An Analysis of the Biopsychosocial Factors including Sex and Pregnancy in Women with Axial Spondyloarthritis; Data from the Ankylosing Spondylitis Registry of Ireland (ASRI)

Dr Sinead Maguire

MB BCh BAO LRCSI MRCPI

Supervisors: Prof Finbar O'Shea & Prof Fiona Wilson

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Department of Rheumatology

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Summary of Thesis:

With advances in pathophysiology, development of novel classification criteria and the advent of new therapeutic agents the field of axial spondyloarthritis (axSpA) is rapidly evolving. Despite this, the impact and interplay between biopsychosocial factors on patient outcomes in axSpA has received limited attention in the published literature. As a result, there are several subpopulations of patients with axSpA who remain poorly understood and require further evaluation. The aim of this thesis was to characterise the impact of these issues as well as to call attention to their unique challenges and needs in the management of axSpA.

To address this aim, a series of studies were designed using cross sectional data from the Ankylosing Spondylitis Registry of Ireland (ASRI). These studies were prefaced by two associated narrative reviews and one systematic review to outline current understanding and current gaps in knowledge.

Before focusing on specific subpopulations, it was important to review newly emerging therapies in the management of axSpA to understand the array of therapeutic options in the pipeline for patients with axSpA. Unlike other forms of inflammatory arthritis, biologic agents in axSpA have previously been limited to anti-TNF agents. Fortunately, two IL-17 inhibitors, Secukinumab and Ixekizumab, and two JAK inhibitors, Tofacitinib and Upadacitinib, have recently been approved for the treatment of axSpA. This review also highlighted several additional ongoing clinical trials in axSpA with alternate therapeutic targets. This is highly encouraging in terms of further expansion of therapeutic agents to treat axSpA and optimisation of patient outcomes.

National registries, such as the ASRI, provide prime opportunities to study specific subpopulations of patients with a given diagnosis. The initial cross-sectional study of the ASRI not only described this patient cohort, but also examined differences in patient populations based on treatment. This demonstrated how evolution in understanding of epidemiology of axSpA was mirrored in the treatment of axSpA over time.

The following three studies focused on psychosocial factors affecting patient outcomes in axSpA, specifically unemployment and depression. These studies identified that both issues are highly prevalent in axSpA and are associated with worse patient outcomes. While unemployment was more common in men, prevalence of depression was similar in both sexes although depression was associated with worse outcomes in women with depression compared to men. Furthermore, axSpA women also had a higher prevalence of undiagnosed depression based on HADS-D scores. These results demonstrated clear differences between sexes in patients with axSpA which required further evaluation.

For this reason, the subsequent study was a dedicated examination of sex differences in axSpA. The results of this study showed axSpA women had a higher burden of certain disease manifestations with worse disease activity and quality of life compared to men. Additionally, limitation of spinal mobility in axSpA women was noted to correspond to a greater limitation in functional ability

compared to axSpA men. This indicates a clear gap in optimisation of outcomes in axSpA between sexes, although reasons for these differences are not immediately apparent. Numerous potential causes for these differences have been proposed including differences in sex hormones, body composition, prevalence of fibromyalgia and even reporting of symptoms.

To examine potential causes of the worse outcomes noted in women with axSpA, the following study considered the impact of body composition, specifically central obesity. Obesity has previously been proven to be associated with worse outcomes in axSpA but there is limited discussion of central obesity in axSpA. This study revealed a shockingly high prevalence of central obesity in axSpA women compared to axSpA men. Presence of central obesity was strongly associated with worse overall quality of life, poorer functional ability and a trend towards greater disease activity. As this is a modifiable state, early recognition with increased use of the waist to hip ratio (WtHpR) could aid in optimising outcomes in axSpA, especially in women.

A discussion of women with axSpA would be incomplete without addressing pregnancy, a common but physiologically challenging life event for many women. The narrative review of chapter 7 highlights the importance of pregnancy planning and pre-conception counselling to optimise disease control and chances of successful conception in women with rheumatic diseases. Close monitoring of disease activity is also essential throughout pregnancy, although this can be a challenge as tools adapted for use in pregnancy are limited. This review highlights the importance of collaboration between rheumatology and obstetrics in the management of women with rheumatic disease throughout the course of their pregnancy.

The previous review outlined the numerous challenges in pregnancy for women with rheumatic diseases. To summarise current understanding of the impact of axSpA on pregnancy a systematic review and meta-analysis was carried out. The findings revealed women with axSpA had a significantly higher prevalence of caesarean section and preterm birth compared to women of the general population. They also had a trend towards increased prevalence of pre-eclampsia, IUGR and numerous fetal complications. Active disease was common in pregnancy and the postpartum period but recording of disease activity varied between studies. This highlighted the need for additional studies to further develop understanding of this topic, as well as to capture social and cultural variations between countries.

In the previous systematic review, it was notable that Irish women were not represented in the published literature. Thus, the final study of this thesis was focused on pregnancy in axSpA using data from the women of the ASRI. The results of this study revealed a startlingly high percentage of axSpA women experiencing at least one complication during their pregnancies. Unlike the systematic review, caesarean section prevalence was similar to that of the general population, however preterm birth and pre-eclampsia were again more prevalent in axSpA women. Prevalence of breastfeeding was also noted to be dramatically lower than in the general population. This data provides Irish clinicians treating women with axSpA during their pregnancy a basis of evidence to inform monitoring and management of these patients.

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List of Figures:

List of Tables:

List of Appendices: see Volume II of Thesis

Academic Output from Thesis:

Published Manuscripts

May 2020 *Rheumatic Disease Clinics of North America*
"The Future of Axial Spondyloarthritis Treatment"
Sinead Maguire, Raj Sengupta, Finbar O'Shea
2020 May; 46(2): 357-365. DOI: 10.1016/j.rdc.2020.01.014

July 2020 *Irish Journal of Medical Science*
"Social Isolation due to the COVID-19 Pandemic has led to Worse Outcomes in Females with Inflammatory Arthritis"
Sinead Maguire, Finbar O'Shea
2020 July; 190, 33-38. DOI: 10.1007/s11845-020-02307-2

August 2020 *Seminars in Arthritis & Rheumatism*
"Pregnancy in Axial Spondyloarthropathy: a Systematic Review and Meta-Analysis"
Sinead Maguire, Tom O'Dwyer, David Mockler, Finbar O'Shea, Fiona Wilson
2020 Dec; 50(6): 1269-1279. DOI: 10.1016/j.semarthrit.2020.08.011

July 2021 *EMJ Rheumatology*
"Management of Pregnancy in Rheumatic Disease"
Sinead Maguire, Finbar O'Shea
2021 Jul; 8(1): 86-93

September 2021 *Joint Bone Spine*
"The Negative Impact of Depression in Women with Axial Spondyloarthropathy"
Sinead Maguire, Phil Gallagher, Finbar O'Shea
2021 Sept; 89(1):105261. DOI: 10.1016/j.jbspin.2021.105261

November 2021 *Scandinavian Journal of Rheumatology*
"The Toll of Unemployment in Axial Spondyloarthropathy: High prevalence and negative impact on outcomes as captured in a national registry"
Sinead Maguire, Fiona Wilson, Phil Gallagher, Finbar O'Shea
2021 Nov 17 (1-4); DOI: 10.1080/03009742.2021.1992861

January 2022 *Journal of Clinical Rheumatology (JCR)*
"The Same but Different? An Analysis of Late Onset Axial Spondyloarthropathy"
Sinead Maguire, Finbar O'Shea
2022 Jan; 28(1): 294-296. DOI: 10.1097/RHU.0000000000001700

January 2022 *Scandinavian Journal of Rheumatology*
"Worse Scores but Similar Patterns of Disease Activity: Interpreting Outcomes in Women with Axial Spondyloarthropathy"
Sinead Maguire, Fiona Wilson, Phil Gallagher, Finbar O'Shea
2022 Jan; 1-8. DOI: 10.1080/03009742.2021.2007609

March 2022 *Clinical & Experimental Rheumatology*
"The Negative Impact of Undiagnosed Depression in Axial Spondyloarthropathy"
Sinead Maguire, Phil Gallagher, Finbar O'Shea

2022 Mar; 40(3): 669-670. DOI: 10.55563/clinexprheumatol/d6518k

March 2022 *The Journal of Rheumatology*
"Central Obesity in Axial Spondyloarthritis: the Missing Link to Understanding Worse Outcomes in Women?"
Sinead Maguire, Fiona Wilson, Phil Gallagher, Finbar O'Shea
2022 Mar; 49 (3); DOI: 10.3899/jrheum.211062

March 2022 *Seminars in Arthritis & Rheumatism*
"What to Expect When Women with Axial Spondyloarthropathy are Expecting: Prevalence of Complications in Women with Axial Spondyloarthropathy"
Sinead Maguire, Fiona Wilson, Phil Gallagher, Muhanad MS Mohamed, Senan Maher, Finbar O'Shea
2022 Mar 10; 54:151993. DOI: 10.1016/j.semarthrit.2022.151993.

May 2022 *Rheumatology International*
"How Advances in Treatment of Axial Spondyloarthropathy Translate to Patient Outcomes: Data from the Ankylosing Spondylitis Registry of Ireland (ASRI)"
Sinead Maguire, Gillian Fitzgerald, Phil Gallagher, Finbar O'Shea
2022 May; 42(5): 831-838. DOI: 10.1007/s00296-021-05067-z

Published Conference Abstracts

April 2019 *Rheumatology (Oxford)*
"High Unemployment Rates in Patients with Ankylosing Spondylitis"
S Maguire, G Fitzgerald, C Sheehy, F O'Shea
58 (Suppl 2) 1038-1039; DOI: 10.1093/rheumatology/kez107.063

June 2019 *Annals of the Rheumatic Diseases*
"The Association of Ankylosing Spondylitis and Unemployment"
S Maguire, G Fitzgerald, C Sheehy, F O'Shea
78 (Suppl 2) 1038-1039; DOI: 10.1136/annrheumdis-2019-eular.2501

November 2019 *Arthritis & Rheumatology*
"Worse outcomes for Females with Spondyloarthropathy"
S Maguire, G Fitzgerald, C Sheehy, F O'Shea
71(Suppl 10)

June 2020 *Annals of the Rheumatic Diseases*
"The Same but Different? Analysis of a Cohort of Patients with Late Onset Ankylosing Spondylitis"
S Maguire, P Gallagher, F O'Shea
79 (Suppl 1) 1139-1140

June 2020 *Annals of the Rheumatic Diseases*
"Understanding Joint Replacement Surgery in Axial Spondyloarthropathy"
S Maguire, P Gallagher, F O'Shea
79 (Suppl 1) 1138-1139

June 2020 *Annals of the Rheumatic Diseases*
"Prescribing Practices in Axial Spondyloarthropathy"
S Maguire, P Gallagher, F O'Shea
79 (Suppl 1) 1647-1648

November 2020 *Arthritis & Rheumatology*
"Pregnancy in Axial Spondyloarthropathy: a Systematic Review & Meta-analysis"
S Maguire, T O'Dwyer, D Mockler, F Wilson, F O'Shea
72 (Supp 10)

November 2020 *Arthritis & Rheumatology*
"Spinal Mobility & Function: How closely do they associate in axial spondyloarthropathy?"
S Maguire, P Gallagher, F O'Shea
72 (Supp 10)

April 2021 *Rheumatology (Oxford)*
"Undiagnosed Depression in Axial Spondyloarthropathy Negatively affects Disease Activity and Quality of Life"
S Maguire, F O'Shea
60 (Supp 1)

April 2021 *Rheumatology (Oxford)*
"Examining BASDAI by Gender: Differing Scores but Similar Patterns of Disease"
Sinead Maguire, Phil Gallagher, Finbar O'Shea
60 (Supp 1)

June 2021 *Annals of the Rheumatic Diseases*
"Looking Beyond BASDAI Total Scores: Analysis of the BASDAI on the Basis of Sex"
Sinead Maguire, Phil Gallagher, Finbar O'Shea
80 (Supp 1): 27

June 2021 *Annals of the Rheumatic Diseases*
"High Prevalence of Abdominal Obesity in Females with Axial Spondyloarthropathy"
S Maguire, F Wilson, P Gallagher, F O'Shea
80 (Supp 1):738

June 2021 *Annals of the Rheumatic Diseases*
"Negative Impact of Undiagnosed Depression in Axial Spondyloarthropathy: Results of a Screening Study"
S Maguire, F O'Shea
80 (Supp 1): 734

