Post myocardial infarction syndrome
300882013	[X]Subsequent myocardial infarction of unspecified site
299709018	Acute myocardial infarction of anterior wall
299707016	Acute myocardial infarction of anterior wall
3381601000006117	Acute myocardial infarction of anterior wall
1234306015	Acute septal infarction
1780501013	Acute non-ST segment elevation myocardial infarction
256459018	ECG: lateral infarction
362461000006119	[X]Acute transmural myocardial infarction of unspecified site
455651000006114	Acute anteroseptal infarction
1234005010	Acute myocardial infarction of infer posterior wall
3745741000006117	Acute myocardial infarction of infer posterior wall
7572331000006110	Acute STEMI (ST elevation myocardial infarction) of inferior wall
5056421000006119	Old inferior myocardial infarction
7662871000006115	Inducible ischaemia manifest on stress test post myocardial infarction
2515471000006117	Septal infarction by electrocardiogram
7572341000006117	Acute inferior ST segment elevation myocardial infarction
7571601000006115	Acute STEMI (ST elevation myocardial infarction) of anterior wall
7574491000006114	Subsequent NSTEMI (non-ST segment elevation myocardial infarction)
7572321000006112	Acute ST segment elevation myocardial infarction of inferior wall
2729671000000118	Acute transmural myocardial infarction
5056411000006110	Old anterior myocardial infarction
6043771000006118	Non-Q wave myocardial infarction
7571581000006113	Acute anterior ST segment elevation myocardial infarction
3202711000006110	Anterolateral infarction by EKG

Chronic obstructive pulmonary diseases

Medcodeid	Term
475431013	chronic obstructive pulmonary disease
457169013	moderate chronic obstructive pulmonary disease
457168017	mild chronic obstructive pulmonary disease
457171013	Severe chronic obstructive pulmonary disease
2716321000006116	COPD
516801000000112	very severe chronic obstructive pulmonary disease
1222335015	chronic obstructive pulmonary disease NOS
193801000006119	pulmonary disease due to mycobacteria
301836011	other specified chronic obstructive pulmonary disease
301853016	other specified interstitial pulmonary disease
1222334016	other specified chronic obstructive pulmonary disease
1948051000006112	Asthma-chronic obstructive pulmonary disease overlap syndrome
4510801000006114	End stage chronic obstructive airways disease
301545019	Chronic obstructive airway disease
2716231000006114	Chronic obstructive lung disease
7970171000006119	Acute exacerbation of chronic obstructive airways disease with asthma
301453013	Acute exacerbation of chronic obstructive airways disease
301456017	Mixed simple and mucopurulent chronic bronchitis
55546100006119	Chronic obstructive pulmonary disease with acute lower respiratory infection
424365019	Acute infective exacerbation of chronic obstructive airways disease
8090191000006114	Acute exacerbation of chronic obstructive bronchitis
6213641000006118	Chronic mucus hypersecretion
7049011000006110	Acute exacerbation of chronic bronchitis
87480013	Chronic tracheobronchitis
508561017	Simple chronic bronchitis
123588010	Mucopurulent chronic bronchitis
506053014	Fetid chronic bronchitis
2010061000006113	Acute non-infective exacerbation of chronic obstructive pulmonary disease
2240631000000119	Eosinophilic bronchitis
301477019	Emphysema NOS

508562012	Catarrhal bronchitis
139979010	Fetid chronic bronchitis
492443010	Bronchiolitis obliterans
301455018	Obstructive chronic bronchitis NOS
640491000006111	Emphysema
301460019	Chronic bullous emphysema
301464011	Zonal bullous emphysema
109301000006114	Tension pneumatocele
301468014	Chronic bullous emphysema NOS
1230190015	MacLeod's unilateral emphysema
216596014	end stage COPD
301539010	Other specified chronic obstructive airways disease
555461000006119	Chronic obstruct pulmonary dis with acute lower respiratory infection
553211000006119	Chron obstruct pulmonary dis with acute exacerbation; unspecified
1484924013	COPD disease monitoring
1484971019	COPD disease monitoring due
977891000006112	COPD disease accident and emergency attendance since last year
977901000006111	emergency COPD disease admission since last appointment
977911000006114	number of COPD disease exacerbations in past year
299001000000116	COPD disturbs sleep
299031000000110	COPD does not disturb sleep
998281000006115	multiple COPD disease emergency hospital admissions
839001000006111	COPD self-management plan given
1488423019	COPD disease follow-up
845451000006118	COPD disease follow-up
149601017	COAD disease follow-up
1488424013	COPD annual review
1780380013	COPD disease monitoring by nurse
1780381012	COPD disease monitoring by doctor
2160051010	emergency hospital admission for COPD disease
27096010	Giant bullous emphysema
396109014	Atrophic (senile) emphysema
640491000006111	Pulmonary emphysema
113497011	centrilobular emphysema

481742015	surgical emphysema
285100019	emphysema bronchitis
909721000006115	Emphysema
7462014	subcutaneous emphysema
19421011	interstitial pulmonary emphysema
461311019	screening for chronic bronchitis or emphysema
301469018	other emphysema
301835010	other emphysema
9337016	panlobular emphysema
301463017	segmental bullous emphysema
396110016	other emphysema NOS
3295361000006115	Emphysema
53589018	acute emphysematous cholecystitis
1227837013	screening for emphysema
2767261000006118	mediastinal emphysema
457581000006111	acute interstitial emphysema
3228301000006115	unilateral emphysema
354323012	emphysematous pyelonephritis
99889013	perinatal interstitial emphysema
301572010	chronic emphysema due to chemical fumes
90243017	traumatic subcutaneous emphysema
2880651000006119	subcutaneous emphysema resulting from a procedure
55602016	compensatory emphysema
899261000006112	traumatic subcutaneous emphysema
3013801000006116	paraseptal emphysema
316340019	perinatal interstitial emphysema and related conditions
354325017	Emphysema pyelitis
5468391000006110	emphysematous
1232475017	perinatal mediastinal emphysema
2767421000006111	obstructive emphysema
3611791000006110	centriacinar emphysema
7627141000006111	pulmonary emphysema co-current with fibrosis of lung
14161371000006110	Emphysema of left lung
14161381000006113	Emphysema of right lung
301470017	acute vesicular emphysema

404571000006112	other conditions related/interstitial emphysema
3476441000006112	perinatal pulmonary interstitial emphysema
3921361000006112	Emphysema of lung
7627151000006113	combined pulmonary fibrosis and emphysema
396109014	atrophic emphysema
3589231000006114	congenital lobar emphysema
4781461000006117	emphysematous bulla
4781471000006112	bullous emphysema
5054311000006111	scar emphysema
316342010	perinatal interstitial emphysema and related conditions
3764021000006117	interstitial emphysema of lung
3476431000006119	perinatal interstitial emphysema
3437401000006110	emphysematous bleb of lung
5054271000006111	pulmonary emphysema in alpha1 PI deficiency
234431000006115	perinatal interstitial emphysema or related conditions
3013821000006114	subpleural emphysema
3476451000006114	perinatal pulmonary interstitial emphysema
4058571000006110	emphysematous cholecystitis
4374681000006116	Chronic emphysema
5054291000006112	toxic emphysema
5054301000006113	chemical emphysema
18268014	Acute bronchitis
396107011	bronchitis
411490016	acute wheezy bronchitis
2163183015	wheezy bronchitis
301441014	bronchitis NOS
350041018	chest infection- unspecified bronchitis
105519017	chronic bronchitis
301122016	Acute bronchitis NOS
58909014	Acute tracheobronchitis
301103013	Acute purulent bronchitis
301437010	tracheobronchitis
142425010	laryngotracheobronchitis
285104011	obstructive chronic bronchitis
301095014	Acute bronchitis and bronchiolitis

301120012	Acute viral bronchitis
411520013	H/O: bronchitis
301459012	chronic bronchitis NOS
183191000006115	recurrent wheezy bronchitis
301450011	chronic asthmatic bronchitis
2475602011	Acute croupous bronchitis
301105018	Acute pneumococcal bronchitis
301121011	Acute bacterial bronchitis
301132011	Acute bronchitis or bronchiolitis NOS
477291000006114	allergic bronchitis NEC
6720721000006111	asthmatic bronchitis
301119018	subacute bronchitis
301451010	chronic wheezy bronchitis
301820014	acute infective bronchitis
508562012	chronic catarrhal bronchitis
456021000006115	Acute bronchitis due to parainfluenza virus
2240631000000119	Eosinophilic bronchitis
301100011	Acute fibrinous bronchitis
301108016	acute haemophilus influenza bronchitis
350044014	Acute bronchitis due to mycoplasma pneumoniae
851261000006116	chronic bronchitis, acute
885281000006118	mucopurulent chronic bronchitis
301116013	Acute bronchitis due to rhinovirus
885041000006119	Acute bronchitis
1174251000000119	aspergillus bronchitis
506053014	purulent chronic bronchitis
456031000006117	Acute bronchitis due to respiratory syncytial virus
12717061000006114	Acute bronchitis and/or bronchiolitis
13651611000006116	Acute bronchitis co-occurrent with wheeze
87480013	chronic tracheobronchitis
301444018	simple chronic bronchitis
301448015	mucopurulent chronic bronchitis
907481000006118	bronchitis
301109012	Acute Neisseria catarrhalis bronchitis
6717641000006116	allergic bronchitis

301106017	Acute streptococcal bronchitis
301457014	other chronic bronchitis
301565014	bronchitis and pneumonitis due to chemical fumes
301566010	Acute bronchitis due to chemical fumes
13651301000006113	bronchitis co-occurrent with wheeze
301456017	mixed simple and mucopurulent chronic bronchitis
301101010	Acute membranous bronchitis
301458016	other chronic bronchitis NOS
1227838015	screening of chronic bronchitis
2475601016	Acute pseudomembranous bronchitis
4780481000006116	Acute parainfluenza virus bronchitis
4780491000006118	acute respiratory syncytial virus bronchitis
13651601000006119	bronchitis co-occurrent with acute wheeze
301568011	bronchitis and pneumonitis due to chemical fumes
3514606010	protracted bacterial bronchitis
455991000006112	Acute bronchitis due to coxsackievirus
456001000006113	Acute bronchitis due to echovirus
5053331000006119	acute mycoplasma bronchitis
7258581000006114	acute exacerbation of chronic asthmatic bronchitis
6015831000006117	acute infective tracheobronchitis
2756071000006111	viral bronchitis
3955621000006112	catarrhal bronchitis
13486511000006115	Acute bronchitis caused by SARS covid
3896411000006114	laryngotracheobronchitis
1709191000006112	aspergillus bronchitis
3873191000006110	fetid chronic bronchitis
4733031000006114	chronic obstructive bronchitis
5573791000006115	acute fibrinous laryngotracheobronchitis
13651461000006115	chronic bronchitis co-occurrent with wheeze
3514603019	acute noninfective bronchitis
4780421000006115	acute Moraxella catarrhalis bronchitis
7715861000006113	Acute bronchitis co-occurrent with bronchiectasis
8033221000006118	chronic obstructive lung disease co-occurrent with acute bronchitis

Depression

Medcodeid	Term
305421000000112	Depression screening using questions
376691000006116	Depression
2534091015	Depression interim review
251629019	H/O depression
2534092010	Depression medication review
675861000006113	reactive depression situational
1488626018	symptoms of depression
401766011	major depression, single episode
359121000006116	reactive depression
294844012	recurrent depression
295537016	chronic depression
882671000006112	Depression
296137015	mild depression
410861011	endogenous depression-recurrent
441826016	endogenous depression
2534096013	depression annual review
294621000000118	depression resolved
613751000006114	Depression screening
882681000006110	depression NOS
138421012	agitated depression
2474715017	on depression register
213641000000111	mild depression
999901000006113	expected from depression quality indicators- patient unstable
346972018	endogenous depression first episode
474171000006112	agitated depression
882401000006115	reactive neurotic depression
2533375017	patient given advice about depression management
294825017	mild major depression, single episode
294826016	moderate major depression, single episode
642461000006116	endogenous depression first letter
1650771000000113	suspected depression

1231868010	puerperal depression
398351000006110	mild anxiety depression
294918011	psychotic reactive depression
142541000006115	severe major depression, single episode
379781000006118	endogenous depression without psychotic symptoms
408541000000117	depression monitoring second letter
1839561000006119	PHQ9 total score 10-14 (moderate depression)
1839571000006114	PHQ9 total score 15-19 (moderate severe depression)
6000711000006112	moderate depression
408601000000116	depression monitoring telephone invitation
419841000006116	persistent anxiety depression
882821000006110	moderate depression
1715181000006114	moderate major depression
1839551000006116	PHQ9 total score 5-9(mild depression)
1839581000006112	PHQ9 total score 20-27 (severe depression)
223741000000112	severe depression
1715191000006112	severe major depression with psychotic features
426971000006119	single episode of reactive depression
513751000006117	bipolar affective disorder, current episode depression
1773563015	depression management programme
408561000000116	depression monitoring third letter
346973011	masked depression
379771000006116	endogenous depression with psychotic symptoms
909681000006110	depression
424651000006114	recurrent episodes of reactive depression
882811000006119	mild depression
882831000006113	severe depression
1715781000006110	severe major depression without psychotic features
294646011	senile dementia with depression
424671000006116	recurrent severe episodes of psychotic depression
300711000000119	referral for guided self-help for depression
7382831000006114	whooley depression screen
8214741000006117	depression monitoring invitation
295536013	post viral depression
367061000006114	psychosis and severe depression co-current and due to bipolar affective disorder