September 2021 *Clinical and Experimental Rheumatology*
"Sex differences in correlation of Spinal Mobility and Functional Impairment in Axial Spondyloarthropathy"
S Maguire, P Gallagher, F O'Shea
39 (5): 1185

September 2021 *Clinical & Experimental Rheumatology*
"Negative Impact of Unemployment in Axial Spondyloarthropathy: Results from the Ankylosing Spondylitis Registry of Ireland"
S Maguire, P Gallagher, F Wilson, F O'Shea
39 (5): 1186

November 2021 *Arthritis & Rheumatology*
"Identifying Predictors of Unemployment in Axial Spondyloarthropathy: Data from the Ankylosing Spondylitis Registry of Ireland"
S Maguire, F Wilson, P Gallagher, F O'Shea
73 (Suppl 10)

November 2021 *Arthritis & Rheumatology*
"High Frequency of Pregnancy Complications in Axial Spondyloarthropathy: Emerging Data from the Ankylosing Spondylitis Registry of Ireland"
S Maguire, F Wilson, P Gallagher, F O'Shea
73 (Suppl 10)

November 2021 *Arthritis & Rheumatology*
"Undiagnosed Depression in Axial Spondyloarthropathy and the Negative Impact on Patient Outcomes: Results of a Screening Study"
S Maguire, P Gallagher, F O'Shea
73 (Suppl 10)

November 2021 *Arthritis & Rheumatology*
"Body Mass Index (BMI) Underestimates Obesity in Females with Axial Spondyloarthropathy"
S Maguire, F Wilson, P Gallagher, F O'Shea
73 (Suppl 10)

April 2022 *Rheumatology (Oxford)*
"Complications in Pregnancy are Common in Women with Axial Spondyloarthropathy: data from the Ankylosing Spondylitis Registry of Ireland"
S Maguire, F Wilson, P Gallagher, F O'Shea
61 (Suppl 1)

<u>Academic Presentations</u>

December 2020 New Horizons in Rheumatology
"Mental Health in Axial Spondyloarthropathy: Importance, Impact & Screening"
Sinead Maguire, Finbar O'Shea
Virtual Meeting

April 2021 British Society of Rheumatology (BSR)
"Examining BASDAI by Gender: Differing Scores but Similar Patterns of Disease"
Sinead Maguire, Phil Gallagher, Finbar O'Shea
Virtual Meeting

June 2021 European League Against Rheumatism Annual Congress (EULAR)
"Looking Beyond BASDAI Total Scores: Analysis of the BASDAI on the Basis of Sex"
Sinead Maguire, Phil Gallagher, Finbar O'Shea
Virtual Meeting

<u>Non-Peer Reviewed Broadcasts</u>

May 2022 "Discussion of Pregnancy in Axial Spondyloarthritis"
Host: Seminars in Arthritis & Rheumatism
Link: https://www.youtube.com/watch?v=9Bbxs54uj_0&t=4s

May 2022 "Pregnancy Outcomes in Axial Spondyloarthritis"
Host: The Rheumatology Physio
Link: https://rheumatology.physio/pregnancy-axspa-podcast/

May 2022 "Depression & Anxiety in Spondyloarthritis: Importance, Impact & Screening"
The Global Spondyloarthritis Summit 2022
Host: Spondyloarthritis Association of America (SAA)
Virtual Meeting

Academic Achievements

September 2018 Irish Society of Rheumatology
3rd place for Best Poster Presentation
"High Unemployment Rates in Irish Patients with Ankylosing Spondylitis"

September 2020 Irish Society of Rheumatology
1st place for Best Poster Presentation
"Pregnancy in Axial Spondyloarthropathy: a Systematic Review & Meta-analysis"

November 2020 Gilead Inflammation Fellowship
Fellowship awarded for innovative Rheumatology research in the UK & Ireland to specialist trainees
"Development of Pregnancy Data in the Ankylosing Spondylitis Registry of Ireland
(ASRI)"

November 2020 EMEUNET Top 10 ACR Abstracts
Selected as one of the top 10 abstracts at the American College of Rheumatology (ACR) annual meeting by the Emerging EULAR Network (EMEUNET)
"Pregnancy in Axial Spondyloarthropathy: a Systematic Review & Meta-analysis"

December 2020 New Horizons in Rheumatology
Best Clinical Research Presentation
"Mental Health Issues in Axial Spondyloarthropathy: Importance, Impact & Screening"

September 2021 Irish Society of Rheumatology
Selected as a Premier poster & awarded 2nd place for presentation
"High Prevalence of Complications in Pregnancies of Women with Axial Spondyloarthropathy: Emerging data from the Ankylosing Spondylitis Registry of Ireland"

April 2022 British Society of Rheumatology (BSR) Annual Meeting
"Complications in Pregnancy are Common in Women with Axial Spondyloarthropathy: data from the Ankylosing Spondylitis Registry of Ireland"
Selected as a featured poster in the Poster Showcase on Spondyloarthritis

Abbreviations:

ACE	Angiotensin converting enzyme
aCL	Anti-cardiolipin
ACPA	Anti-citrullinated antibodies
ACR	American College of Rheumatology
ANOVA	Analysis of variance
anti-dsDNA	Anti-double stranded Deoxyribonucleic Acid antibodies
aPL	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
AS	Ankylosing Spondylitis
AS-WIS	Ankylosing Spondylitis Work Instability Scale
ASAS	Assessment of Spondyloarthritis International Society
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASQoL	Ankylosing Spondylitis Quality of Life scale
ASRI	Ankylosing Spondylitis Registry of Ireland
ASspiMRI-a	Ankylosing Spondylitis spine MRI score for activity
axSpA	Axial spondyloarthritis
BAS-G	Bath Ankylosing Spondylitis Global score
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
Beta-2GP1	Beta-2-glycoprotein
BILAG2004-P	British Isles Lupus Assessment Group 2004 for Pregnancy
BMI	Body Mass Index
BMO	Bone marrow oedema
BSR	British Society of Rheumatology
CDAI	Clinical Disease Activity Index
CDC	Centre for Disease Control
CI	Confidence Interval
CKD	Chronic kidney disease
Cm	Centimetres
COMOSPA	Comorbidities in Spondyloarthritis study
COVID-19	Coronavirus 2019
COX	Cyclooxygenase
CRP	C reactive protein
CS	Caesarean section
CSF	Cerebral spinal fluid
CT	Computed Tomography
CTL	Cytotoxic T lymphocytes
CWP	Chronic widespread pain
DEXA	Dual energy x-ray absorptiometry
DISH	Diffuse skeletal hyperostosis
DM	Dermatomyositis
DMARD	Disease modifying anti-rheumatic drug

DSM	Diagnostic and Statistical Manual of Mental Disorders
DUET	Dublin uveitis evaluation tool
DVU	Discovertebral unit
Dx	Diagnosis
EAM	Extra-articular manifestation
EGPA	Eosinophilic granulomatosis with polyangiitis
EMA	European Medical Agency
EMS	Early morning stiffness
ENRADAS	Effects of NSAIDs on Radiographic Damage in AS
ERAP	Endoplasmic reticulum aminopeptidase
ESR	Erythrocyte sedimentation rate
ESSG	European Spondyloarthropathy Study Group
EULAR	European League Against Rheumatism
EuNEp	European Network of Pregnancy Registers
FDA	US Food and Drug Administration
GDM	Gestational Diabetes Mellitus
GESPIC	German Spondyloarthritis Inception Cohort
GRN	Global reference norms
HADS-D	Hospital Anxiety and Depression Scale for Depression
HAQ	Health Assessment Questionnaire
HELLP	Haemolysis, elevated liver enzymes, low platelet count
HLA-B27	Human Leukocyte Antigen B27
HTN	Hypertension
IA	Inflammatory Arthritis
IBD	Inflammatory bowel disease
IBM SPSS	International Business Machine Statistical Package for the Social Sciences
IBP	Inflammatory back pain
Ig	Immunoglobulin
IHD	Ischemic heart disease
IL	Interleukin
IQR	Interquartile range
IUGR	Intrauterine growth restriction
IVF	In Vitro fertilisation
IVIG	Intravenous Immunoglobulin
JAK	Janus kinase
JoAS	Juvenile onset Ankylosing Spondylitis
Kg	Kilograms
LAC	Lupus anticoagulant
LAI-P	Lupus Activity in Pregnancy
LBW	Low birthweight
LO	Late onset
m-SLAM	modified Systemic Lupus Activity Measure
MACE	Major adverse cardiovascular event
MANOVA	Multivariate analysis of variance
Mg	Milligrams

MHC	Major histocompatibility complex
MIC	Minimal important change
mNY	Modified New York
MPA	Microscopic polyangiitis
MRI	Magnetic resonance imaging
mSASSS	Modified Stroke Ankylosing Spondylitis Spinal Score
MSK	Musculoskeletal
NICU	Neonatal Intensive Care Unit
NOS	Newcastle Ottawa Score
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OASIS	Outcome in Ankylosing Spondylitis International Society
OMERACT	Outcome measures in Rheumatology
OR	Odds ratio
PAH	Pulmonary hypertension
PARA	Pregnancy induced Amelioration of Rheumatoid Arthritis
PDA	Patent Ductus Arteriosus
PGADA	Patient Global Assessment of Disease Activity
PHQ-4	Patient Health Questionnaire 4
PHQ-9	Patient Health Questionnaire 9
PM	Polymyositis
PPROM	Premature rupture of membranes
PRISMA	Preferred Reporting Items for Systematic review and Meta-Analyses
PRO	Patient reported outcomes
PsA	Psoriatic Arthritis
r-axSpA	Radiographic axial spondyloarthritis
RA	Rheumatoid Arthritis
RADAI	Rheumatoid Arthritis Disease Activity Index
RMD	Rheumatic disease
ROC	Receiver operating characteristic
SAA	Spondylitis Association of America
SARS	Severe acute respiratory syndrome
SD	Standard deviation
SGA	Small for gestational age
SIJ	Sacroiliac joint
SLE	Systemic Lupus Erythematosus
SLEPDAI	SLE Pregnancy Disease Activity Index
SpA	Spondyloarthritis
SPACE	Spondyloarthritis Caught Early
SPARCC	Spondyloarthritis Research Consortium of Canada
SPARTAN	Spondyloarthritis Research and Treatment Network
SSc	Systemic Sclerosis
TNF	Tumour necrosis factor
VAT	Visceral adipose tissue

VU	Vertebral unit
WHO	World Health Organisation
WPAI	Work productivity and activity impairment
WPS	Work productivity survey
WtHpR	Waist to Hip Ratio
XR	X-ray

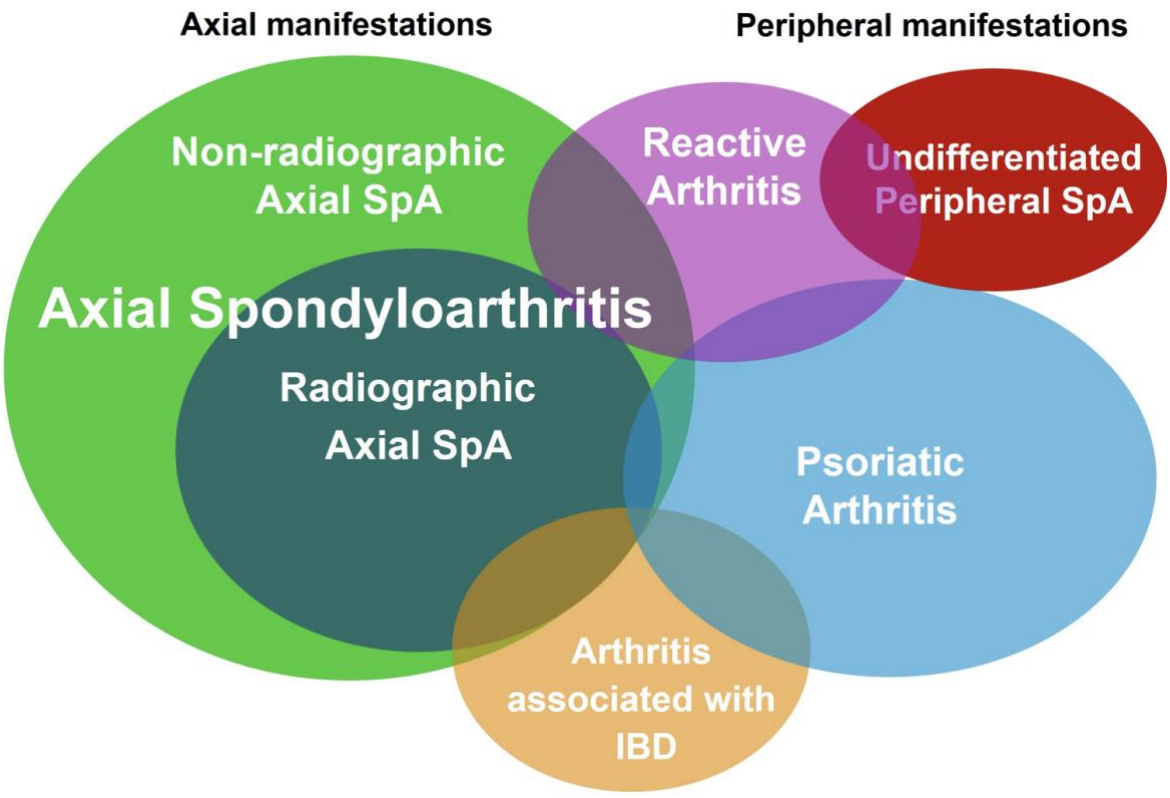
Table of Contents:

Chapter 1: Introduction

1.1 Definition:

Axial spondyloarthritis (axSpA) is an autoinflammatory arthritis predominantly involving the axial skeleton and sacroiliac joints (SIJ)[1]. The term axSpA refers to both radiographic axSpA (r-axSpA), previously called ankylosing spondylitis, and non-radiographic axSpA (nr-axSpA) with some overlap with reactive arthritis, inflammatory bowel arthropathy and even psoriatic arthritis[2,3] (Figure 1.1). Inflammation at these sites causes erosions, ossification and eventually results in fusion of the affected joint[4]. This can result in significant pain and physical disability for patients left in a state of high disease activity[5]. Diagnosis can be challenging, as the differential diagnosis for back pain is broad. However, advances in imaging and increased understanding of this disease process has helped to improve detection of axSpA.