396081000006116	major depression, recurrent without psychotic symptoms
424541000006111	recurrent severe episodes /major depression psychotic symptom
424641000006112	recurrent episodes of psychogenic depression
426961000006114	single episode of psychotic depression
504361000006116	Beck depression inventory
635311000006117	ST depression
294843018	recurrent major depression in full remission
366561000006119	atypical depression
423611000006111	prolonged single episode of reactive depression
426941000006110	single episode of psychotic depression
1715771000006112	mild major depression
294642013	presenile dementia with depression
1785881000006119	antenatal depression
426921000006115	single episode of major depression and psychotic symptoms
451129016	bone marrow depression
8459491000006110	depression monitoring invitation SMS
142521000006110	major depression, single episode in partial remission
426891000006114	single episode of agitated depression without psychotic symptoms
294655014	arteriosclerotic dementia with depression
2957311000006113	severe major depression with psychotic features
294831019	single episode of major depression in full remission
1222477019	postoperative depression
613761000006111	congenital depression in skull
1680571000006118	on full dose depression treatment
423041000006119	post-schizophrenic depression
1823881000006110	depression confirmed
5359011000006112	depression -motion
8053541000006119	positive screening for depression on PHQ-9
13962531000006113	Follow-up depression
398841000006119	monopolar depression NOS
295535012	Depressive disorder
376721000006114	Depressive episode
488211000006112	mixed anxiety and depressive disorder
525921000006119	brief depressive adjustment reaction
253619019	O/E - depressed

2164006016	Depressed
401872015	Depressive episode, unspecified
376711000006118	Depressive disorder NOS
401873013	Recurrent depressive disorder
407062014	C/O - feeling depressed
401871010	Other depressive episodes
294832014	single major depressive episode NOS
399961000006118	Depressive neurosis
379431000006113	Dysthymia
376741000006119	Depressive neurosis
425411000006110	SAD- seasonal affective disorder
424631000006119	recurrent episodes of depressive reaction
426911000006111	single episode of depressive reaction
296138013	moderate depressive episode
401866015	severe depressive episode without psychotic symptoms
1494612017	Depressive symptoms
2164005017	Depressed mood
613781000006118	depressive personality disorder
369982012	seasonal affective disorder
398561000006117	mild anxiety and depressive disorder
931341000006115	expected from mental health quality indicators-patient unsuitable
294838013	recurrent major depressive episodes, moderate
182721000006111	recurrent major depressive episodes
202561000006114	prolonged depressive adjustment reaction
424561000006110	recurrent brief depressive episodes
296198011	recurrent depressive disorder, currently in remission
294845013	recurrent major depressive episode NOS
182771000006112	recurrent major depressive episodes severe
294894013	Atypical depressive disorder
425751000006115	seasonal depressive disorder
294837015	recurrent major depressive episode, mild
296180012	recurrent depressive disorder, current episode mild
283005012	patient advised to see solicitor
376701000006116	depressive conduct disorder
424531000006118	recurrent depression disorder cur epi severe without psychological symptoms

294824018	single major depressive episode, unspecified
294836012	recurrent major depressive episodes, unspecified
295494011	brief depressive reaction NOS
401876017	recurrent depressive disorder, unspecified
296199015	Other recurrent depressive disorders
182801000006114	recurrent major depressive episodes, partial/unspecific remission
426931000006117	single episode of masked depression NOS
426991000006118	single episode vital depression without psychotic symptoms
432511000006119	vital depression, recurrent without psychotic symptoms

Anxiety

Medcodeid	Term
488211000006112	mixed anxiety and depressive disorder
488201000006114	anxiety disorder
294963012	anxiety state
363661000006113	anxiety NOS
481154010	generalised anxiety disorder
294960010	chronic anxiety
398561000006117	mixed anxiety and depressive disorder
251630012	H/O anxiety
304838011	anxiety state
294961014	recurrent anxiety
3287741000006111	anxiety
296249012	anxiety disorder unspecified
388071000006116	generalised anxiety disorder
363681000006115	anxiety state
223641000000116	phobic anxiety disorder
296238018	other anxiety disorders
296239014	panic disorder
363671000006118	anxiety reaction
398351000006110	mild anxiety depression
1901341000006113	GAD -2 generalised anxiety disorder 2 scale score

296224013	phobic anxiety disorder
363651000006111	anxiety neurosis
2335491000000117	anxiety screening
2335571000000115	patient given advice about management of anxiety
342665019	anxiety management training
419841000006116	persistent anxiety depression
441512015	separation anxiety disorder
296237011	phobic anxiety disorder, unspecified
300681000000118	referral for guided self-help for anxiety
908651000006112	high parental anxiety
296245018	other mixed anxiety disorders
296722013	separation anxiety disorder
1976491000006113	mixed anxiety and depressive reaction
2391701000000114	anxiety screening declined
401881014	other specified anxiety disorders
504351000006118	Beck anxiety inventory
647711000006111	EPNDS question 4 - anxiety
6025521000006113	anxiety counselling
403931000006116	organic anxiety disorder
5886481000006112	anxiety attack
909691000006113	anxiety management
2848311000006117	GAD generalised anxiety disorder
296236019	other phobic anxiety disorders
2882975016	short health anxiety inventory
363641000006114	anxiety hysteria
420641000006116	phobic anxiety disorder of childhood
2618241000000117	anxiety resolved
2618361000000113	referral for psychological management of anxiety
5717641000006118	level of anxiety
378291000006117	dream anxiety disorder
626101000006114	disturbance of anxiety and fearfulness in childhood and adolescence NOS
5248991000006117	anxiety and fear
8278471000006118	GAD -2 generalised anxiety disorder 2 scale
1956641000006116	Keele ENHANCE trial anxiety/dep- refer to IAPT programme
2287071000000115	anxiety about breathlessness

5249061000006116	anxiety about body function or health
2168401000000116	referral for psychological management of anxiety declined
2848291000006116	generalised anxiety disorder
5886461000006119	parental anxiety
2652351000000117	signposting to anxiety UK
7317151000006110	assessment using hospital anxiety and depression scale
7663271000006111	management of anxiety
2017961000006113	Keele INCLUDE study- anxiety/depression
4391041000006110	separation anxiety disorder
4948981000006112	alleviating anxiety
5024071000006118	anxiety depression
5249261000006112	anxiety about behaviour or performance
494481000006113	anxiety about not coping with parenthood
5549571000006113	depression anxiety scales
5628441000006118	performance anxiety
8297491000006114	education about anxiety
2907991000006110	social anxiety disorder
4937701000006118	acknowledging anxiety
12127531000006113	recurrent mild major depressive disorder co-current with anxiety
12127551000006118	recurrent moderate major depressive disorder co-current with anxiety
853241000006119	phobic anxiety
2391581000000111	referral for guided self-help for anxiety declined
4944401000006116	anxiety about treatment
3265831000006118	adjustment disorder with anxiety
5605281000006110	anxiety about dying

Osteoarthritis

Medcodeid	Term
1776248011	osteoarthritis
221521000000114	osteoarthritis of knee
310024016	osteoarthritis NOS of knee
41261000006115	osteoarthritis and allied disorders
221511000000115	osteoarthritis of hip
800731000006117	Generalised osteoarthritis
310020013	osteoarthritis NOS of hip
400187015	osteoarthritis NOS of lower leg
41281000006113	osteoarthritis NOS
800751000006112	polyarticular osteoarthritis
400182014	osteoarthritis NOS
889921000006110	osteoarthritis of knee joint
18181000006118	osteoarthritis of spine
400188013	localised, primary osteoarthritis of the ankle and/or foot
251795011	H/O: osteoarthritis
240071000006115	patellofemoral osteoarthritis
359433019	osteoarthritis of lumbar spine
889911000006119	osteoarthritis of hip joint
889861000006112	osteoarthritis of multiple joint
359385016	osteoarthritis of ankle
508047017	osteoarthritis of spine
219611000000112	osteoarthritis of cervical spine
309896011	localised, primary osteoarthritis of the lower leg
359384017	osteoarthritis of foot joint
41301000006112	osteoarthritis of first metatarsophalangeal joint
309881012	localised, primary osteoarthritis
310010015	osteoarthritis NOS, other specified site
310016014	osteoarthritis NOS of wrist
310026019	osteoarthritis NOS of ankle
359383011	osteoarthritis of toe joint
359389010	osteoarthritis of finger

54641000006115	osteoarthritis of wrist
889901000006117	osteoarthritis - hand joint
309880013	Generalised osteoarthritis NOS
309892013	localised, primary osteoarthritis of the hand
309953017	localised, osteoarthritis, unspecified, of the hand
400175010	Generalised osteoarthritis of the hand
400181019	localised osteoarthritis, unspecified of the lower leg
400184010	osteoarthritis NOS of the forearm
1492276018	osteoarthritis of cervical spine
18191000006115	osteoarthritis spine
31101000006110	osteoarthritis of first metacarpophalangeal joint
221491000000111	osteoarthritis of elbow
736781000006114	localised, osteoarthritis, unspecified , pelvic region/thigh
736911000006116	localised, primary osteoarthritis of the pelvic region and thigh
889931000006113	osteoarthritis - ankle/foot
309942011	localised osteoarthritis
309965018	localised, osteoarthritis, unspecified , of the ankle and foot
310014012	osteoarthritis NOS of elbow
309898012	localised, primary osteoarthritis of the ankle and foot
359402016	osteoarthritis of spinal facet joint
359420013	osteoarthritis of knee
31031000006115	osteoarthritis of distal interphalangeal joint
1492281010	osteoarthritis of thoracic spine
309972017	osteoarthritis of multiple joint
400183016	osteoarthritis NOS, of the upper arm
18051000006110	osteoarthritis of proximal interphalangeal joint
309899016	localised, primary osteoarthritis of other specified site
310028018	osteoarthritis of talonavicular joint
457121010	localised, primary osteoarthritis of toe
889891000006116	osteoarthritis of wrist joint
889941000006115	osteoarthritis of other joint
309911018	localised, primary osteoarthritis NOS
309914014	localised, secondary osteoarthritis
309930018	localised, secondary osteoarthritis of the lower leg

309971012	localised, osteoarthritis , unspecified , NOS
309987010	osteoarthritis NOS, of unspecified site
310027011	osteoarthritis of subtalar joint
457118013	localised, primary osteoarthritis of the wrist
736701000006117	localised, osteoarthritis , unspecified , of other spec site
5140431000006112	osteoarthritis of finger joint
309933016	localised, secondary osteoarthritis of the ankle and foot
309983014	osteoarthritis of more than one site, unspecified, NOS
310029014	osteoarthritis NOS of other tarsal joint
2476044012	osteoarthritis of spine NOS
31071000006117	osteoarthritis NOS of IP joint of toe
889881000006119	osteoarthritis of elbow joint
457122015	localised, primary osteoarthritis of elbow
736171000006110	localised, secondary osteoarthritis of the pelvic region and thigh
309979014	oligoarticular osteoarthritis, unspecified, of lower leg
265861000006116	oligoarticular osteoarthritis, unspecified, multiple sites
309889014	localised, primary osteoarthritis of the forearm
309941016	localised, secondary osteoarthritis NOS
31091000006116	osteoarthritis NOS of lesser MTP joint
265841000006115	oligoarticular osteoarthritis, unspecified, of unspecified sites
309884016	localised, primary osteoarthritis of the unspecified sites
309923012	localised, secondary osteoarthritis of the hand
309945013	localised, osteoarthritis, unspecified, of unspecified site
309977011	oligoarticular osteoarthritis, unspecified, of hand
309888018	localised, osteoarthritis, unspecified, of the upper arm
309934010	localised, secondary osteoarthritis of another specified site
18121000006117	osteoarthritis NOS of tibio-fibular joint
31041000006113	osteoarthritis NOS of distal radio-ulnar joint
264501000006118	oligoarticular osteoarthritis, unspecified, of other specified sites
265871000006111	oligoarticular osteoarthritis, unspecified, of ankle/foot
905311000006112	osteoarthritis
909181000006117	osteoarthritis
989361000006114	osteoarthritis of hip joint

1785201000006112	expected from osteoarthritis quality indicators - patient unsuitable
309922019	localised, secondary osteoarthritis of the forearm
309949019	localised, osteoarthritis, unspecified of the upper arm
264471000006113	oligoarticular osteoarthritis, unspecified, of pelvis/thigh
6564781000006111	referral to rheumatology service for osteoarthritis
8103651000006111	osteoarthritis of right hip joint
8103621000006119	osteoarthritis of left knee joint
8103661000006113	osteoarthritis of right knee joint
5140211000006119	idiopathic osteoarthritis
5140571000006114	OA-osteoarthritis of knee
8103611000006110	osteoarthritis of left hip joint
309915010	localised, secondary osteoarthritis of un specified site
2641211000006114	OA-osteoarthritis of spine
309919016	localised, secondary osteoarthritis of the upper arm
989371000006119	osteoarthritis - knee joint
5140541000006118	OA-osteoarthritis of hip
1785191000006114	exception reporting - osteoarthritis quality indicators
1785211000006110	expected from osteoarthritis quality indicators - informed dissent
2853461000006115	osteoarthritis - hand joint
309975015	oligoarticular osteoarthritis, unspecified, of upper arm
370721000000116	delivery of rehabilitation for osteoarthritis
989351000006112	osteoarthritis - wrist joint
3110361000006110	osteoarthritis basilar joint of thumb
7278801000006118	secondary OA
309976019	oligoarticular osteoarthritis, unspecified, of forearm
932071000006116	exacerbation of OA
5140621000006112	OA-osteoarthritis of ankle
6549791000006116	exacerbation of OA
6566761000006110	OA-osteoarthritis
7380001000006110	osteoarthritis of patellofemoral joint
8448071000006113	osteoarthritis of right foot
9490001000006114	bilateral patellofemoral joint OA
12720161000006119	localised, osteoarthritis, unspecified, of the pelvic region and thigh
3110351000006113	osteoarthritis of first carpometacarpal joint