Figure 1.1: Terminology of spondyloarthritis (SpA). Image from the ASAS educational slide library adapted from Proft et al 2018[6]



1.2 History:

One of the earliest descriptions of ankylosing spondylitis was published by Bernard Connors, an Irish physician working in France. In 1695 he detailed the unusual anatomical findings of a skeleton with fusion of the SIJs, lumbar spine and costochondral joints[7]. He described the extent of the fusion made the skeleton appear to be "one uniform continuous bone[8]." His drawings (figure 1.2) and associated dissertation on the topic represent the first pathological description of ankylosing spondylitis in literature[9]. During the 1800s a number of prominent Neurologists reported case series detailing the clinical findings and named the disease Bechterew-Marie-Strümpell disease[10].

Figure 1.2: Bernard Connor's drawings published with his description of the skeletal remains he studied while in Reims, France[7]

The term ankylosing spondylitis was introduced by a German pathologist, Dr Eugen Fraenkel in 1904[11]. Discovery of radiography led to advancements in detection and understanding of radiographic features of the disease in large patient cohorts. During this time, the disease was recognised as an inflammatory arthritis but thought to be part of the spectrum of rheumatoid arthritis. It wasn't until 1974 when Moll and Wright proposed criteria for "seronegative spondyloarthritides" that AS began to be considered as a separate entity[12,13].

Medical researchers would later prove a long history of humans affected by the disease now called axSpA, dating back as far as 1500 B.C. to the early Egyptians[14]. One of the earliest familial studies in axSpA involved the remains of several prominent members of the Medici family who ruled Florence during the 15th and 16th century. Examination of these remains, during removal of the bodies from the familial Medici chapel in 1945, concluded at least four members of the prominent Renaissance family had evidence of axSpA[15].

Further advancements were made with the identification of the HLA-B27 gene in 1973[16]. Prior to this, physicians had suspected a genetic link due to high frequency of the disease within affected families. The importance of HLA-B27 in pathogenesis is discussed in greater detail below. The first published diagnostic criteria for AS was the Rome criteria in 1963, which was the first of many criteria which sought to accurately diagnose and categorise AS in the general population[17]. Evolution of classification criteria and imaging led use of the term axial spondyloarthritis, which included both non-radiographic axSpA (nr-axSpA) and radiographic axSpA (r-axSpA) replacing the term of ankylosing spondylitis.

1.3 Epidemiology:

Onset of symptoms is commonly in the third decade of life. Unfortunately, many patients will face a considerable delay averaging 7.4 years prior to being diagnosed by a rheumatologist and offered appropriate treatment[18]. Although this is improving, a significant proportion of newly diagnosed axSpA patients report a delay in diagnosis of a number of years, and further work is needed to correct this issue[19].

Changes in classification criteria and terminology have resulted in the term axSpA to refer to both r-axSpA, previously called ankylosing spondylitis (AS), and nr-axSpA. This expansion of classification beyond AS has resulted in a significant shift in the sex distribution of the disease. Historically AS was understood to have a strong male predominance with a male to female ratio as high as 8:1, with more recent studies placing this closer to 3:1[20]. In addition, females with axSpA tend to have a higher prevalence of nr-axSpA, with nr-axSpA having an overall equal distribution between sexes. Despite this change in understanding of sex distribution of axSpA, it continues to be perceived as a disease affecting primarily males leaving many females struggling to achieve a diagnosis[20]. Ongoing education campaigns are needed to correct this perception.

Prevalence of axSpA varies significantly by geographic location and population studied, with worldwide estimates ranging from 0.1 to 1.4%[21]. The significant variation in prevalence is mainly driven by geographic differences in Human Leukocyte Antigen-B27 (HLA-B27) distribution, which is more commonly found in those of northern European descent[22]. Increased use of electronic databases for medical records could be used to improve these estimates, however streamlining of data collection and improved diagnostic coding is needed to accurately capture this information[23].

1.4 Pathogenesis:

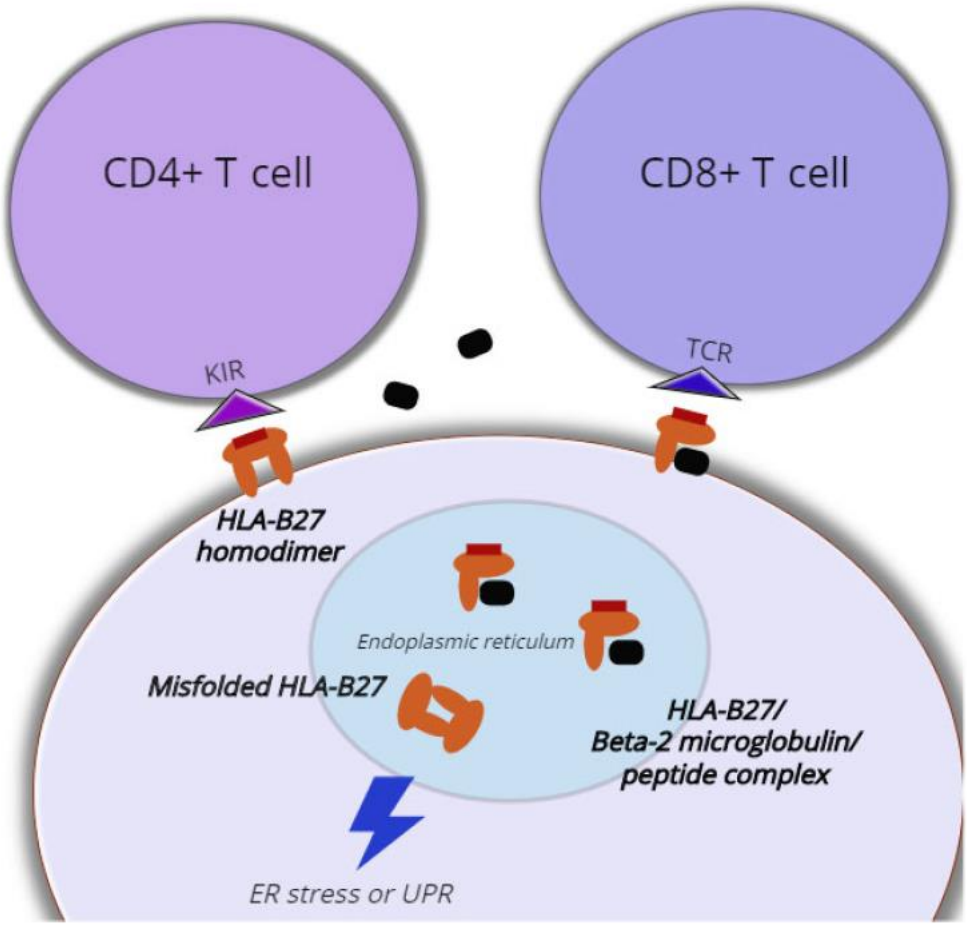
Much of what is known about the pathogenesis of axSpA has been focused on ankylosing spondylitis (AS) and HLA-B27. Despite the volume of research dedicated to this focus, exactly how HLA-B27 triggers the autoinflammatory response of axSpA is unclear[24]. Three main hypotheses have been proposed to explain the role of HLA-B27 in the pathogenesis of axSpA[25](figure 1.3).

The “arthritogenic peptide theory” was proposed in 1992 and suggested that a cell mediated immune reaction could be driven by cytotoxic T lymphocytes (CTL) which recognize self-peptides presented by HLA-B27[26]. This hypothesis also raises the possibility that certain bacterial infections could prime the cytotoxic T lymphocyte for cross-reactivity with HLA-B27. This hypothesis was challenged by a 2015 analysis which examined self-peptides from HLA-B27 allotypes and compared binding motifs. The study suggested that the theories be re-assessed regarding altered conformation of bound peptides, T cell selection, and changes in self-peptide presentation[27].

The second hypothesis to be proposed was in 1999 and referred to as “the unfolded protein response hypothesis.” This was centered on the concept that segments of the HLA-B27 protein would misfold in the endoplasmic reticulum leading to accumulation which would trigger a stress response[28]. The unfolded protein response causes overexpression of interleukin-23 (IL-23) activating the IL-23/IL-17 axis[29].

The most recent theory was the “HLA-B27 homodimer model” which demonstrated that HLA-B27 can form homodimers[30] which have abnormal interactions with CD4 T cells and natural killer cells allowing binding of killer cell immunoglobulin like receptors on these cells which stimulates release of IL-17[31].

Figure 1.3: Summary depiction of the three hypotheses of the role of HLA-B27 in the pathogenesis of axSpA as portrayed by de Koning et al[24]



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Although HLA-B27 is very important in explaining the genetics and heritability of axSpA, there is a significant amount of genetic predisposition that remains unaccounted for[32]. One study calculated that only 20.4% of genetic predisposition could be contributed to major histocompatibility complex (MHC) variants such as HLA-B27[33]. Recent research has demonstrated the practical importance of endoplasmic reticulum aminopeptidase (ERAP) and the receptor for interleukin-23 (IL-23). ERAP aids in preparation of peptides for MHC class 1 presentation to immune effector cells, while IL-23 activates T helper cells to release proinflammatory cells including IL-17[34,1].

Overexpression of IL-23 has been noted to be associated with development of enthesitis and induction of osteoproliferation[35]. Left uncontrolled, this leads to syndesmophyte formation and can result in joint fusion. A study comparing subchondral bone marrow of facet joint in patients with AS compared to those with osteoarthritis (OA) found higher concentrations of IL-23 in the AS cohort[36]. Mechanical strain has also been shown to significantly contribute to inflammation in the enthesis[37] with some proposing the disease related inflammation could be

triggered by a combination of localized dysregulation of the immune response and a local stress response[38].

1.5 Patterns of Disease:

1.5.1 Spondyloarthritis

Clinical presentation of axSpA is most commonly with symptoms of inflammatory back pain (IBP) due to sacroiliitis. This is characterized by stiffness and pain which improves with movement and is aggravated by rest. Symptoms predominantly involve the lower spine due to involvement of the SIJs, but can affect any part of the spine. There are a number of criteria for inflammatory back pain, many features of which have been incorporated into classification criteria for axSpA. The various criteria for inflammatory back pain have a number of overlapping features (table 1.1), however the ASAS IBP criteria has proven to offer the most balanced sensitivity and specificity, as compared to the Calin and Berlin criteria[39]. These criteria can help distinguish inflammatory back pain from other common causes such as degenerative disease and non-specific low back strain but must be applied only when other differentials are considered to be less likely.

If left in a state of persistent disease, axSpA can result in fusion of the affected joints. Clinically this appears as loss of lumbar lordosis and increased thoracic kyphosis. Thankfully with advances in diagnostics and treatments this is less commonly encountered in clinical medicine. However, these changes can be slow and subtle requiring regular measurements of spinal mobility and imaging to capture. For this reason, physical examination remains a cornerstone for axSpA monitoring.

Table 1.1: Inflammatory Back Pain Criteria comparison

	Calin[40]	**Berlin[41]**	**ASAS IBP[42]**
Year of Publication	1977	2006	2009
Criteria	Age at onset <40 years Duration > 3 months Insidious onset Morning stiffness Improvement with exercise	Morning stiffness >30 mins Improvement with exercise, not rest Pain in the second half of the night causing waking Alternating buttock pain	Age at onset <40 years Insidious onset Improvement with exercise No improvement with rest Night pain (which improves on getting up)
Fulfilment	Meet 4 of 5 criteria	Meet 2 of 4 criteria	Meet 4 of 5 criteria

1.5.2 Peripheral Involvement

Although the disease predominantly involves the axial skeleton, some patients also develop involvement of peripheral joints. As mentioned before the enthesis is a site of crucial importance and inflammation here can be driven by a combination of mechanical stress and immune mediated inflammation. A recent study reported up to 55.8% of axSpA patients in their cohort with recent onset axSpA had peripheral enthesitis with the plantar fascia and Achilles tendon the most common sites affected[43]. Diagnosing enthesitis has been aided by advances in ultrasound and other imaging modalities, however this remains a challenging clinical entity to diagnose accurately[44,45].

Peripheral arthritis is estimated to occur in up to 29.7% of people with axSpA, with no difference in prevalence between r-axSpA and nr-axSpA[46,47]. Monitoring patterns of peripheral arthritis is essential to differentiate between psoriatic arthritis (PsA) and axSpA.

Dactylitis is inflammation of the soft tissues of an entire digit giving an oedematous appearance often described as a sausage-like appearance[48]. This is more commonly found in PsA but can also occur in axSpA[49], with data from the Spanish ESPeranza registry reporting a prevalence of 9.5% in their cohort[50].

1.5.3 Extra-articular Manifestations

1.5.3.1 Acute Anterior Uveitis

Uveitis is one of the most common extra-articular manifestations (EAMs) of axSpA and is calculated to affect up to 32.7% of axSpA patients during the course of their disease[51,52]. Presence of uveitis is associated with longer disease duration and presence of HLA-B27[53,54]. Uveitis is most commonly unilateral (87%), acute onset (89%) with anterior involvement of the iris and ciliary body(91%)[52]. Common clinical symptoms include photosensitivity, blurring of vision and pain. Recurrence is common in up to 50% of affected axSpA patients with a variable time period between flares[55].

Due to the frequency of this EAM, a number of studies have focused on detecting axSpA in patients with uveitis presenting to ophthalmology[56]. The Dublin Uveitis Evaluation Tool (DUET) is a tool developed to help ophthalmologists discern when a uveitis patient should be referred onto Rheumatology. Early results show the DUET performed well with a sensitivity of 95% and specificity of 98%[57].

1.4.3.2 Psoriasis

Skin involvement in the form of psoriasis varies in prevalence, but a systematic review calculated a pooled prevalence of 9.3%[58]. This prevalence has been shown to be comparable between both r-axSpA and nr-axSpA[47,59]. Data from the Outcome in Ankylosing Spondylitis International Study (OASIS) demonstrated that psoriasis was associated with increased age (OR 1.05, 95% CI 1.00-1.11) and lower C reactive protein (OR 0.77, 95% CI 0.59-1.00)[60].

1.4.3.3 Inflammatory Bowel Disease

Interleukin 23 (IL-23) is produced in the gut and is thought to be the link between colitis and arthritis[61]. A recent meta-analysis found that up to 13% of patients with inflammatory bowel disease (IBD) have underlying spondyloarthritis[62]. Conversely IBD is estimated to affect up to 4% of patients with axSpA[63]. There appears to be no difference in prevalence of IBD between r-axSpA and nr-axSpA with pooled prevalence of 4.1% versus 6.4% reported respectively[47]. In addition, IBD patients have a significantly higher incidence of subclinical sacroiliitis compared to the general population[64]. AxSpA in the setting of IBD has been shown to be associated with male sex (OR 1.8), known peripheral arthritis (OR 4.7) and an inflammatory phenotype[65]. A number of studies have found high prevalence of subclinical colitis in patients with axSpA[66]. The significance of this is not fully known as less than 10% of these patients will go on to develop clinical IBD[67]. However, chronic gut inflammation has been shown to be associated with greater degree of bone marrow oedema of the SIJs on magnetic resonance imaging (MRI)[68].

However, this has led to extensive research into the gut microbiome, in which significant variation has been found between patients with axSpA and controls[69]. This research has suggested the alteration of the gut flora could be part of the pathophysiology of axSpA rather than a result of a systemic inflammatory response[70], with an altered immune response activation driven by alteration in intestinal permeability and molecular mimicry[71].

1.6 Imaging AxSpA:

1.6.1 Conventional Radiography

Radiography has been the cornerstone of axSpA imaging, diagnostics and classification for many years[4]. There is a wide array of radiographic abnormalities due to localized inflammation driving enhanced turnover of cortical bone resulting in both osteodestructive and osteoproliferative changes of the axial skeleton[72].

Plain radiographs of the SIJs are the gold standard for initial assessment in a patient with suspected axSpA to evaluate for inflammatory sacroiliitis. The need for radiographic evidence of sacroiliitis was included in publications contributing to the earliest classification criteria for AS[73] and was later included as a core endpoint of axSpA research[74]. Inflammation of the SIJ initially appears as loss of distinction of the joint line; typically seen in the lower one third of the ilium, due to inflammation of the subchondral bone marrow in the cartilaginous portion of the joint[75]. This will advance to cause widening of the SIJ with erosions becoming apparent on either or both sides of the joint. Progressive inflammation will result in full ankylosis of the SIJs. Publication of the New York criteria for grading of radiographic changes in AS aided in standardized reporting and comparison of these features between patient cohorts (table 1.2). Unfortunately, in the early stages of disease, radiographs have poor sensitivity and with significant variability between observers noted[76].

Table 1.2: New York criteria grading of radiographic changes of the SIJs in ankylosing spondylitis

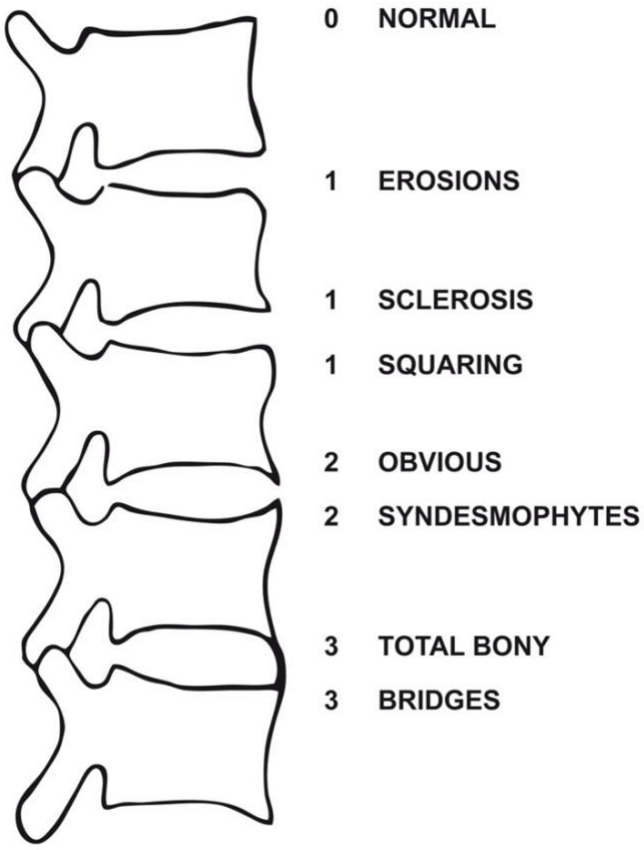
Grade	Radiographic features
0	Normal
1	Suspicious changes -some blurring of joint margins
2	Minimal abnormality - sclerosis with some erosion
3	Unequivocal abnormality - definite sclerosis on both sides of joint, severe erosions with widening of joint space narrowing or partial ankylosis
4	Severe abnormality - complete ankylosis

With advancements in imaging modalities, nr-axSpA was increasingly detected and it was thought that r-axSpA represented a later or more established stage of disease. This led to the term of pre-radiographic axSpA for patients with normal x-rays (XR) SIJs but symptoms of inflammatory back pain. However, this theory was disproved by data from prospective studies demonstrating progression to radiographic sacroiliitis in only 11.6% after two years[77] and 33.% at 8 years[78].

A significant proportion of axSpA patients have radiographic evidence of spinal disease[79]. Typical findings include squaring of the vertebrae, syndesmophytes, erosions and ankylosis[80]. Syndesmophytes are one of the most commonly encountered of these changes and are a key factor in scores to quantify extent of spinal radiographic damage, the gold standard of which is the modified Stroke AS Spinal Score (mSASSS)(figure 1.4)[81]. Progression of radiographic changes in the spine have been shown to vary considerably between individuals[82]. However, development of structural changes in the spine has been shown to have a direct impact on functional status and spinal mobility in patients with axSpA[83]. Factors associated with

radiographic progression include increased disease activity[84], smoking[85], HLA-B27 positivity[86], high level of inflammation on MRI[87] and male sex[88].

Figure 1.4: Depiction of the mSASSS for radiographic involvement of the spine, the scoring system involves scoring of each vertebrae corner to generate a total maximum score of 72[81]. Image from the ASAS educational slide library



1.6.2 Computed Tomography

Computed tomography (CT) can be more sensitive in detecting structural changes at an earlier stage, however this comes with a significantly higher dose of radiation than conventional XRs[72]. Caution must be urged in use of CT in certain populations, as certain findings such as joint space narrowing and subchondral sclerosis which are common consequences of aging can be confused with axSpA[89].

1.6.3 Scintigraphy

This nuclear medicine scan relies on abnormal uptake of radionucleotide techmetium^{99} to detect areas of increased metabolism as a surrogate marker for inflammation. Despite considerable research dedicated to this modality, a systematic review demonstrated a poor

overall sensitivity of 51.8% as compared to MRI for detection of sacroiliitis and concluded that it had limited diagnostic utility in evaluation of axSpA[90].

1.6.4 Magnetic Resonance Imaging

The increased availability of magnetic resonance imaging (MRI) has led to rapid advancements in detection of axSpA. MRI provides detailed imaging of both anatomic structures and pathological changes not visible on other imaging modalities. This is especially useful for visualizing complex regions such as the SIJ for pathognomonic abnormalities such as bone marrow oedema indicating active sacroiliitis as defined by the ASAS and Outcome Measures in Rheumatology (OMERACT) MRI working group[91,92] (table 1.3).

Table 1.3: Definition of sacroiliitis on MRI as per the ASAS/OMERACT MRI working group[92]

Findings indicative of Sacroiliitis on MRI
● Active inflammatory lesions of the SIJ ● Bone Marrow Oedema (BMO) or osteitis highly suggestive of SpA located in subchondral of periarticular bone marrow ● Other active inflammatory lesions without either BMO or osteitis is not sufficient to meet the definition of MRI sacroiliitis ● Structural lesions likely reflect previous inflammation, but isolated lesions without BMO or osteitis are not sufficient to meet definition of MRI sacroiliitis
Amount of Signal Required
● One BMO lesion on at least 2 consecutive slices ● More than one BMO lesion on a single slice

Further work by the ASAS MRI working group has published a validated international consensus statement on definitions of MRI lesions in the SIJs indicative of disease activity and structural changes[93]. As per these definitions MRI lesions indicating disease activity included: bone marrow oedema (BMO) on a T2 weighted sequence sensitive for free water, joint space enhancement, inflammation at an erosion, enthesitis and joint space fluid. MRI SIJ lesions indicative of structural changes include erosions, fat metaplasia, and backfill or fat metaplasia in an erosion cavity. Recognition of these lesions as features of axSpA have aided in the diagnostic utility of MRI in diagnosing axSpA[94]. These lesions are frequently monitored as part of clinical trials and have demonstrated clear response to decrease in disease activity and treatment[95]. Validated scoring systems to quantify MRI changes of axSpA have aided in the ongoing use of MRI as an essential diagnostic tool (table 1.4).