5140381000006116	OA-osteoarthritis of elbow
3619871000006116	spinal OA
7569871000006118	OA of midfoot
8101991000006113	OA of left ankle joint
5140251000006118	primary OA
5140411000006118	OA-osteoarthritis of wrist
8448121000006113	osteoarthritis of left foot
9489971000006112	osteoarthritis of right patellofemoral joint
3205591000006116	chronic OA
5140731000006118	OA-osteoarthritis of toe joint
11860791000006118	osteoarthritis of joint of right hand
1839121000006117	osteoarthritis of spinal facet joint
2641201000006111	OA-osteoarthritis of the spine
6478091000006119	cervical OA
7710061000006113	osteoarthritis of lumbar spinal facet joint
8102021000006117	osteoarthritis of joint of left wrist
7533361000006111	osteoarthritis of calcaneocuboid joint
8096361000006118	osteoarthritis of bilateral first carpometacarpal joint
8102041000006112	osteoarthritis of joint of right elbow
9489991000006113	osteoarthritis of left patellofemoral joint
3517972015	bilateral osteoarthritis of sacroiliac joints
4809421000006113	generalised osteoarthritis
5140241000006115	primary generalized OA
18061000006112	inflammation of sacroiliac joint
400186012	degenerative joint disease of pelvis
359388019	thumb osteoarthritis
400185011	degenerative joint disease of hand
309950019	osteitis of forearm
309877012	Erosive OA
359399017	primary generalised OA
309862016	degenerative joint disease involving multiple joints
309969012	arthrosis of first carpometacarpal joint, unspecified
523461000006116	Bouchard’s nodes with arthropathy
309878019	Heberden’s nodes with arthropathy

Other MSK conditions

Medcodeid	Term
484754019	Knee joint pain
248581000006113	Joint pain
310825019	Wrist joint pain
198184013	hip joint pain
637511000006115	elbow joint pain
486238018	multiple joint pain
310803013	hand joint pain
310840017	ankle joint pain
890671000006110	Ankle/foot joint pain
890701000006111	joint pain NOS
310821011	Elbow joint pain
11902311000006117	sacroiliac joint pain
310935012	Metacarpophalangeal joint pain
890681000006113	other joint pain
11902271000006117	first metatarsophalangeal joint pain
491000006119	finger joint painful on movement
11902261000006112	metacarpophalangeal joint pain
5621121000006111	foot joint pain
11902321000006113	subtalar joint pain
11902331000006111	talonavicular joint
5865271000006117	Hip joint painful on movement
5866111000006114	Knee joint painful on movement
5861721000006110	Wrist joint painful on movement
5863851000006113	Thumb joint painful on movement
4814091000006119	distal radioulnar joint pain
4814211000006117	tibiofibular joint pain
5621061000006116	lumbar facet joint pain
5850321000006111	cervical facet joint pain
5869211000006111	Toe joint pain
991491000006111	Joint pain NOS
4814321000006118	lesser metatarsophalangeal joint pain

5502581000006112	ankle and/or foot joint pain
5621141000006116	metatarsophalangeal joint pain
5850341000006116	thoracic facet joint pain
11902281000006119	finger joint painful on movement
9479731000006117	Bilateral foot joint pain
8243761000006114	H/O multiple joint pain
1955261000006110	Keele ENHANCE - joint pain knee
1956091000006115	Keele ENHANCE - joint pain duration more than 3 months
1956111000006112	Keele ENHANCE - joint pain hip
1956191000006119	Keele ENHANCE - joint pain verbal advice -pain relief
1955241000006111	Keele ENHANCE - joint pain hand
1956101000006114	Keele ENHANCE - joint pain score hand
1956171000006115	Keele ENHANCE - joint pain verbal advice - increasing activity
1956691000006113	Keele ENHANCE - joint pain written advice -OA
1956251000006117	Keele ENHANCE - joint pain- no follow-up appointment needed
2742391000000119	chronic sacroiliac joint pain
1956341000006114	Keele ENHANCE - joint pain- refer to podiatry
1955251000006113	Keele ENHANCE - joint pain hip
1955271000006115	Keele ENHANCE - joint pain foot
8035661000006111	Acute knee joint pain
2125271000000119	neck pain
51875014	Knee pain
494960013	Foot pain
369388017	Ankle pain
310802015	Arthralgia of hand
764331000006110	Foot pain
496539011	Hand pain
150521017	pain in limb
486291000006115	Anterior knee pain
491791000006117	Arthralgia of 1st metatarsophalangeal joint
310839019	Arthralgia of ankle
484753013	Arthralgia of knee
1230691015	Arthralgia of hip
491931000006119	Arthralgia of PIP joint of finger
491891000006111	Arthralgia of metatarsophalangeal joint

310826018	Arthralgia of wrist
400251019	Arthralgia of ankle and foot
400250018	Arthralgia of lower leg
400249018	Arthralgia of pelvic region and thigh
310802015	Arthralgia of hand
400248014	Arthralgia of the forearm
310792015	Arthralgia of unspecified site
310815012	Arthralgia of other specified
1228298012	Arthralgia of multiple joints
310855014	Arthralgia NOS
400259017	Musculoskeletal pain - joints
312494011	Other Musculoskeletal disorders
312504018	Musculoskeletal pain
252311015	Backache
252314011	C/O: low back pain
252316013	C/O: upper back pain
415888015	chronic low back pain
252841013	C/O: pelvic pain
454068014	C/O: pain in toe
454069018	C/O: pain in hallux
123425013	elbow pain
3498921000006118	sacral back pain
400314010	Myalgia
311696015	myalgia, unspecified
1705881000006115	Myofascial pain syndrome
400314010	Muscle pain
311617011	Other specific muscle disorder NOS
317145011	[D]Musculoskeletal pain
312729010	Musculoskeletal diseases NOS
400259017	Musculoskeletal pain - joints
377851000006114	[X]Disorders of muscles
312644015	[X]Disorder of muscle, unspecific

9.14 Appendix 14. Data management (nested case-control study)

- Risk factors

Each risk factor code list was merged with the participant's observation files to extract risk factors data. Ethnicity and IMD data were extracted from HES-patient file and IMD. The resulting dataset was merged with the case-control database. Then, the following steps of data management were followed to prepare the data for the analysis.

- The closest recording of risk factor to the index date was captured.
- Age was calculated from the year of birth to the index-date.
- Age was categorised to 6 age groups (18- 30, 31- 40, 41-50, 51-60, 61-70, and ≥ 71 years).
- All height and weight and BMI records were obtained. Records without any measurements or with implausible measurements were excluded. Weight recorders <20 Kg and > 200 kg were excluded (Bhaskaran et al., 2013). Height records > 200 cm was excluded. BMI was calculated using this formula, body weight /(height/100)^2. BMI data out of pre-specified plausible range (10 - 80 kg/m2) was excluded (Bhaskaran et al., 2013, Bhaskaran et al., 2018). BMI then was categorised into one of the 4 categories below (Itani et al., 2020, Akyea et al., 2021, NHS, 2023).

    - below 18.5 – underweight
    - between 18.5 and 24.9 – healthy weight
    - between 25 and 29.9 – overweight
    - 30 or over – obese

- To prepare the data for imputation, each variable was transformed to the appropriate format (e.g. smoking status to factor variable)

- Comorbidities

Each comorbidity code list was merged with the patient's observation files to extract comorbidities data. The resulting dataset was merged with the case-control database. Then, the following steps of data management were followed to prepare the data for the analysis.

- The closest recording of predefined comorbidity to the index date was captured.
- Participants were coded 0 if they have no comorbidity and 1 if they have comorbidity.

9.15 Appendix 15. False Discovery rate (FDR) test method

Benjamini – Hochberg procedure

False discovery rate is an approach to manage multiple testing. This is the proportion of (significant results) that are false positives. One approach for controlling the false discovery rates was reported by Simes (1986) and developed by Benjamini and Hochberg (1995).

Steps for calculating adjusted p-values using the Benjamini-Hochberg procedure:

1. Sort the p-values in ascending order.
2. Assign a rank or position (denoted as “i”) to each p-value based on its position in the sorted list.
3. Compare each p value to its Benjamini and Hochberg adjusted p-value = (i/m) Q, where (m) is the total number of tests, (i) is the rank, and (Q) is the study p value
4. The adjusted p value less than the alpha error is considered significant

- R code for calculating adjusted P-value

```
fdrs<-p.adjust(p-values, method="BH")

print(fdrs)
```

9.16 Appendix 16. Multicollinearity assessment

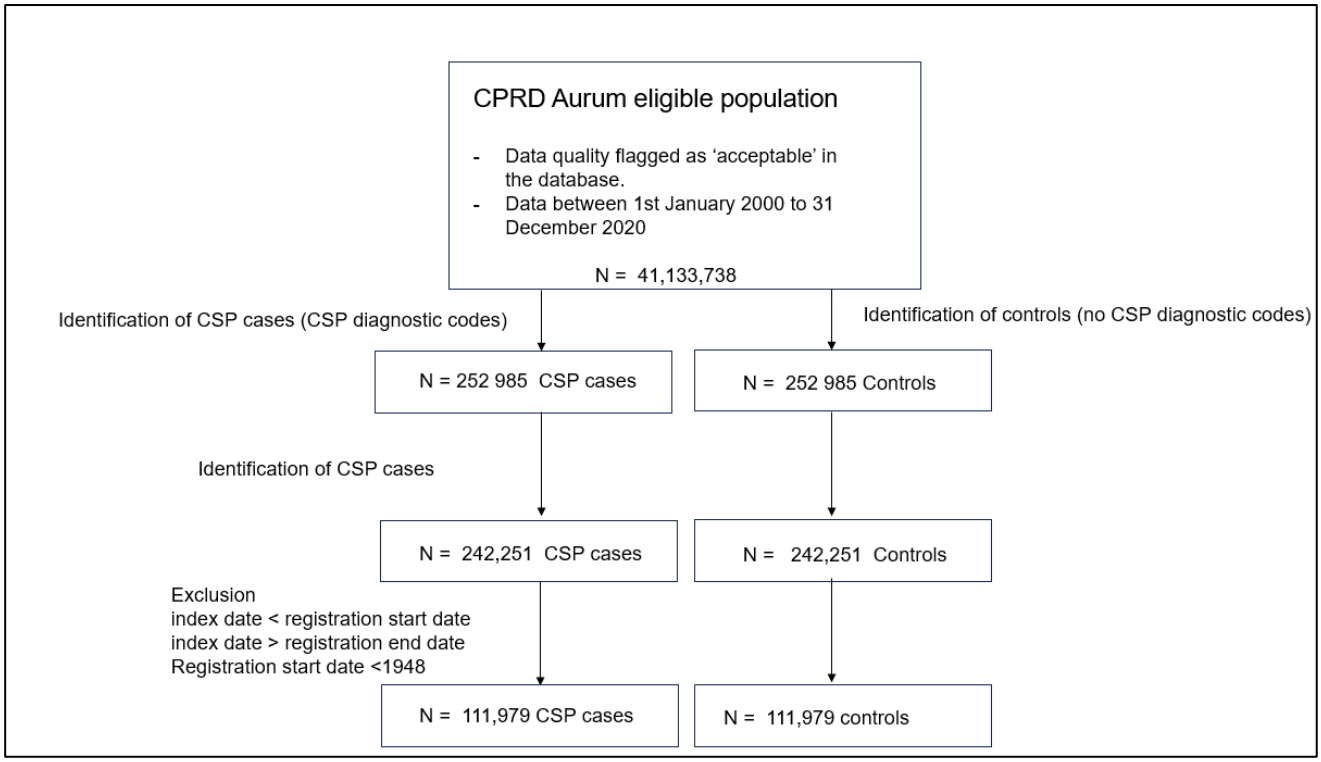
Table 9-7 Multicollinearity assessment for the case-control study

Variable	VIF
Ethnicity	1.21
Smoking	1.12
Alcohol	1.18
BMI	1.13
IMD	1.10
DM	1.23
Ischaemic heart disease	1.39
Urinary incontinence	1.03
Diverticular diseases	1.02
Diaphragmatic hernia	1.02
sarcopenia	1.00
Benign prostatic hypertrophy	1.01
hypothyroidism	1.02
tinnitus	1.01
hypertension	1.47
hyperlipidaemia	1.04
Thyroid	1.00
Myocardial infarction	1.34
Congestive heart failure	1.31
insomnia	1.07

COPD	1.05
depression	1.36
Anxiety	1.17
OA	1.10
fatigue	1.02
Other MSK	1.13
fibromyalgia	1.05
Scleroderma	1.00

9.17 Appendix 17. Selection of study population and sample size calculation

Figure 9.24 Selection of the study population



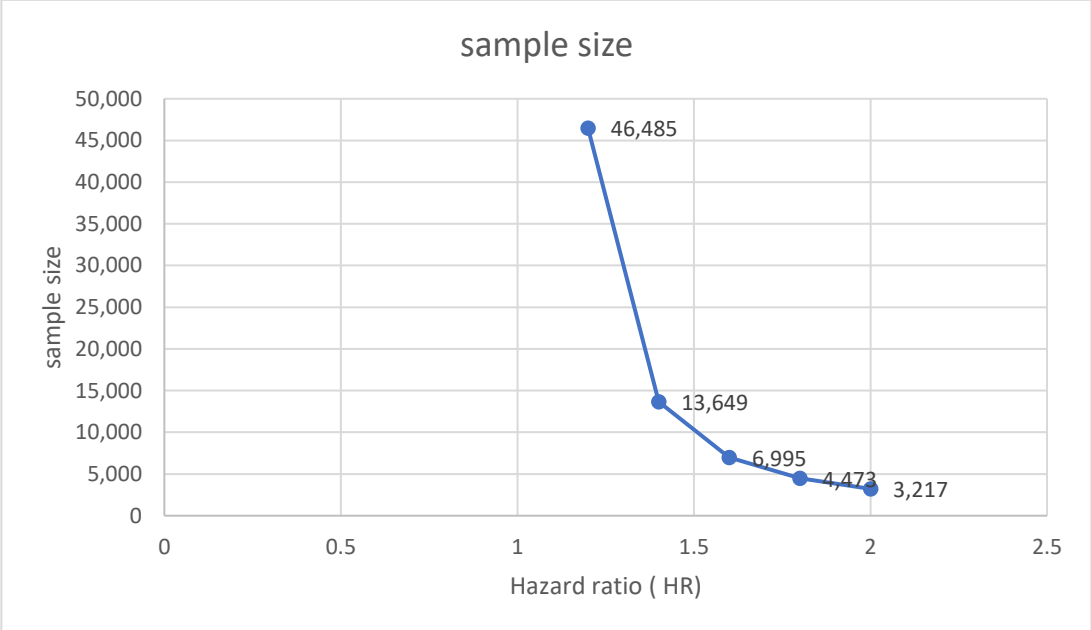
- Sample size calculation for the cohort study.