Table 1.4: Validated scoring systems of MRI in axSpA

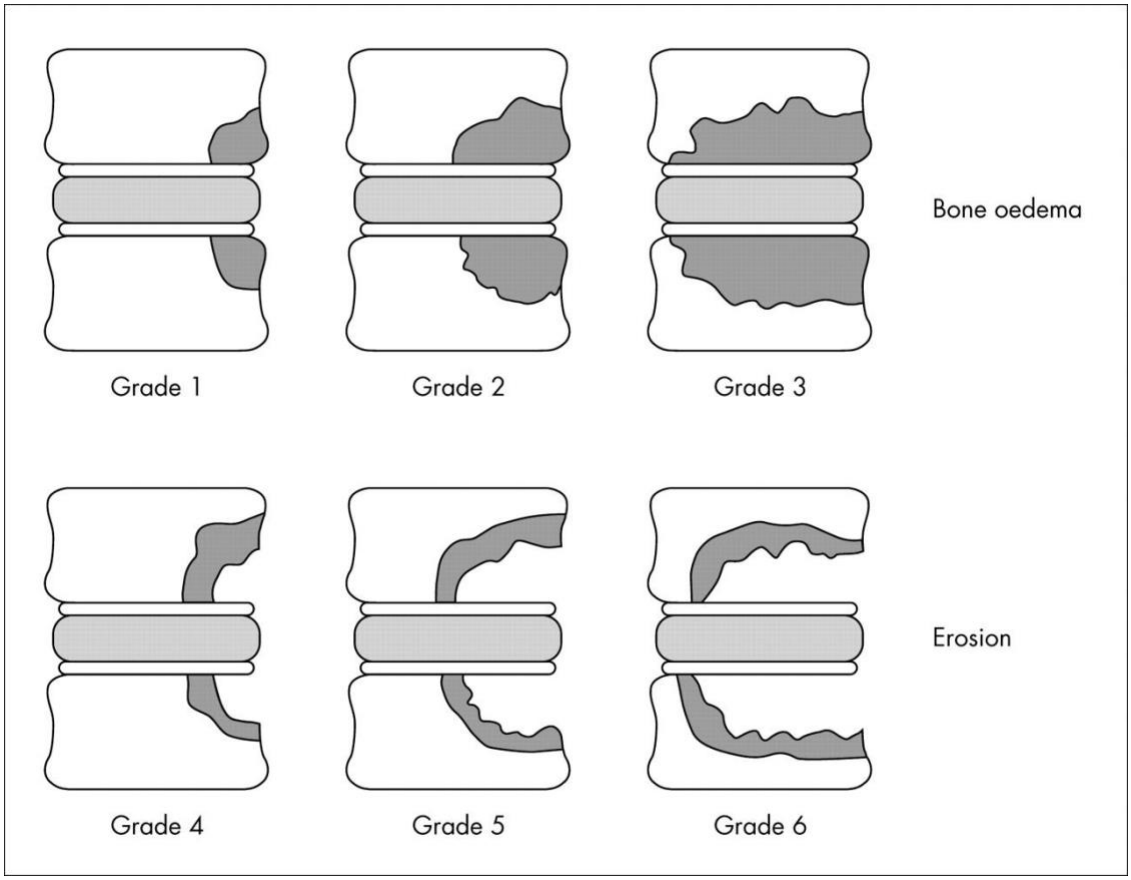
	Berlin[96]	ASspiMRI-a[97]	SPARCC[98]
Spinal MRIs	0 -no inflammation 1 -BMO <25% 2 -BMO =25-50% 3 -BMO >50% (score volume of BMO for each discovertebral unit)	0 -normal, no lesions 1 - mild enhancement & BMO, covering <25% of VU 2 -moderate BMO, covering <50% of VU 3 -severe BMO, covering >50% of VU 4 -BMO & erosion covering <25% of VU 5 -BMO & erosion covering <50% of VU 6 -BMO & erosion covering >50% of VU	12 consecutive slices of DVU Each DVU is divided into quadrants Quadrants assessed for presence of BMO = +1 +1 for depth of BMO +1for intensity of BMO
MRI SIJs	0 -no inflammation 1 -enhancement in joint space or erosions, or volume of BMO <10% 2 -BMO =10-33% 3 -BMO =33-66% 4 =BMO >66% (grades the four quadrants of each SIJ)		6 consecutive semi-coronal slices of the cartilaginous surface of SIJ BMO scored for each quadrant of each slice 0 =absent 1 =present +1 =if signal is intense relative to CSF

***Abbreviations**: ASspiMRI-a -Ankylosing Spondylitis spine MRI score for activity, SPARCC -Spondyloarthritis Research Consortium of Canada, BMO -bone marrow oedema, VU -vertebral units, DVU -discovertebral unit, CSF -cerebrospinal fluid, SIJ -sacroiliac joint*

Although MRI of the spine is considered to be the most sensitive modality in detecting active inflammation in axSpA[99], these lesions have never been a component of axSpA classification criteria. However, previous research has established that spondylitis can occur prior to or in the absence of sacroiliitis[100,101]. This prompted the ASAS and OMERACT MRI working group to release formalized definitions of positive spinal MRI findings in the context of axSpA[102].

Three scoring systems have been developed to limit inter-reader variability when interpreting spinal MRIs in axSpA: the Berlin MRI score[96], the Ankylosing Spondylitis spine MRI activity index (ASspiMRI-a)(figure 1.5)[97], and the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system[98] (table 1.4). A comparison study of these three scoring systems demonstrated that SPARCC had the lowest inter-reader variability, but that all scores were sensitive and reliable at detecting inflammatory changes in the spine[103].

Figure 1.5: Grading of spinal lesions on MRI as per the ASspiMRI-a[97]



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1.7 Challenges to Diagnosing AxSpA:

Despite advances in diagnostics, the diagnosis of axSpA can prove a challenge, even to the practiced Rheumatologist. The appearance of syndesmophytes can appear similar to ossification encountered in diffuse idiopathic skeletal hyperostosis (DISH)[104]. This pathological condition is characterized by ossification of ligaments and enthesis with a predilection for involvement of the axial skeleton[105]. This condition commonly occurs later in life with some research suggesting an association with metabolic syndrome[106,107]. It has even been proposed that obesity could be driving increased osteogenesis of DISH, but this remains to be validated[108]. Unlike axSpA, DISH is not associated with symptoms of IBP and tends to begin later in life.

Osteitis condensans ilii is another condition which can often be confused with axSpA. This is a non-inflammatory condition resulting in bony sclerosis of the ileal region of the SIJs. More common in females, especially in the later stages of pregnancy and postpartum, it is thought to be due to mechanical stress[109]. Diagnosis is based on history and the classic radiographic findings of triangular pattern of dense sclerosis in the anteroinferior aspect of the ileal side of the SIJ[110].

With the recent recognition of nr-axSpA, increased reliance is being placed on MRI of the SIJs. While MRI is a highly sensitive tool which can detect early evidence of sacroiliitis, we must interpret the images in the context of the clinical history. A recent study examined MRI SIJs comparing results between axSpA patients in the Spondyloarthritis Caught Early (SPACE) cohort, postpartum women and frequent runners[111]. MRIs were scored according to the Assessment of Spondyloarthritis Society (ASAS) definition and the Spondyloarthritis Research Consortium of Canada (SPARCC) index. The results showed that a significant proportion of the healthy volunteers and postpartum women met the ASAS definition of MRI sacroiliitis. The postpartum findings have been shown to occur irrespective of mode of delivery and can persist for up to 6 months following delivery[112]. Another study examined MRIs from healthy controls with no back pain and found a high frequency of inflammatory lesions, with an increasing frequency of lesions associated with older age[113]. This reinforces the importance of clinical history in the context of evaluating imaging results.

1.8 Outcome Measures:

1.8.1 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a self-administered questionnaire composed of six questions with answers captured via a visual analogue scale from zero to ten. The scores of the six questions are averaged with scores greater than four to be indicative of active disease[114]. Following a thorough validation process, this simple tool has proven to be an effective and reliable way to quantify disease activity in axSpA[115]. The BASDAI continues to prove its reliability against newer tools which seek to more accurately capture axSpA activity[116]. Despite being developed for AS or r-axSpA, the BASDAI has demonstrated effectiveness in quantifying disease activity in axSpA as a whole[117,118]. The BASDAI was endorsed by the Assessment of Spondyloarthritis International Society (ASAS) as a tool for quantification of disease activity and monitoring of response to treatment in axSpA[119].

1.8.2 Bath Ankylosing Spondylitis Functional Index (BASFI)

The Bath Ankylosing Spondylitis Functional Index (BASFI) was developed and validated in 1994. The BASFI is a series of ten questions capturing information on ability to perform simple daily activities with answers recorded on a visual analogue scale from zero to ten[120]. The questions in the BASFI were designed specifically for AS but are commonly used for axSpA and have been shown to perform well compared to other functional indices[121,122]. It has been evaluated extensively and proven to be a sensitive and validated tool for capture of axSpA patients' functional abilities[123].

1.8.3 Bath Ankylosing Spondylitis Mobility Index (BASMI)

The BASMI is made up of a series of five measurements derived from a focused physical examination commonly performed on axSpA patients[124]. These measurements capture spinal mobility at all parts of the axial skeleton and include: cervical rotation, tragus to wall distance, lateral lumbar flexion, modified Schober's test and intermalleolar distance. The measurements are then quantified and given a score of zero to ten which is averaged to generate an overall score. This tool was shown to be reliable in capturing subtle limitations of spinal mobility and functioned well in a variety of axSpA cohorts[125,126].

1.8.4 Ankylosing Spondylitis Quality of Life Scale (ASQoL)

First published in 2003 the ASQoL was developed to capture changes in quality of life and was composed of eighteen questions on sleep, mood, coping ability, independence and motivation[127]. It is currently one of the most frequently used disease specific measures of

quality of life in axSpA studies[128,129]. The ASQoL has been proven to correlate well with measures of disease activity in times of active disease[130].

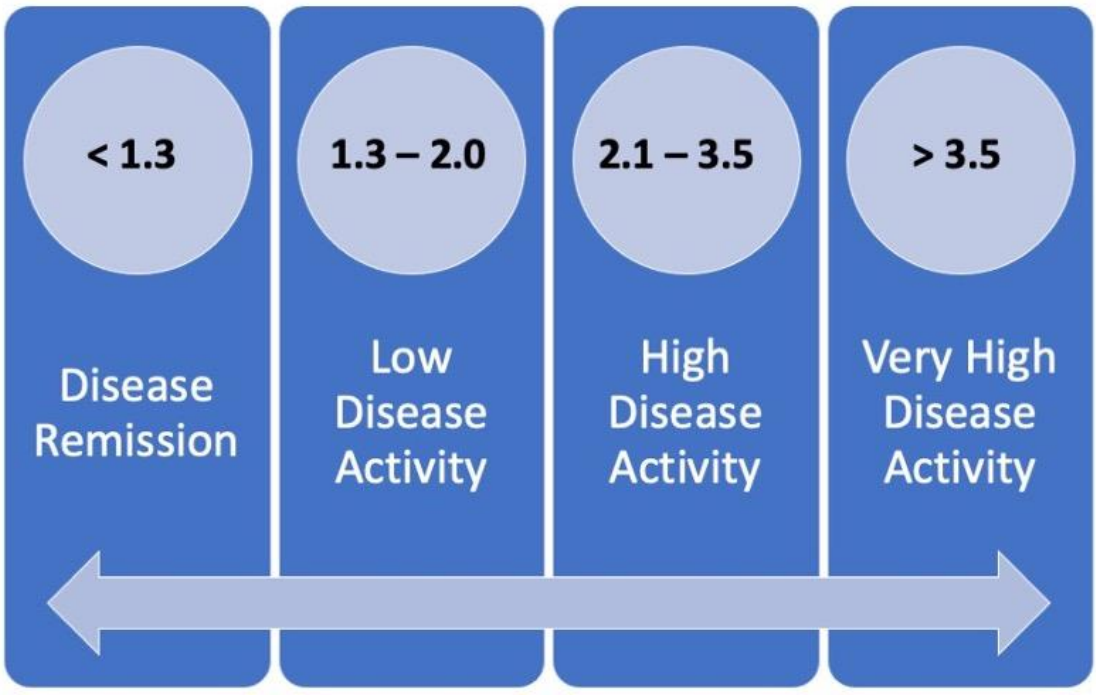
1.8.5 Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S)

The HAQ-S was adapted from the original HAQ to best reflect physical function and potential impairment in patients with r-axSpA or AS[131]. These modifications included questions on static posture and neck function. This self-administered questionnaire contains a series of questions on everyday activities including dressing, feeding and reach. Responses are scored from zero to three with zero indicating no limitation and three indicating the person is unable to do this task. The HAQ allowed quick capture of numerous aspects of a patient's daily living providing an overall impression of a patient's welfare[132].