The sample size calculation for cohort study was based on a COX regression model where shoulder pain was used as a primary exposure and diabetes was used as an incident outcome. Given a background incident risk of 4% for diabetes in the UK population (González et al., 2009), a minimum hazard ratio (HR) of 1.2 in people with shoulder pain (standard deviation of ln HR=0.5), and a multiple correlation coefficient (R2) of 0.2 among covariates in the model, the sample size needed is 46485. This will give a power of 90% at a significant level of 0.05 for the study and allow dropouts of 15%. (In et al., 2020, Park et al., 2023).

Similar calculation was repeated according to other HRs, e.g., for a more clinically meaningful hazard ratio of 2, the sample size needed 3271.

Significance level (alpha) = 0.05
Power =0.9
Hazard ratio (HR) = 1.2
Standard deviation (SD) of ln HR= 0.5
Correlation R2) = 0.2
Proportion of withdrawal (Pr_W) = 0.15
Probability of event (Pr_E) = 0.04
The sample size calculation for different hazard ratios (HR) ranging from 1.2 to 2 (1.2, 1.4, 1.6. 1.8. 2) is presented in figure 2 below.

Figure 9.25 Sample size calculation for different hazard ratios.



9.18 Appendix 18. Data management (cohort study)

Mortality data management

- Merge the cohort with death database.
- Calculate end date either end of study date (31/12/2020), or death date or end of registration (transfer-out date).
- Code patient with death date = end date as 1, others 0
- Death database$ death variable<-ifelse (death database$ date of death == Death database$enddate,1,0)
- Death database$ death variable[is.na(Death database$ date of death)] <- 0
- Calculate person years (End date-index date)
- Person years/365.2

Comorbidities data management

- Merge the cohort with each comorbidity database.
- Choose first observation for each patient.
- Code patient observations before or at index date = NA
- Code patient observation > index date either 1(have comorbidity) or zero (don't have comorbidity).
- Code event date > end date = 0
- Calculate end date either end of study date (31/12/2020), date of comorbidity event or death date or end of registration (transfer-out date) or last collection date.
- Calculate person years (End date-index date)
- Person years/365.2

9.19 Appendix 19. Associations of comorbidities with rotator cuff conditions

Table 9-8 Associations of comorbidities and rotator cuff diseases

Comorbidities	Crude HR, p-value	Adjusted HR*, p-value**
Metabolic/endocrine		
Diabetes	1.29(1.24,1.34), p<0.0001	1.21(1.16,1.26), p<0.0001
Hypothyroidism	1.17(1.06,1.28), p=0.001	1.15(1.04,1.26), p=0.004
Hyperlipidaemi**a**	1.38(1.30,1.46), p<0.0001	1.35(1.27,1.42), p<0.0001
Cardiovascular/Circulatory		
Congestive heart failure	1.13(1.07,1.19), p<0.0001	1.02(0.96,1.08), p=0.39
Hypertension	1.12(1.08,1.16), p<0.0001	1.01(0.98,1.05), p=0.35
Ischemic heart diseases	1.41(1.31,1.53), p<0.0001	1.25(1.15,1.35), p<0.0001
Myocardial Infarction	1.43(1.24,1.64), p<0.0001	1.25(1.08,1.44), p=0.001
Respiratory		
COPD	1.41(1.32,1.50), p<0.0001	1.29(1.21,1.38), p<0.0001
Psychological		
Depression	1.57(1.51,1.63), p<0.0001	1.34(1.29,1.40), p<0.0001
Anxiety	1.43(1.35,1.52), p<0.0001	1.34(1.26,1.42), p<0.0001
Musculoskeletal		
OA	1.91(1.82,1.99), p<0.0001	1.79(1.71,1.88), p<0.0001
Other MSK conditions	1.85(1.79,1.91), p<0.0001	1.69(1.63,1.75), p<0.0001
Fibromyalgia	2.16(1.98,2.37), p<0.0001	1.86(1.69,2.04), p<0.0001
Fatigue	1.59(1.45,1.76), p<0.0001	1.41(1.28,1.56), p<0.0001
Sarcopenia	1.42 (0.68,2.99), p=0.34	1.38(0.64,2.94), p=0.39
Genito-urinary		
Urinary incontinence	1.69(1.53,1.86), p<0.0001	1.48(1.34,1.64), p<0.0001
Benign Prostatic Hyperplasia	1.47(1.33,1.62), p<0.0001	1.42(1.29,1.58), p<0.0001
Digestive		
Diverticular disease	1.51(1.40,1.63), p<0.0001	1.39(1.28,1.50), p<0.0001
Diaphragmatic hernia	1.67(1.53,1.82), p<0.0001	1.52(1.39,1.66), p<0.0001
Others		
Insomnia	1.82(1.69,1.96), p<0.0001	1.65(1.53,1.79), p<0.0001
Tinnitus	1.65(1.51,1.80), p<0.0001	1.52(1.39,1.67), p<0.0001
Scleroderma	0.45(0.15,1.31), p=0.14	0.42(0.14,1.24), p=0.12

*Adjusted for observation period, age, sex, practice, index date, risk factors and all comorbidities, a, for male only, COPD, chronic obstructive pulmonary diseases. MSK, musculoskeletal, **FDR adjusted p-value.

9.20 Appendix 20. Multicollinearity assessment

Multicollinearity assessment using the Variance Inflation Factor (VIF)

Table 9-9 Multicollinearity assessment for comorbidities

Variable	VIF
Shoulder pain	1.03
Sex	1.16
Index date	1.13
Age	1.18
practice	`1.42
IMD	1.28
Ethnicity	1.42
Smoking	1.14
Alcohol	1.31
BMI	1.09
Ischaemic heart disease	1.30
Urinary incontinence	1.05
Diverticular diseases	1.02
Diaphragmatic hernia	1.02
sarcopenia	1.00
Benign prostatic hypertrophy	1.02
Fibromyalgia	1.04
hypothyroidism	1.27
tinnitus	1.01

hypertension	1.27
hyperlipidaemia	1.11
Myocardial infarction	1.28
Congestive heart failure	1.19
COPD	1.03
depression	1.22
Anxiety	1.14
OA	1.08
fatigue	1.02
Other MSK	1.08
Scleroderma	1.00

Table 9-10 Multicollinearity assessment for Mortality

Variable	VIF
Shoulder pain	1.04
Sex	1.22
Index date	1.30
Age	1.32
practice	`1.07
IMD	1.16
Registration period	1.05
Ethnicity	1.17
Smoking	1.15

Alcohol	1.23
BMI	1.17
Ischaemic heart disease	1.32
Urinary incontinence	1.06
Diverticular diseases	1.02
Diaphragmatic hernia	1.02
sarcopenia	1.00
Benign prostatic hypertrophy	1.03
Fibromyalgia	1.03
hypothyroidism	1.04
tinnitus	1.01
hypertension	1.31
hyperlipidaemia	1.12
Myocardial infarction	1.27
Congestive heart failure	1.17
COPD	1.04
depression	1.22
Anxiety	1.13
OA	1.08
fatigue	1.02
Other MSK	1.09
Scleroderma	1.00

9.21 Appendix 21. Log-log plots

Log-log plot to present the testing of the proportional hazard assumption for death between cases and controls.

Figure 9.26 Log-log plot for all-cause mortality

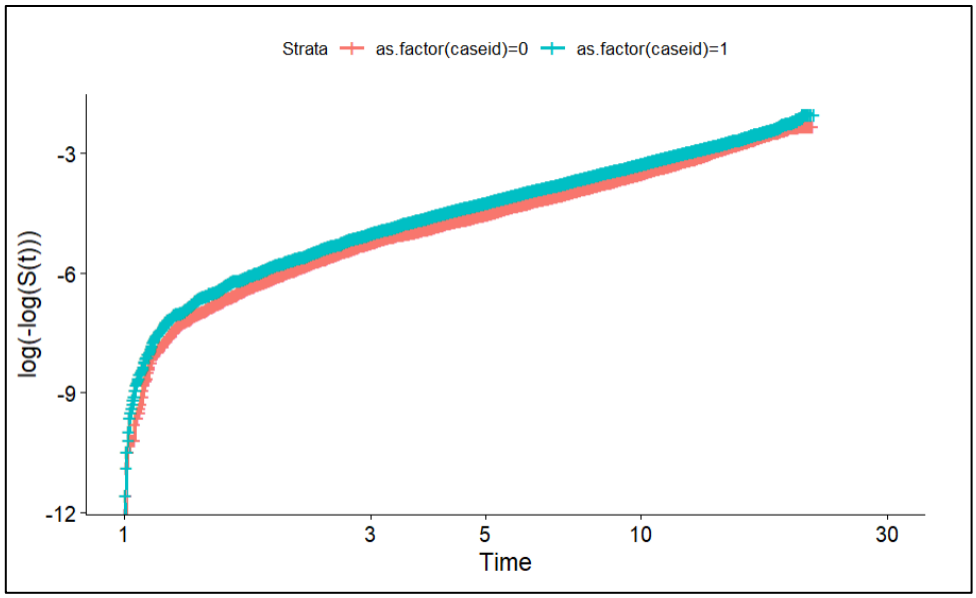
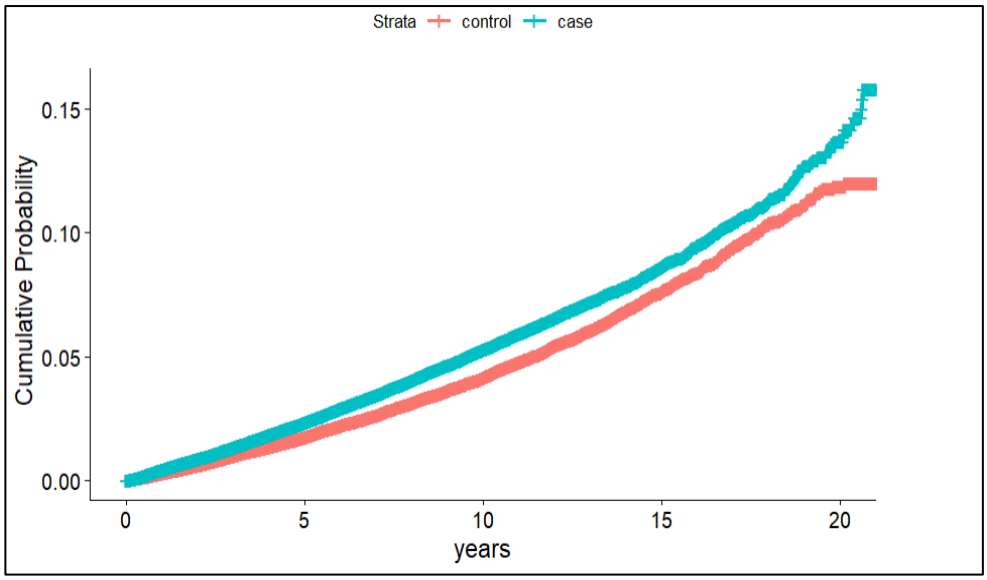


Figure 9.27 Cumulative Probability of all-cause mortality in the CSP and control group



Log-log plots to present the testing of the proportional hazard assumption for comorbidities between cases and controls.