1.8.6 Ankylosing Spondylitis Disease Activity Score (ASDAS)

The ASDAS is one of the more recent outcome measures developed by the ASAS and was first published in 2008. The ASDAS is a composite score made up of scores from both objective and reported responses[133]. Unlike other outcome measures the ASDAS includes serological markers of inflammation, the C-reactive protein (CRP) or the erythrocyte sedimentation rate (ESR). The ASDAS has been proven to function well not only in established disease but also in very early stages of disease[134]. In addition, cut-offs have been established to delineate disease into four states ranging from inactive to very high disease activity[135,136](figure 1.6).

Figure 1.6: Levels of disease activity as described by ASDAS scores[136]



The ASDAS was endorsed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) for use in axSpA research in 2011[136]. Since then, it has been used for monitoring response to therapy in a number of clinical trials and demonstrated excellent discriminatory function[137,138]. Scores generated from the ASDAS have also been shown to correlate well with level and intensity of spinal inflammation detected on magnetic resonance imaging (MRI) scans in axSpA patients[139].

1.8.7 Bath Ankylosing Spondylitis Global Score (BAS-G)

The BAS-G is one of the simplest outcome measures used in axSpA. Composed of only two questions with answers recorded via a visual analogue score from zero to ten, this score gives an overall result for how the patient perceives their well-being[140]. It has been shown to correlate well with other patient reported outcomes, but not with objective clinical measurements captured within the BASMI[128]. As the BAS-G is unidimensional, it is not often used for monitoring changes in response to therapies in clinical trials[141].

1.9 Classification Criteria:

1.9.1 Rome Criteria

The first formal classification criteria for r-axSpA, then called AS, was known as the Rome Criteria and proposed in 1961[142]. This criteria incorporated both clinical symptoms, physical examination findings and radiographic results including a grading system for radiographic sacroiliitis (table 1.6)[143]. Prior to this, classification had been focused on clinical history alone to identify inflammatory back pain[40]. Although the criteria performed well, further revisions were proposed in New York leading to the New York criteria for AS being published in 1966[144]. Unlike the Rome Criteria, this included a grading system for radiographic sacroiliitis (table 1.5).

Table 1.5: Grading of radiographic changes in ankylosing spondylitis as per the New York Criteria

Grade	Radiographic features
0	Normal
1	Suspicious changes -some blurring of joint margins
2	Minimal abnormality - sclerosis with some erosion
3	Unequivocal abnormality - definite sclerosis on both sides of joint, severe erosions with widening of joint space narrowing or partial ankylosis
4	Severe abnormality - complete ankylosis

1.9.2 Modified New York Criteria (mNY)

Further investigation and use of the New York criteria in AS cohorts demonstrated a lack of sensitivity of certain components[17,145]. These criteria removed the nonspecific symptom of "backache" and replaced it with low back pain for at least three months which is improved by exercise but not relieved by rest. A study comparing the sensitivity of the Rome, New York and mNY validated the improved sensitivity and specificity of the mNY in a large AS population[143]. The mNY were simple to apply and were used extensively in clinical research in AS during this time[146]. However, a number of clinicians increasingly noted the presence of a cohort of patients who met the criteria for IBP and were HLA-B27 positive but did not have radiographic sacroiliitis[147]. Some criticized that although mNY allowed classification of established disease, it did not reliably capture early disease[148].

1.9.3 Amor Criteria & the European Spondyloarthropathy Study Group Criteria (ESSG)

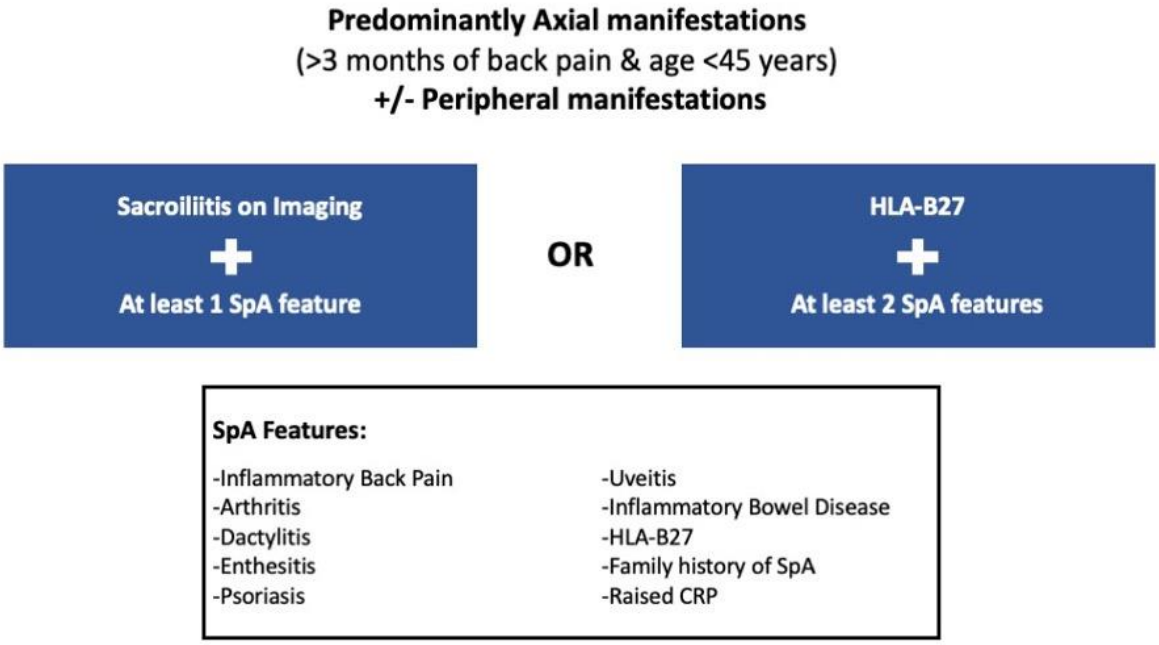
The Amor criteria was the first diagnostic criteria to incorporate HLA-B27 status into classification for AS[149]. However, this criterion was developed for the broader clinical spectrum of spondyloarthritis (SpA) which included reactive arthritis and psoriatic arthritis as well as ankylosing spondylitis. The Amor criteria weighted clinical features, radiographic results, serology and treatment response with a score of six or greater fulfilling classification criteria for SpA.

Shortly after the Amor criteria was released another criteria for classification of SpA was released by the ESSG in 1991[150]. This new classification system demonstrated a high sensitivity and specificity for "seronegative spondyloarthropathies." Unlike the Amor, all items were weighted equally but patients must have symptoms of IBP[151]. The criteria proved to perform well in various populations[152] but still struggled to capture patients with early disease especially those without radiographic sacroiliitis[153].

1.9.4 ASAS Criteria for Axial Spondyloarthritis

Advancement in imaging led to increased use of MRI which revealed a cohort of patients with symptoms of IBP and evidence of sacroiliitis on MRI. Many of these patients did not meet classification criteria for AS, yet seemed to respond to similar treatments including physiotherapy and NSAIDs. In 2009 ASAS released new classification criteria that introduced the concept of axial spondyloarthritis (axSpA) which it separated into radiographic and non-radiographic (figure 1.7)[2,154].This new criteria classified patients on based on the predominant location of their symptoms, axial or peripheral, with further classification criteria for peripheral SpA(figure 1.8)[155].

Figure 1.7: The revised ASAS classification criteria for axial SpA[2]



The criteria for axial disease were validated in patients with at least 3 months of back pain with age of symptom onset before the age of 45 years. In these criteria r-axSpA replaced the term AS and referred to patients with inflammatory sacroiliitis on x-ray. Conversely, nr-axSpA referred to inflammatory sacroiliitis on MRI only, thus increasing Rheumatologists' reliance on this valuable diagnostic tool[156]. Initially nr-axSpA was viewed as an early form of r-axSpA, however later studies demonstrated a significant proportion of patients do not evolve into r-axSpA[157].

Figure 1.8: ASAS Classification criteria for peripheral SpA[155]

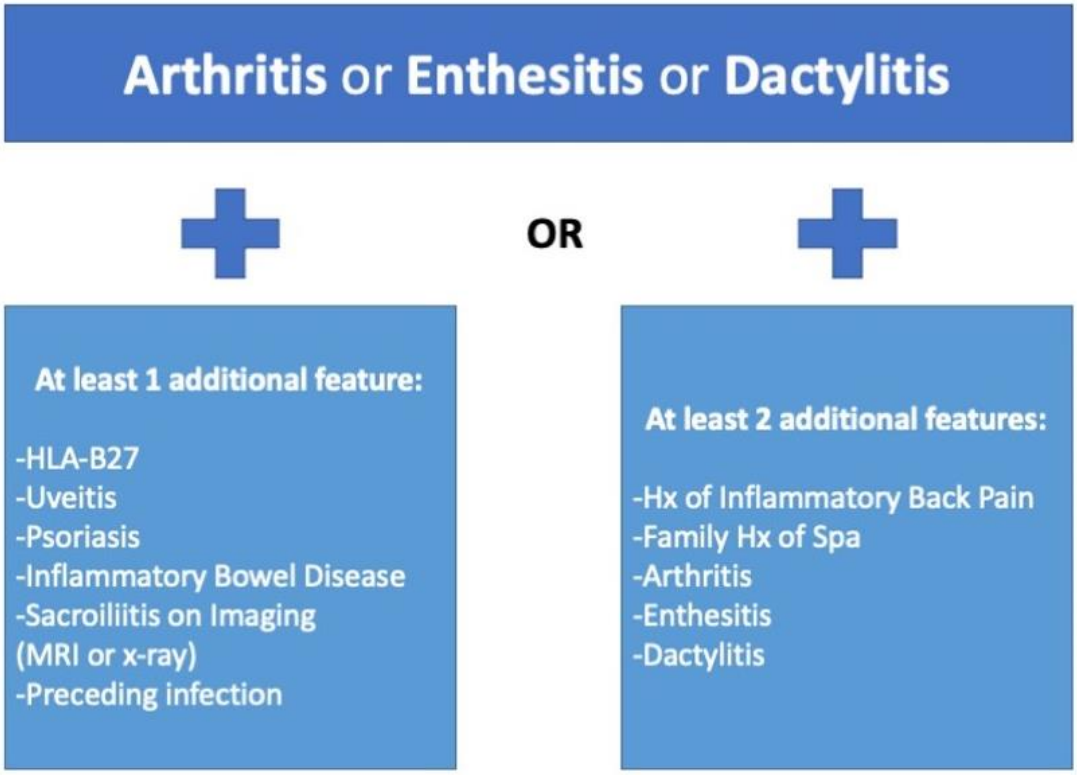


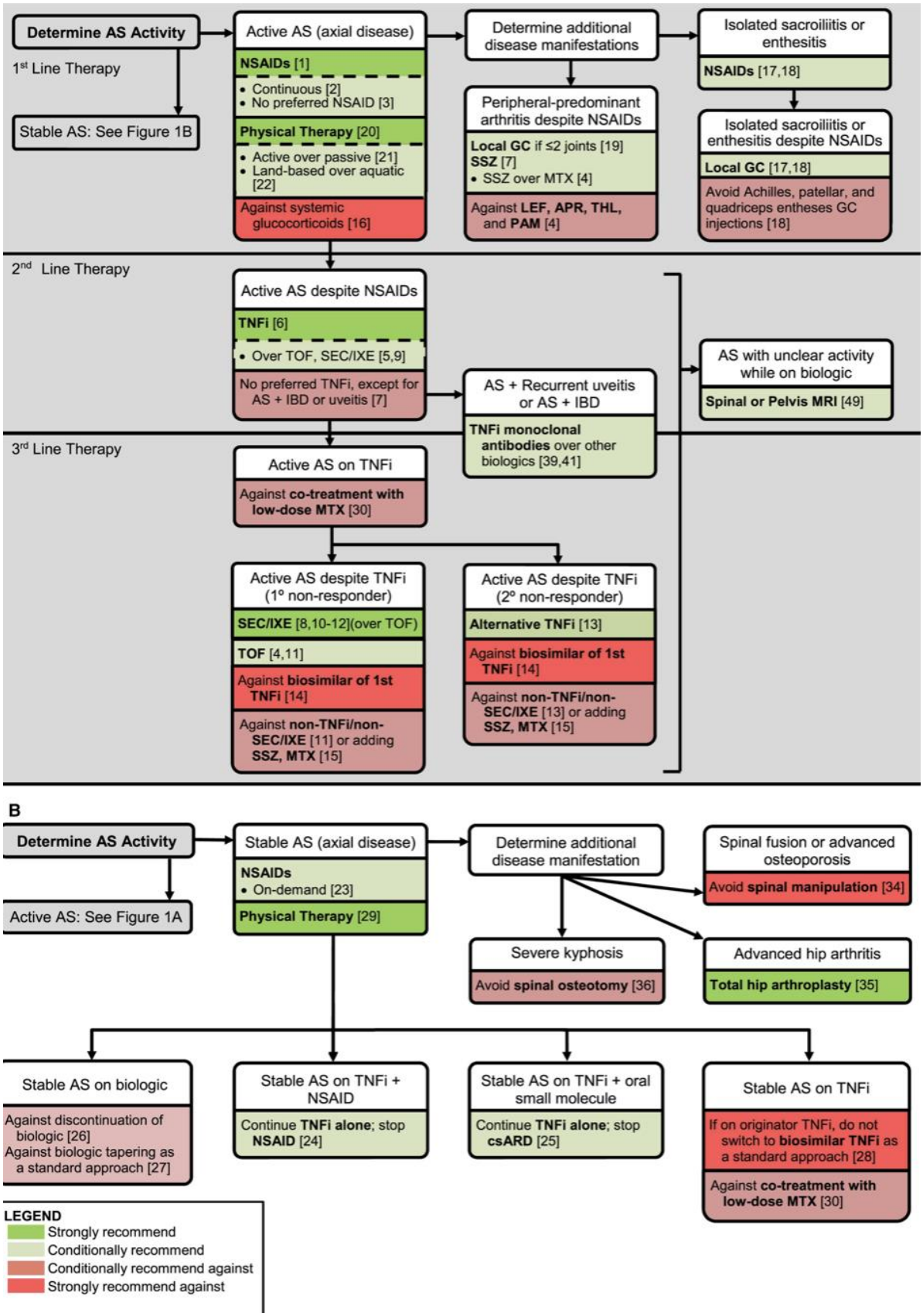
Table 1.6: Evolving classification criteria from AS to axSpA