Figure 9.28 Log-log plot for diabetes

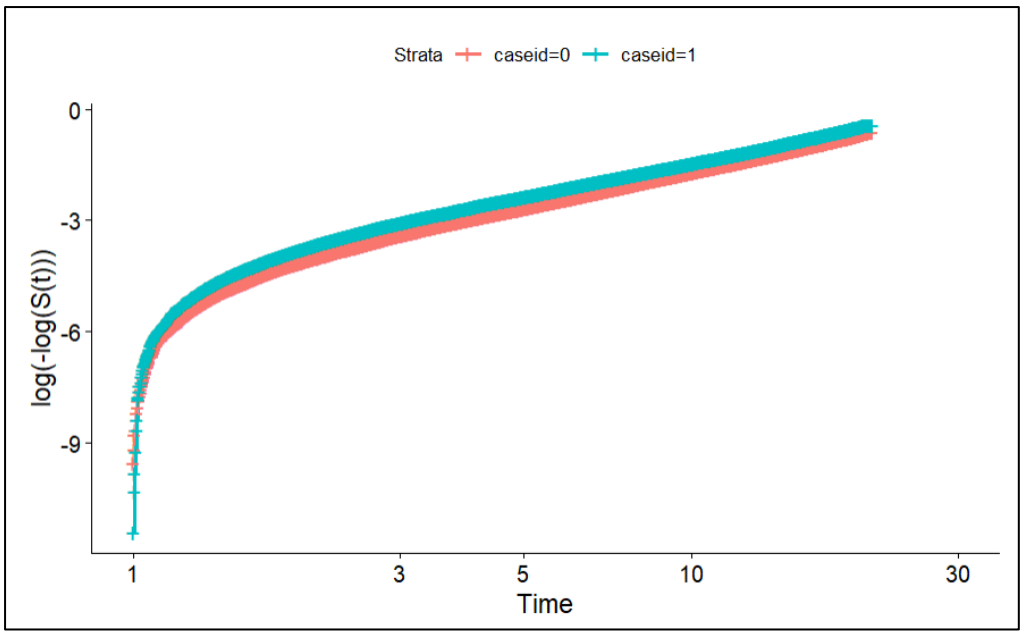


Figure 9.29 Log-log plot for hypothyroidism

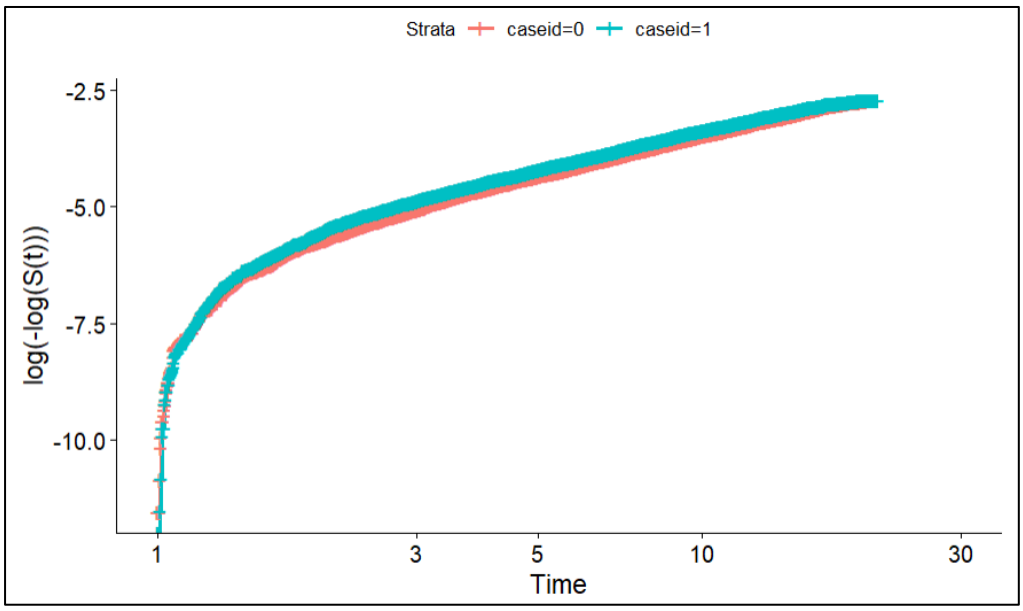


Figure 9.30 Log-log plot for congestive heart failure

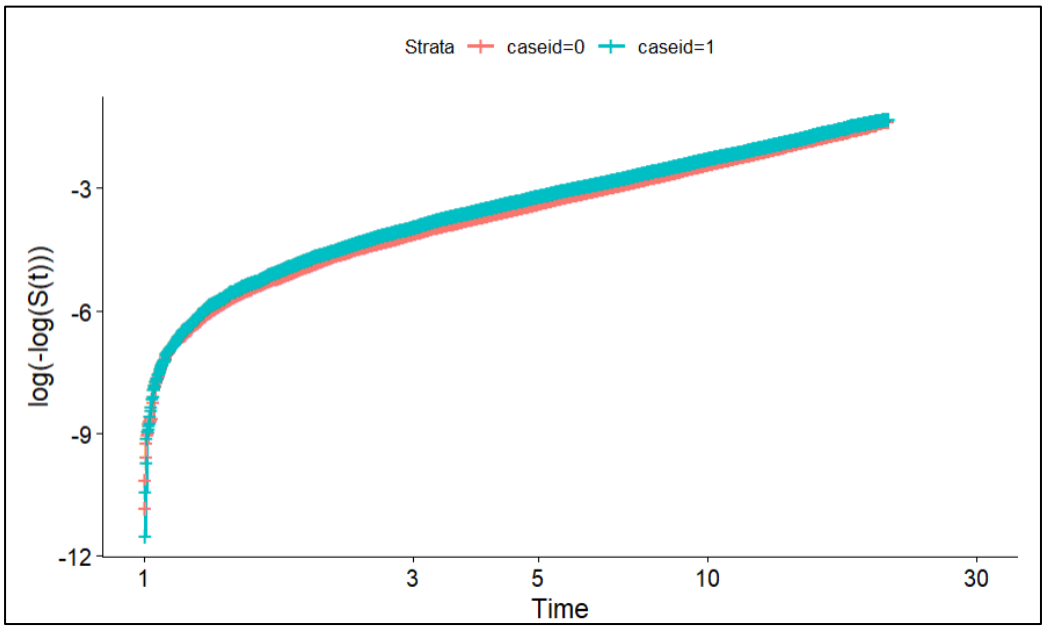


Figure 9.31 Log-log plot for hyperlipidaemia

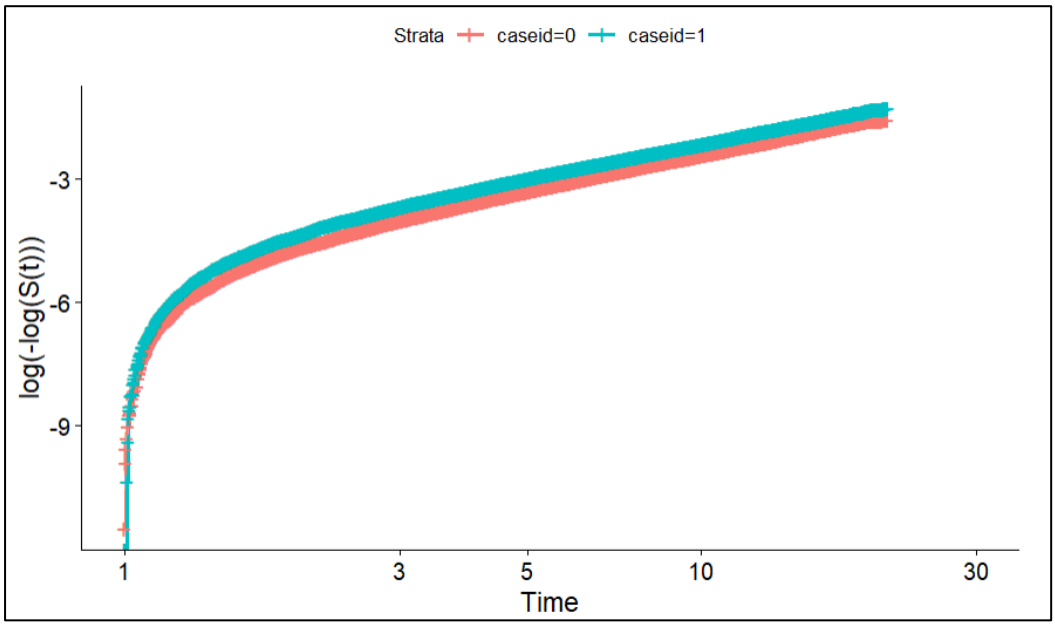


Figure 9.32 Log-log plot for hypertension

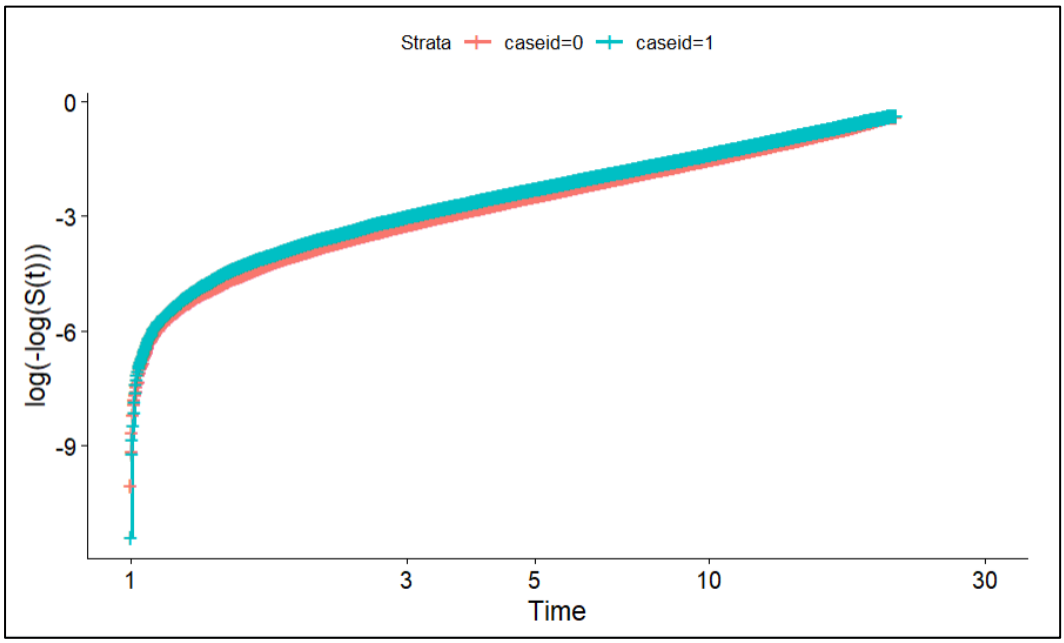


Figure 9.33 Log-log plot for Ischaemic heart disease

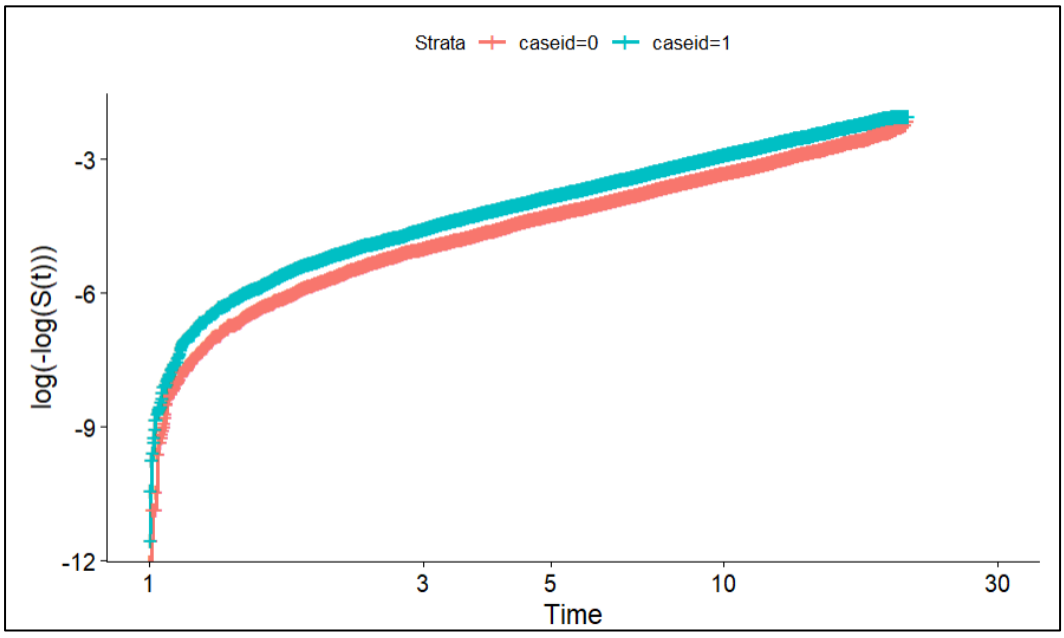


Figure 9.34 Log-log plot for myocardial infarction

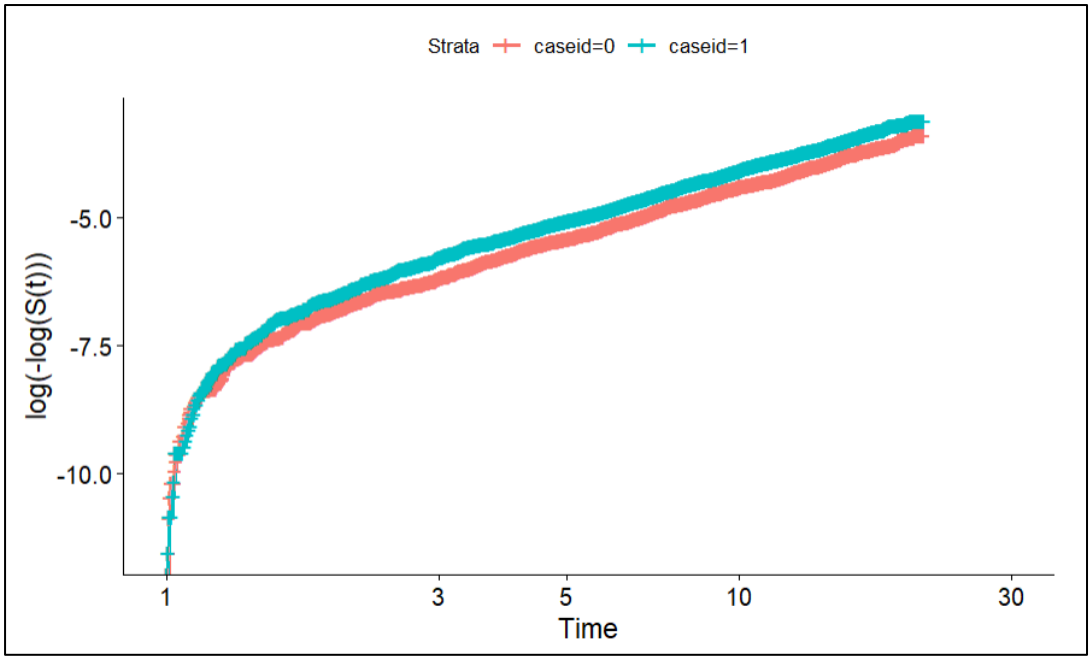


Figure 9.35 Log-log plot for chronic obstructive pulmonary disease

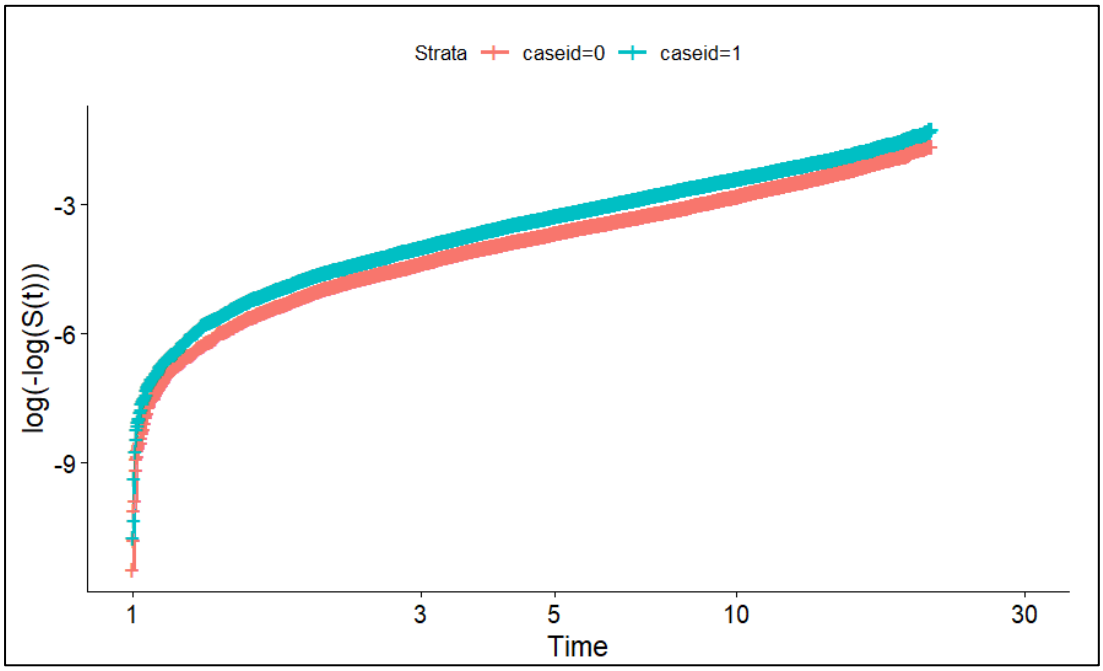


Figure 9.36 Log-log plot for depression

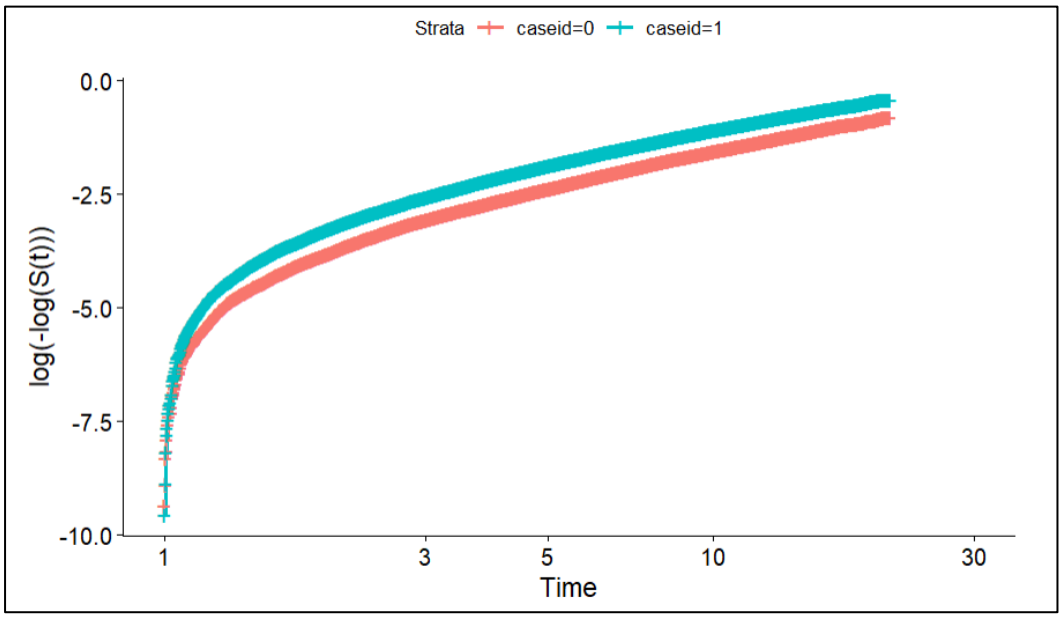


Figure 9.37 Log-log plot for anxiety

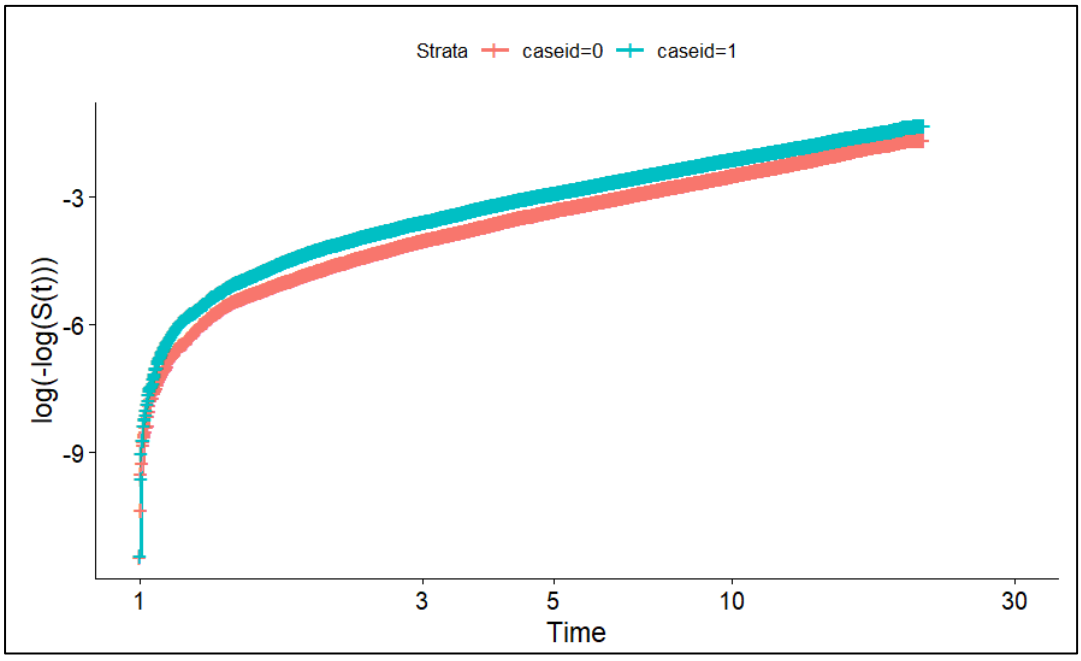


Figure 9.38 Log-log plot for osteoarthritis

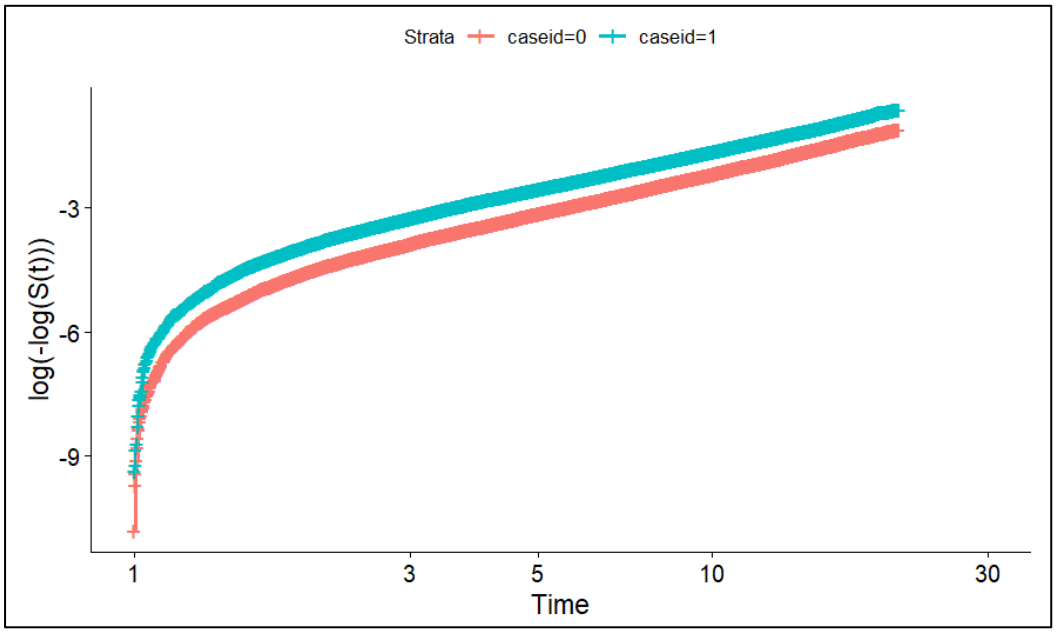


Figure 9.39 Log-log plot for musculoskeletal disorder

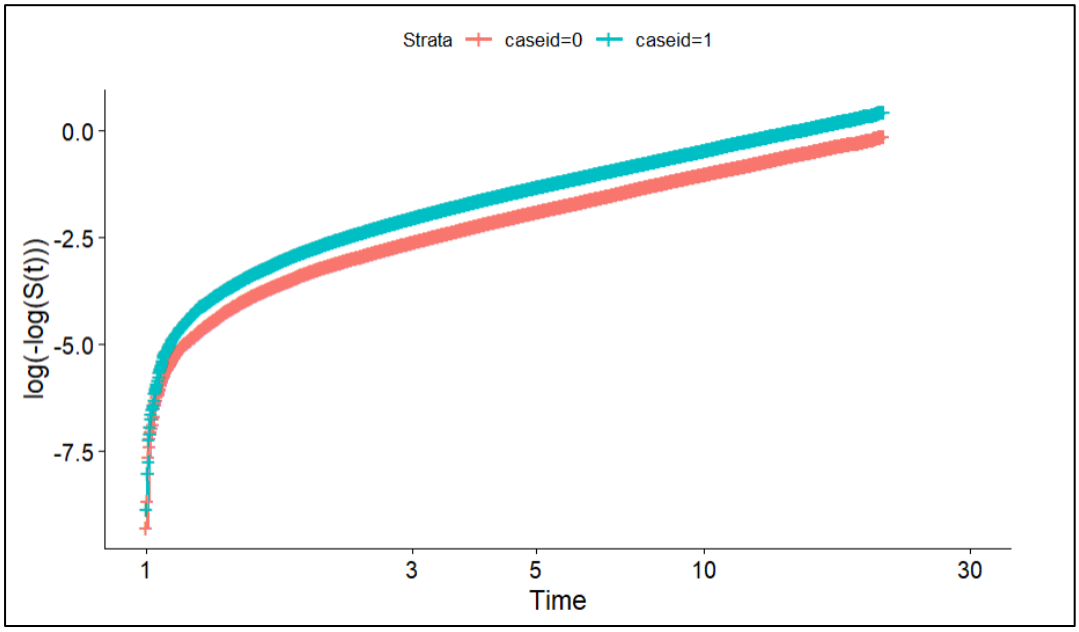


Figure 9.40 Log-log plot for fibromyalgia

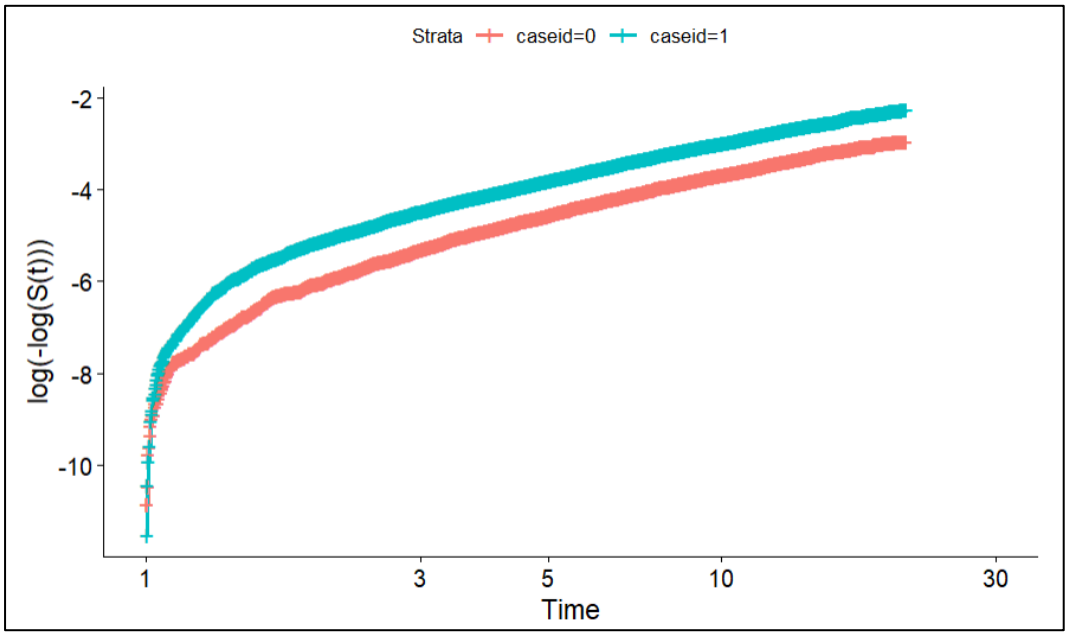


Figure 9.41 Log-log plot for insomnia

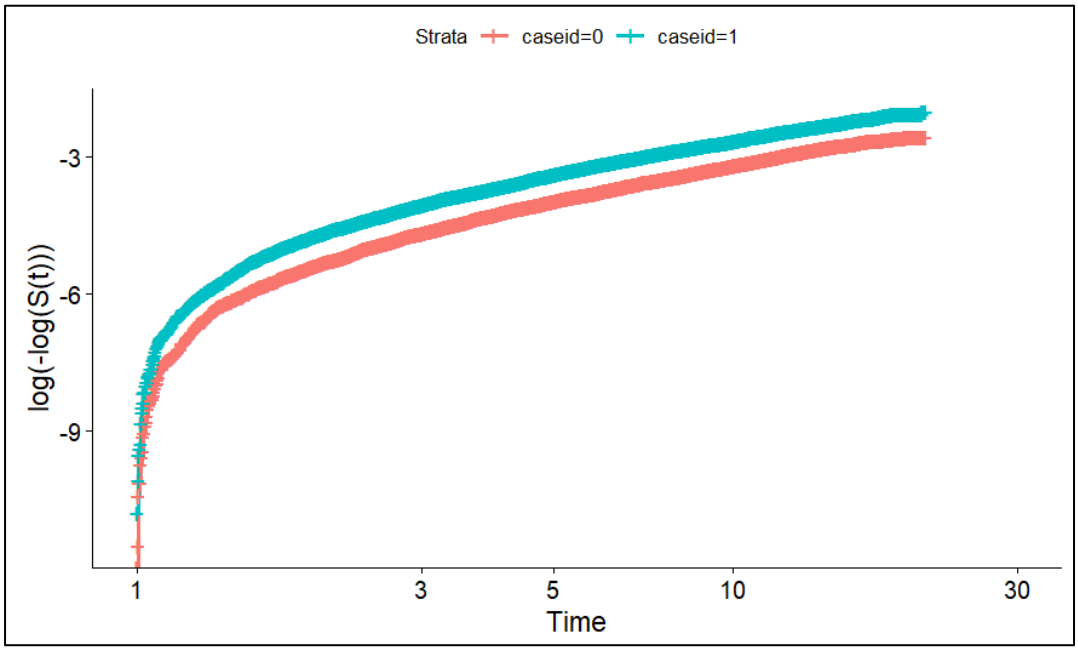


Figure 9.42 Log-log plot for fatigue

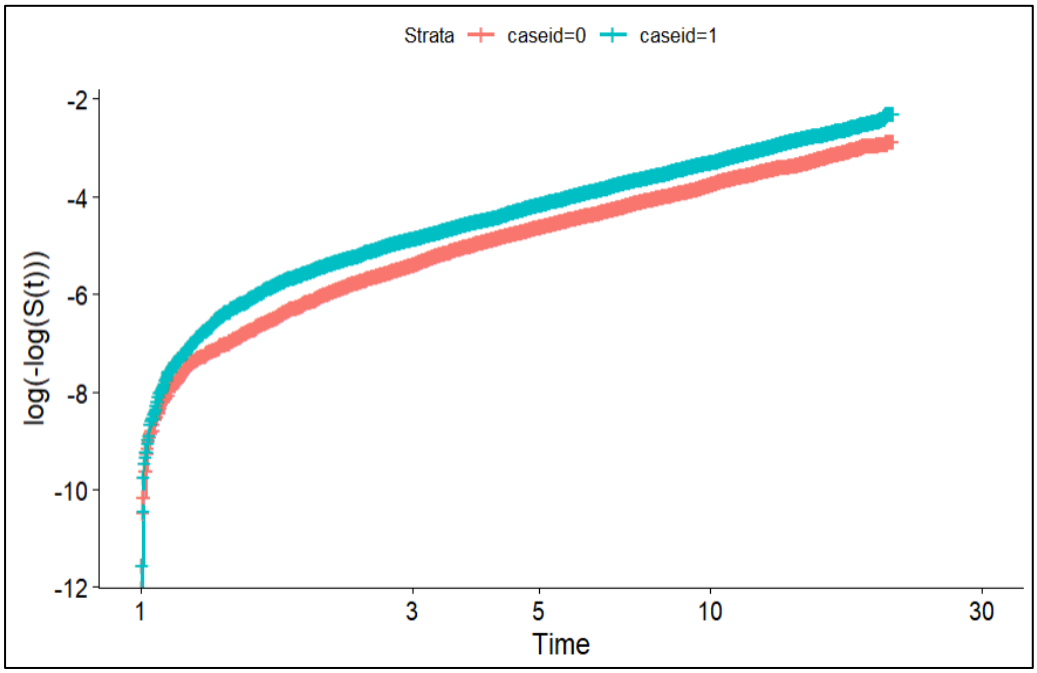


Figure 9.43 Log-log plot for sarcopenia

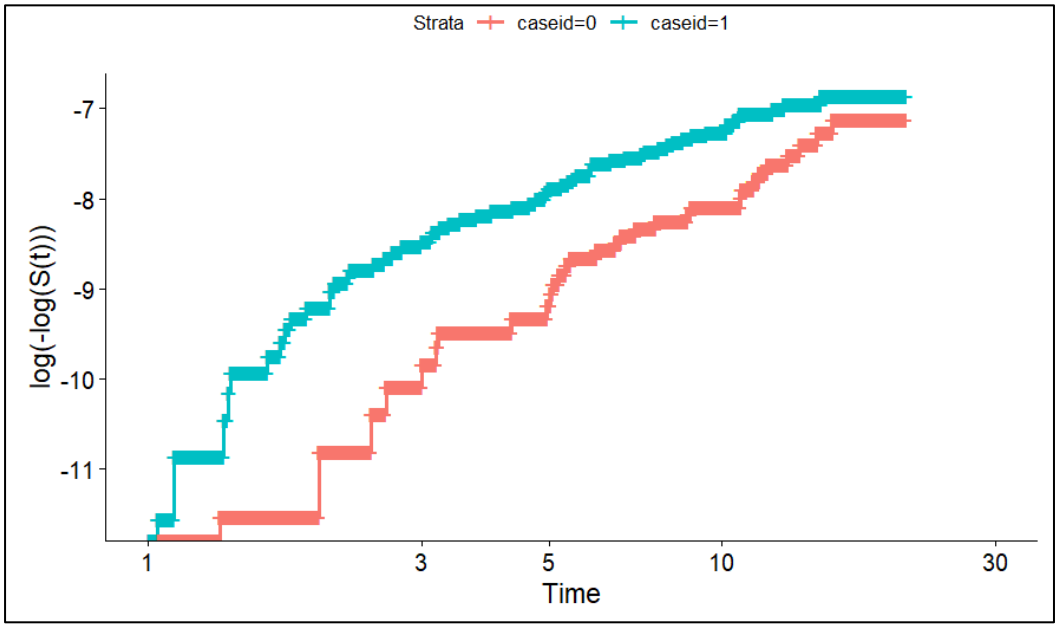


Figure 9.44 Log-log plot for tinnitus

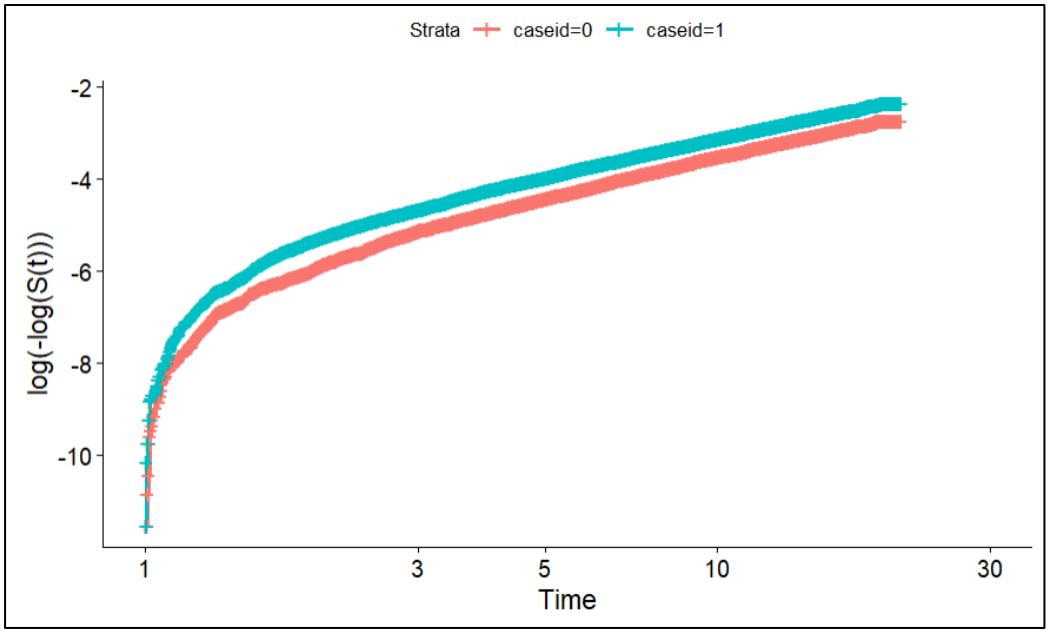


Figure 9.45 Log-log plot for scleroderma

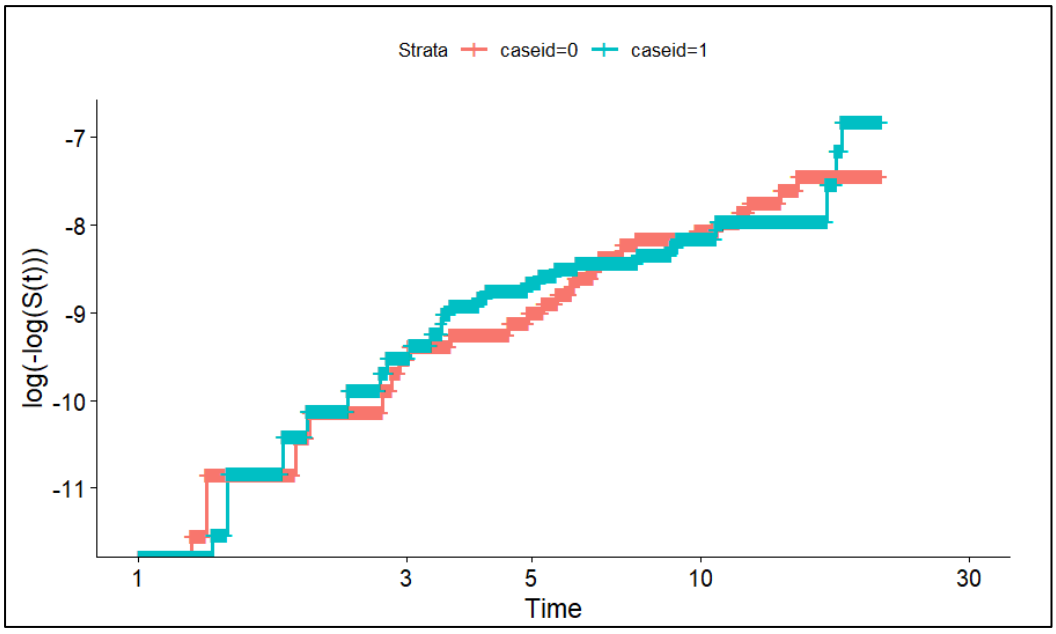


Figure 9.46 Log-log plot for urinary incontinence

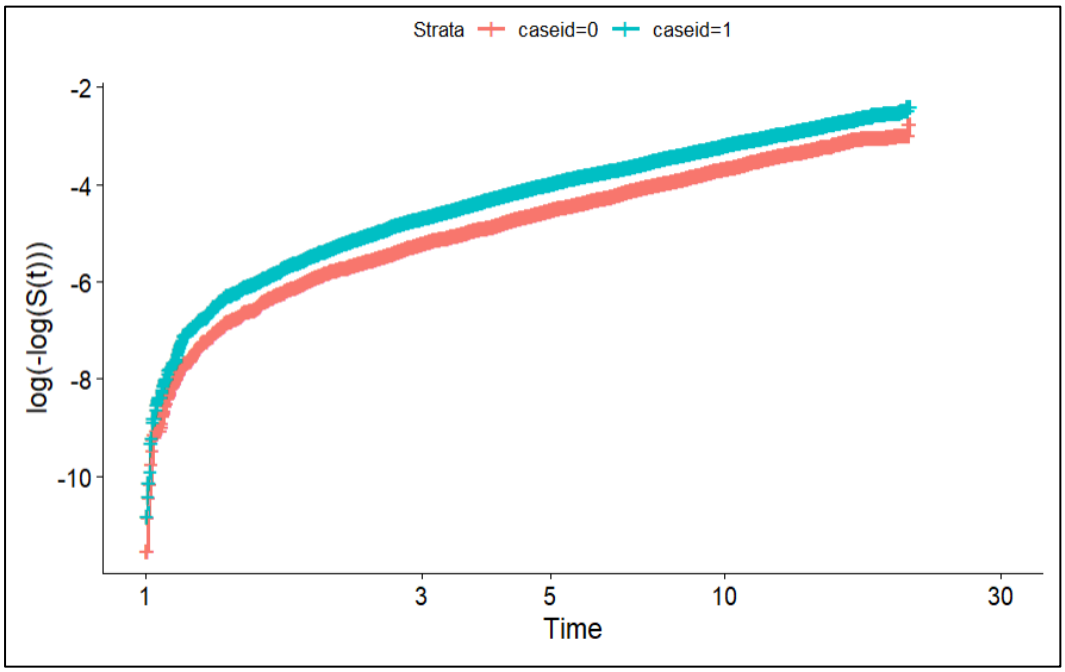


Figure 9.47 Log-log plot for diverticular disease

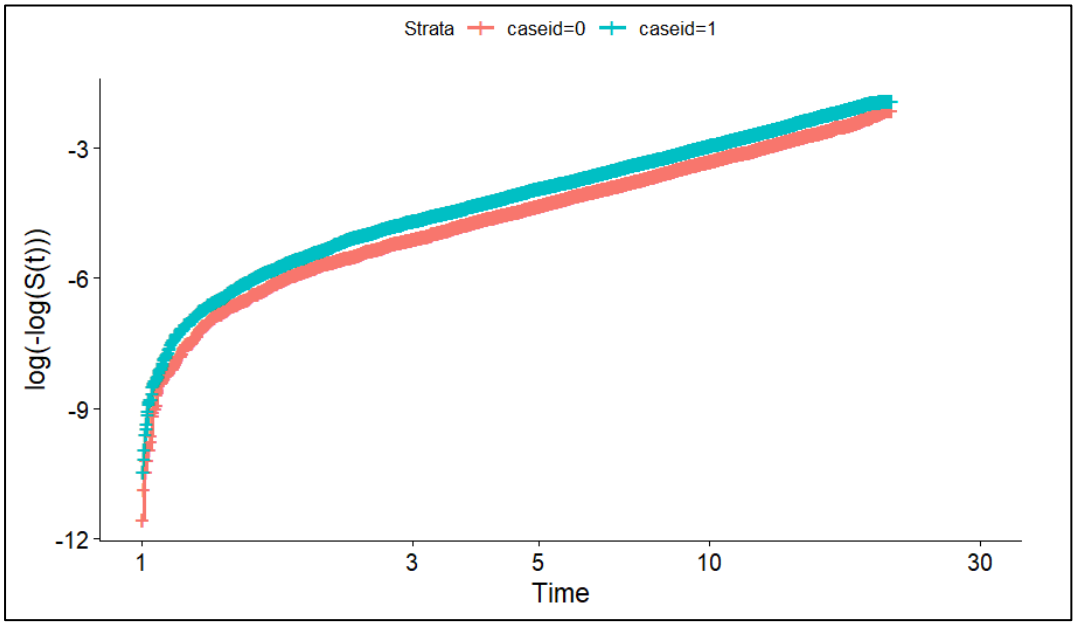


Figure 9.48 Log-log plot for diaphragmatic hernia

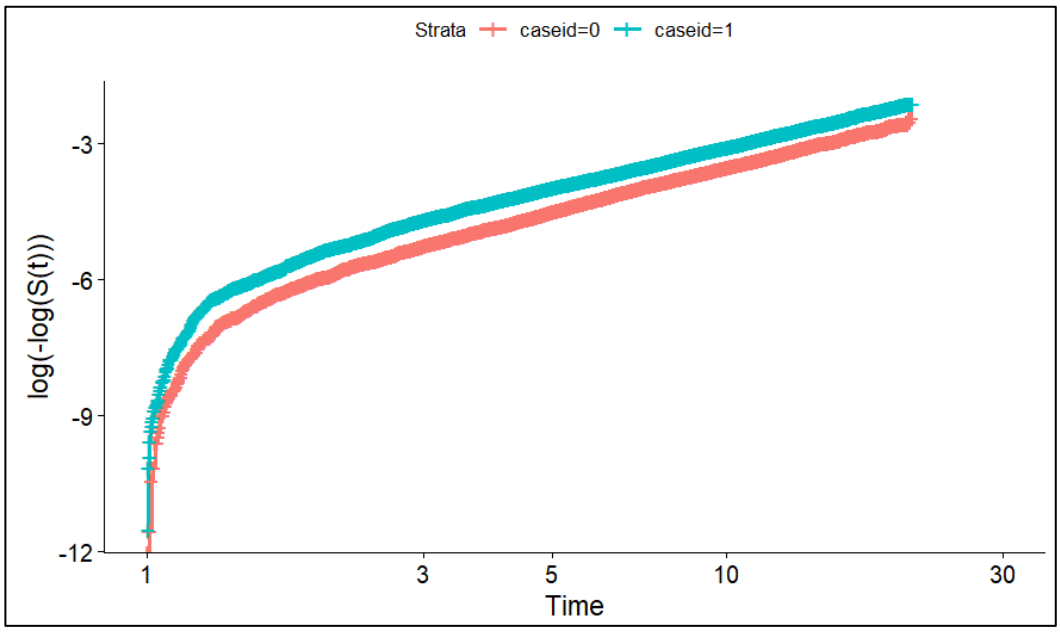
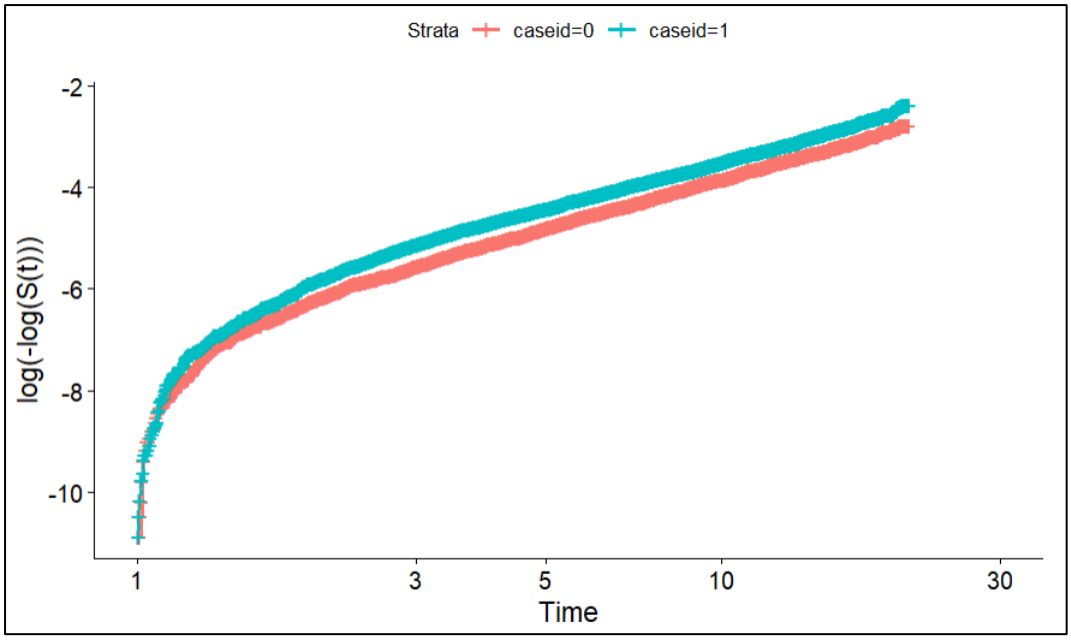


Figure 9.49 Log-log plot for benign prostatic hyperplasia



9.22 Appendix 22. First Patient and public involvement input

- **Lay summary for PPI**

Title: Chronic shoulder pain in the United Kingdom

Chronic shoulder pain is a common complaint that can lead to sleeping difficulties, work disability, functional limitations in daily activities and increased utilisation of healthcare services. In the United Kingdom (UK), about 2.4% of patients aged between 18 and 60 years old consulted their general practitioners (GPs) for chronic shoulder pain in 2000. Chronic shoulder pain increases with age and is more common in females than males. Other chronic pain conditions are becoming more common, and this may be due to a number of risk factors including an ageing population, the presence of other health conditions and lifestyle factors such as stress. Whether chronic shoulder pain has become more common in the UK, its variation across the country, risk factors and consequences, remain largely unknown. Therefore, this research aims to investigate the trend of chronic shoulder pain over the past 20 years in the UK, looking at variation between regions, use of health services, other related diseases and resultant deaths in the UK population.

Methods

An electronic health database was used from 2000 to 2020 in the Clinical Practice Research Datalink (CPRD). The CPRD contains routinely

collected anonymised electronic health records from general practices throughout the UK. Access to patient anonymised data within the CPRD has been approved by the Independent Scientific Advisory Committee (ISAC).

Chronic shoulder pain is defined as pain in the shoulder for more than three months. People aged 20 or more will be eligible for this study as chronic shoulder pain is less likely to occur before this age. The frequency of shoulder pain will be calculated for each year at 1 July by people with chronic shoulder pain divided by the total number of people eligible at that time.

Incidence will be calculated for each year from 1 January to 31 December by the new cases of chronic shoulder pain during the year divided by the total number of people without chronic shoulder pain at 1 January of each year.