	Rome	mNY	Amor	ESSG	ASAS
Year of publication	1961	1984	1990	1991	2009
Developed for	AS	AS	SpA	SpA	axSpA
Clinical criteria	LBP > 3 months, not relieved by rest Thoracic pain & stiffness Limited motion of lumbar spine Limited chest expansion Iritis	LBP >3 months, improved by exercise and not relieved by rest Limitation of lumbar spine in sagittal and frontal planes Limited chest expansion adjusted for age & sex	Nocturnal back pain or EMS (1) Asymmetric oligoarthritis (2) Buttock pain (1) alternating (2) Dactylitis (2) Heel pain or enthesopathy (2) Non-gonococcal urethritis or cervicitis (1) Psoriasis, balanitis or IBD (2) HLA-B27+ or family hx of AS, reactive arthritis, uveitis, psoriasis or IBD (2) Improvement with NSAIDs (2) Iritis (1)	IBP or synovitis + one of the following: Family hx of AS, reactive arthritis, IBD or psoriasis Hx of IBD Hx of Psoriasis Alternating buttock pain Achilles tendonitis or plantar fasciitis Diarrhoea prior to onset of arthritis Non-gonococcal urethritis or cervicitis in the month prior to onset of arthritis	SpA features IBP Arthritis Enthesitis Uveitis Dactylitis Psoriasis Colitis Response to NSAIDs Family hx for SpA HLA-B27 + CRP elevation
Radiology criteria	Bilateral sacroiliitis	Bilateral sacroiliitis: grade 2-4 or Unilateral sacroiliitis: grade 3-4	Sacroiliitis by NY criteria (3)	Sacroiliitis by NY criteria	Active inflammation on MRI or Definite radiographic sacroiliitis as per mNY criteria
Classification requirements	Radiology criteria + 1 clinical criteria or 4 clinical criteria	Radiology criteria + 1 clinical criteria	Score >6 (must also have abnormal SIJ x-rays and be HLA-B27+)	IBP or synovitis + 1 additional feature (above)	Sacroiliitis on imaging + at least 1 SpA feature HLA-B27 (+) + at least 2 SpA features

1.10 Management of AxSpA:

Management of axSpA is centred around three core aims: to decrease disease activity, significantly reduce or resolve symptoms and improve or preserve function[158]. A number of treatment guidelines for axSpA have been released, most recently as a collaborative effort between the American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and the Spondyloarthritis Research and Treatment Network (SPARTAN) (figure 1.9)[159,160]. These guidelines include both pharmacologic and non-pharmacologic interventions, with level of disease activity driving the need for escalation of treatment.

Figure 1.9: Treatment guidelines based on level of disease activity and strength of evidence[159]



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1.10.1 Pharmacotherapy

1.10.1.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

First line pharmacologic therapy for patients with symptoms of axSpA is with non-steroidal anti-inflammatory drugs (NSAIDs). These medications act by inhibition of both cyclooxygenase one (COX-1) and two (COX-2) which is termed non-selective COX inhibition. Certain NSAIDs selectively inhibit only COX-2 which drives biosynthesis of prostaglandins; a key component of an inflammatory response[161]. Since becoming available in the 1960s, NSAIDs have become one of the most commonly used classes of medications worldwide[162]. Their use in axSpA has persisted as this class of medication has proven benefit in improving functional ability and level of pain in active axSpA[163], with no one NSAID proven to be more efficacious than another[164] and response rates of 35-70% reported overall[165,166].

There has been a significant body of research focusing on NSAIDs and effect on radiographic progression of disease. A clinical trial in 2005 found decreased radiographic progression in axSpA patients on continuous NSAIDs despite adjusting for baseline levels of radiographic damage and disease activity[167]. These findings were confirmed with publication of data from the German Spondyloarthritis Inception Cohort (GESPIC) which demonstrated that high NSAID intake over two years was associated with decreased likelihood of radiographic progression as defined by worsening mSASSS[168]. This was challenged by the ENRADAS (Effects of NSAIDs on Radiographic Damage in AS) trial[169] and the disease modifying ability of NSAIDs remains a hotly debated topic in academia[170].

1.10.1.2 Tumour Necrosis Factor (TNF) Inhibitors

The discovery of biologic therapies was a significant breakthrough in the treatment of inflammatory arthropathies. This was especially important for axSpA where those with predominantly axial symptoms failed to demonstrate response to treatment with conventional disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate and sulfasalazine. TNF inhibitors were the first class of biologic agents with proven efficacy in axSpA, providing an escalated treatment option for patients with active disease despite regular NSAID use[171]. Current treatment guidelines do not recommend any one TNF inhibitor over another for axSpA patients being commenced on a biologic agent[159]. These medications not only improved disease activity[172], but also improve evidence of active disease on MRI[173,174] in both radiographic and non-radiographic axSpA. There are a number of TNF inhibitors licensed to treat axSpA, all of which have demonstrated an acceptable safety profile[175].

Treatment with TNF inhibitors has been shown to be equally effective in the management of both r-axSpA and nr-axSpA as recently proven in a large national registry study of axSpA patients who were biologic naive[176]. Overall response rates to TNF inhibitors differed

between r-axSpA and nr-axSpA (60% vs 50% respectively) similar to findings of other studies[177,178]. Patients fulfilling the clinical arm of the ASAS classification of axSpA were found to have lower rates of response to treatment with TNF inhibitors as compared to those fulfilling the imaging arm of the classification criteria[179]. A number of factors have been identified as predictors of response to anti-TNF therapy, including younger age and raised inflammatory markers at baseline. Male gender and lower reported levels of fatigue have been reported as predictors of prolonged drug use survival[180-182].

Two key lifestyle factors can also affect response to TNF inhibitors: smoking and obesity. Obesity has been shown to be associated with worse baseline patient reported outcome measures and increased risk of syndesmophyte formation[183,184]. It has also been shown to be associated with decreased clinical response to anti-TNF therapy[185]. Smoking has been found to be associated with increased burden of disease at baseline in axSpA[186]. A recent systematic review evaluated both of these modifiable risk factors and found obesity was consistently associated with poor treatment response with TNF inhibitors. The evidence on smoking is less conclusive but suggests that smokers also have a decreased treatment response[187]. However, a further study demonstrated that non-smokers have a higher prevalence of prolonged remission as calculated by the ASDAS-CRP[188]. These findings, along with the known increased cardiometabolic risk of smoking and obesity, indicate proactive management of these risk factors in axSpA patients is essential.

1.10.2 Non-Pharmacologic Treatments

Management of axSpA requires a combination of both pharmacologic and non-pharmacologic modalities of treatment, as outlined by the most recent ASAS treatment guidelines[189]. This often requires multidisciplinary team input to allow for monitoring and optimization of a patient's therapy.

Exercise is one of the cornerstones of therapy in management of axSpA which helps to maintain both muscular fitness and range of motion[190]. Numerous studies have demonstrated the beneficial role of various modalities of exercise on not only patients' lifestyle, but also patient outcomes[191,192]. A systematic review even suggested that exercise may help in pain reduction and patient global assessments[193]. Evidence has shown that a multimodal approach with a combination of independent and supervised training sessions are the most effective at encouraging adherence to regular exercise programs in axSpA[194]. Studies on exercise in axSpA have significant variation and so it is difficult to draw conclusions on superiority of one form of exercise over another[195].

Exercise has the additional benefit of helping axSpA patients maintain a healthy weight. This is important not only to overall health but also to controlling disease activity as obesity has

been demonstrated to be associated with worse disease outcomes, greater radiographic burden of disease and greater functional impairment[183,184,196].

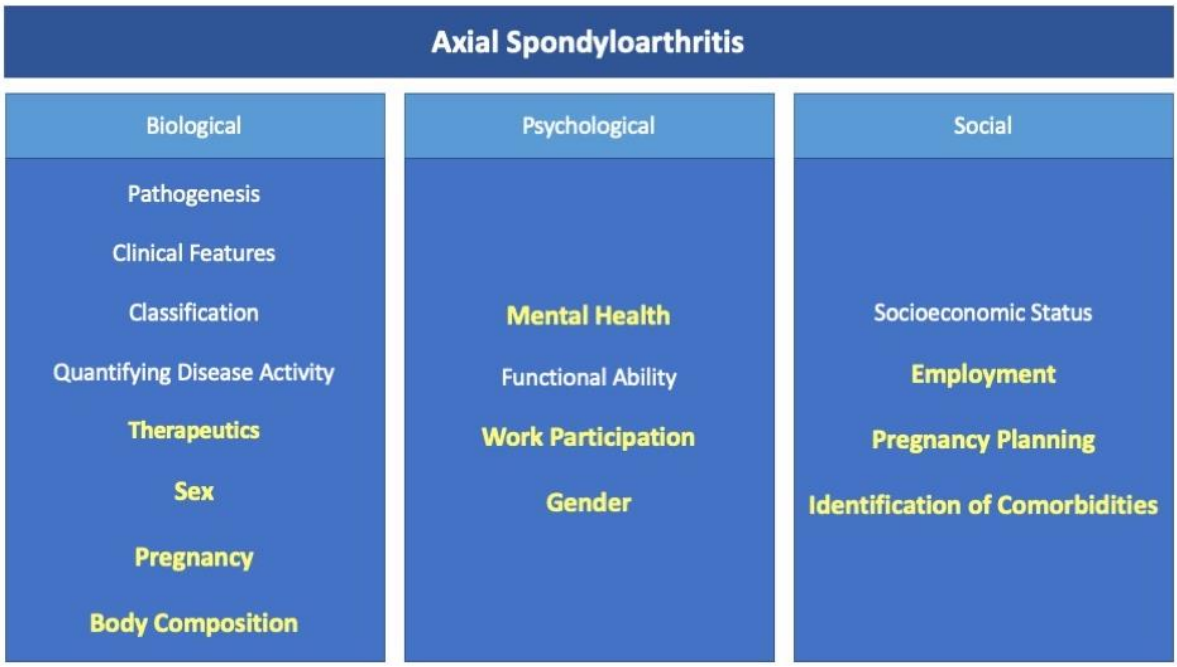
For some patients with axSpA a period of physiotherapy is needed for rehabilitation prior to independent exercise. Physiotherapy should be initiated promptly once a diagnosis is reached, regardless of the stage of the disease[197]. A number of studies have established that this is an effective intervention with factors such as involvement, patient education and individual motivation associated with improved outcomes[198]. It has also been shown to be superior to patient education alone and behavioural coaching[199].

1.11 Summary:

Axial spondyloarthritis (axSpA) is an autoinflammatory arthritis involving the axial spine and sacroiliac joints with an age of onset typically in the third decade of life. The clinical and radiological features are well documented and are key components of existent classification criteria. Treatment involves an integrated approach of both pharmacologic and non-pharmacologic interventions. Current research focus has been on therapeutics, with a strong emphasis on preventing disease progression, and diagnostics, to address the considerable delay in diagnosis currently facing axSpA patients.