Number of GP consultations per year will be calculated per person and the average annual GP consultations will be compared between people with chronic shoulder pain and those without. Similarly other diseases and death rate between the two groups will be compared too.

- Plans for disseminating and communicating study results

The findings from this study will be presented at conferences and published in peer reviewed journals. The summary of the study findings will be shared with GPs, stakeholders, the social media, and through the Pain Centre Versus Arthritis and NIHR BRC Nottingham (Musculoskeletal

theme). The CPRD will also be informed about the results of the study for dissemination on the CPRD website.

Questions:

1- Have you had chronic shoulder pain? Yes/No
2- What other conditions do you have? _____
3- Do you think this project is worth doing? Yes/No
4- Do you think this research will benefit patients with chronic shoulder pain, YES/No. if so, how? _____
5- Is there any part of this study that needs to be improved, or have we missed anything that you think more important?
_____
6- To make this research meaningful to people with chronic shoulder pain and public, we would like to have your inputs from time to time. Are you happy for us to approach you again for this purpose? Yes/No

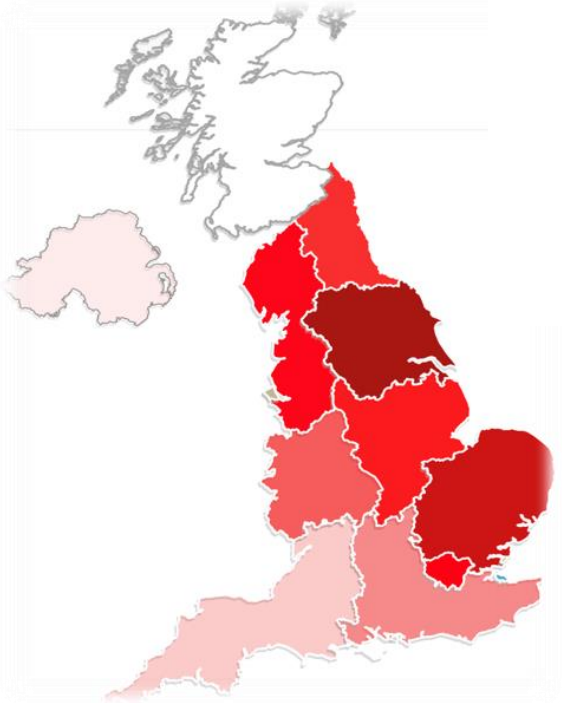
9.23 Appendix 23. Final Patient and public involvement Brochure

Chronic Shoulder pain is a common musculoskeletal complaint .It is defined as pain in the shoulder lasting for more than three months. Chronic shoulder pain affects between 5 - 47% of adults worldwide. In the United Kingdom,about 2.4% of patients aged between 18 and 60 years oldconsulted their general practitioners for shoulder pain in 2000. This research aimed to investigate the trends in prevalence and incidence of CSP over the past 20 years in the UK, looking at variation between age groups, genders and geographic regions.

We used GP healthcare records- the UK Clinical Practice Research Datalink which include 24 million people for this study. People aged 20 or more were included for the analysis. We calculated annual prevalence (current cases in the total population) on 1 July of each year and annual incidence (new cases developed each year) of chronic shoulder pain in the past 20 years between 1998 and 2019.

Finding

We found that one in 100 people aged 20 or more in the UK have chronic shoulder pain. The risk increases with age and women are more likely to have this condition compared to men. While the prevalence increased, the incidence decreased in the past 20 years in the UK. The prevalence and incidence are different between UK areas with Yorkshire and East England at the highest, suggesting an unequal burden of the condition in the UK. Having insight into the burden of chronic shoulder pain in the UK might help to inform strategies to reduce the occurrence of this condition in the UK and to understand the impact of shoulder pain on primary healthcare utilization.



The occurrence of chronic shoulder pain in UK areas in 2019 **(dark shades indicate high occurrence / Light shade indicate low occurrence)**

Acknowledgment

We would like to thank all participants for their involvement in this study, the University of Nottingham for sponsoring this project, Kuwait Cultural Office for the PhD studentship and Dr. Barbara Iyenfor advice on the diagnosis of chronic shoulder pain.

For contact: Nouf.Alotaibi@nottingham.ac.uk

Questions

1. Do you think the results were presented in a clear and understandable way? Yes/No . If no, How this could be improved

   _____

2. Do you think this project is worth doing? Yes/No
3. Do you think this research will benefit patients with chronic shoulder pain, YES/No. if so, how? _____
4. Is there any part of this study that needs to be improved or have we missed anything that you think important?

   _____

For contact: Nouf.Alotaibi@nottingham.ac.uk