Recent research has highlighted several additional areas within axSpA which require further exploration. This includes a higher prevalence of numerous comorbidities and worse levels of unemployment in axSpA compared to the general population. Additionally, despite changes in understanding of epidemiology regarding sex distribution, there is limited research specifically examining the impact of axSpA in women. There is even less available data on pregnancy in axSpA, in spite of extensive evidence describing age of onset to be in the childbearing years. Evaluating these issues from an integrated bio-psycho-social perspective would provide a more complete picture of the full impact of axSpA on an affected individual. This would also allow the development of effective interventions to better address issues associated with worse patient outcomes.

Figure 1.10: Bio-psycho-social aspects of care to consider in axSpA. Highlighted in yellow are topics discussed within the context of this thesis.



1.12 Aims of Thesis:

This thesis is centred around specific subpopulations within axSpA which require further exploration from a biopsychosocial aspect to fully capture the impact on disease activity and patient outcomes. This will allow a multidimensional assessment of these axSpA subpopulations and the challenges they face. Use of data from a large national registry of axSpA patients provided a well characterized cohort which allowed for such detailed analysis. This thesis and the research it contains, were developed with the following aims:

-To review emerging therapies in axSpA management

-To investigate how specific biopsychosocial variables, affect axSpA activity and outcomes using data from a large national registry (the ASRI: Ankylosing Spondylitis Registry of Ireland)

-To capture prevalence and impact of specific comorbidities in patients with axSpA

-To characterize how axSpA presents and behaves in women in addition to detailed analysis to understand sex differences in axSpA

-To analyse pregnancy in axSpA in terms of pregnancy complications, fetal complications, disease activity and breastfeeding

1.13 Outline of Thesis:

Chapter two discusses the future of treatment of axial spondyloarthritis. This chapter discusses use of biologic therapies beyond anti-tumour necrosis factor (anti-TNF) therapies which were previously the mainstay of treatment in axSpA. Detailed discussion of clinical trials associated with these new therapies including both those with proven efficacy and those which were unsuccessful.

Chapter three is focused on the Ankylosing Spondylitis Registry of Ireland (ASRI) including the importance of national registries and their role in Rheumatology research. The objectives and patient enrolment in the ASRI will also be detailed within this chapter. This will include a series of analyses focusing on patterns of disease, prevalence of co-morbidities and prescribing practices in axSpA using the data from the ASRI. This chapter will also discuss late onset axSpA which is a subset of axSpA rarely mentioned in recent axSpA literature but is known to occur in up to 6% of axSpA patients. This analysis discusses similarities in patterns of disease and radiographic findings between late and typical onset axSpA, in addition to providing a review of the literature on this topic to date.

Chapter four highlights the impact of two commonly encountered issues in patients with axSpA: unemployment and depression. This will include examination of the prevalence of unemployment in axSpA and impact on patient outcomes. Additional analyses will discuss mental health issues in axSpA specifically focused on the impact of these issues in axSpA women. A two-part analysis focused on depression, examines the prevalence and impact of depression in the ASRI followed by a prospective study screening for undiagnosed depression. This chapter concludes with an analysis of the psychological impact of the COVID-19 pandemic in patients with axSpA.

Chapter five delves further into the sex differences noted in the previous analyses and is centred on women with axSpA. Due to relatively recent recognition of non-radiographic axSpA (nr-axSpA) this has been previously thought to be a predominantly male disease. As such there is limited information on axSpA in women. This chapter begins by detailing sex differences from a series of analyses using data from the ASRI. This also includes a focused analysis of a number of outcome measures to better characterize these differences and provide insights on interpretation of outcomes in women with axSpA.

Continuing to discuss differences between men and women with axSpA, **chapter six** will be focused on anthropometric measurements. These analyses will capture variation in anthropometric measurements between sexes in addition to examining the impact of these differences on reporting of axSpA disease activity.

As most axSpA females are in their childbearing years at time of diagnosis, it is important to examine pregnancy as part of the discussion of this population. **Chapter seven** introduces the

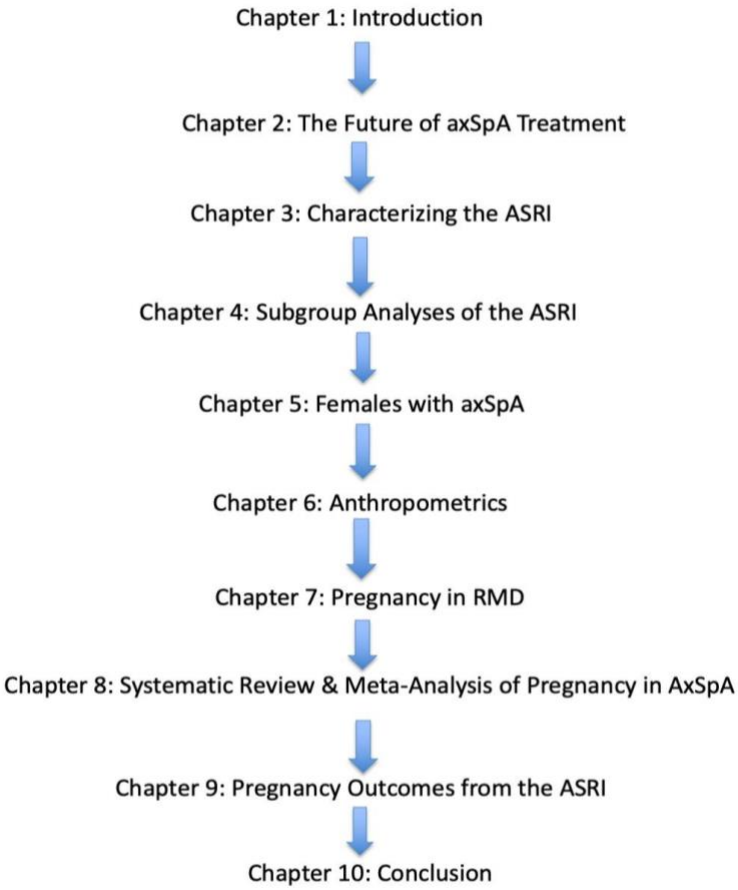
next three chapters of the thesis focused on pregnancy. This chapter begins by discussing the challenges and key principles in the management of pregnancy in women with rheumatic disease. This chapter will also discuss disease activity during pregnancy and tools for monitoring for several commonly encountered rheumatic diseases.

This leads into **chapter eight** which is focused on pregnancy specifically in axSpA. The chapter details what is currently known about pregnancy in axSpA with a systematic review and meta-analysis on pregnancy and fetal outcomes in axSpA pregnancies. It also raises questions that remain unanswered by this literature and suggestions for how this could be evaluated going forward.

Chapter nine is the final chapter on pregnancy in axSpA. This chapter presents pregnancy data from women enrolled in the ASRI and discusses the results in the context of generalized reference norms and the general population of Ireland.

The thesis concludes with a **chapter ten**, which discusses significant findings from the studies conducted as part of this thesis. This chapter also explains how this research fits into current understanding of this area and future directions for additional research.

Figure 1.11: Outline and overview of the thesis



Chapter 2. The Future of Treatment in Axial Spondyloarthritis

Publication resulting from material contained within this chapter:

S Maguire, R Sengupta, F O'Shea. The Future of Axial Spondyloarthritis Treatment. *Rheumatic Disease Clinics of North America*. 2020 May; 46(2): 357-365. DOI: 10.1016/j.rdc.2020.01.014

(Full manuscript in Appendix A)

2.1 Summary:

Axial spondyloarthropathy (axSpA) treatment with biologic DMARDs previously focused on anti-TNF agents. Significant advances in research led to new therapeutic options such as Secukinumab and more recently Ixekizumab, both IL-17 inhibitors, which have been approved for the treatment of axSpA. Tofacitinib and Upadacitinib, are two JAK inhibitors which have demonstrated excellent clinical responses in axSpA resulting in their approval for treatment of axSpA. A number of newer agents have been developed to inhibit IL-17, IL-23 and JAK. Early trials are promising, however further research is needed. The rapid expansion of therapies available to treat axSpA could lead to improved disease control and decreased burden of disease.

2.2 Background:

There have been rapid developments in the availability of new therapeutic options in axial SpA over the last number of years. Different recommendations have been published to reflect this changing landscape. In 2016, ASAS / EULAR updated their management recommendations for patients with axial SpA [189]. More recently, the American College of Rheumatology (ACR) / Spondylitis Association of America / Spondyloarthritis Research and Treatment Network (SPARTAN) updated their recommendations for the treatment of Ankylosing Spondylitis (AS) and non-radiographic axial SpA [159]. Recommendation 9 of the ASAS / EULAR guidelines confirm the use of an anti-TNF agent for patients with persistent high disease activity despite conventional therapy. A similar recommendation is present in the ACR/SPARTAN guidelines.

The biggest change in treatment in the last few years has been the development of medications that work on an alternative pathway to the anti-TNF agents which are known to have response rates of 50-60%[177,178]. Evidence now suggests that Interleukin (IL) – 17 plays a role as an inflammatory mediator in AS. Secukinumab is a recombinant, fully human monoclonal anti-human IL-17A antibody of the IgG1/kappa isotype. Secukinumab has been available for the treatment of axial SpA patients for the last 3 years. A significant body of evidence exists for the benefit of Secukinumab in axial SpA across a series of trials – MEASURE 1-5 study program [200-203](table 2.1).

Table 2.1: MEASURE 4 Study Outcomes

	Week	Placebo (%)	Secukinumab 150mg (%)	*p value*	Secukinumab 150mg + loading (%)	*p value*
ASAS20	4	39	53.8	*0.36*	49.1	*0.36*
	16	47	61.5	*0.05*	59.5	*0.06*
	52		72		71.7	
	104		77.5		74	
ASAS40	4	17.9	26.5	*0.36*	29.3	*0.36*
	16	28.2	35.9	*0.36*	38.8	*0.19*
	52		54.1		51.3	
	104		58.9		51.9	

Most recent information from this series of studies now has 5-year data demonstrating efficacy of Secukinumab in axial SpA [204]. In addition, the MEASURE 1 study has shown a low rate of radiographic progression in this cohort. No radiographic progression (mSASS change from baseline of <2 units) was seen in 79% of patients receiving Secukinumab over 4 years[205].

Recommendation 10 from the ASAS /EULAR Management guidelines suggest that if an anti-TNF therapy fails switching to another anti-TNF or an anti IL-17 agent should be considered.

The authors state that in patients with a primary non-response to the first anti-TNF agent it may be a more rational approach to switch to another class (specifically an anti IL-17 agent).

2.3 New to Market Treatments

2.3.1 JAK Inhibitors

2.3.1.1 Tofacitinib

TNF blockers have been the cornerstone of treatment for axial spondyloarthritis over the last two decades. Aside from biological DMARDs (bDMARDs), new treatments in the form of small molecule treatments (targeted synthetic DMARDs) are showing promise in this disease area. One of the first tsDMARD being assessed in axSpA is a Janus-kinase (JAK) inhibitor – tofacitinib, which preferentially inhibits signalling via JAK 1 and 3. A preliminary phase II study showed 63% of Tofacitinib 5mg bd patients achieved a ASAS20 response compared to 40% placebo patients at 12 weeks [206](table 2). One hundred and sixty-four patients who had baseline MRI and week 12 follow up MRI scans during this phase II study showed 18% patients treated with tofacitinib 5mg bd achieved MIC (Minimal Important Change) for SPARC SIJ and spine scores compared to 0% placebo. There was a trend for greater clinical improvements in the tofacitinib patients who achieved MIC SPARC scores [207].

Whilst no treatment-related serious adverse events were identified in the phase II study, the FDA have since issued a "black box" warning regarding an increased risk of thromboembolism with tofacitinib 10mg bd following a safety trial in rheumatoid arthritis[208,209]. However studies evaluating this risk in JAK inhibitors compared to treatment with TNF inhibitors have demonstrated that this risk is low and often associated with the presence of other risk factors for thromboembolism[210].

Concerns regarding increased risk of cardiovascular events and malignancies in patients treated with tofacitinib triggered the ORAL Surveillance trial[211]. This was a randomised, open label, non-inferiority, safety endpoint trial involving rheumatoid arthritis patients with at least one cardiovascular risk factor (n=4,362)[212]. The primary endpoints were major adverse cardiovascular events (MACE) and cancer. Participants treated with tofacitinib were found to have a higher incidence of both MACE (3.4% vs 2.5%) and cancer (4.2% vs 2.9%) compared to those on TNF inhibitors. The results of this study are newly released and the implications of these findings on clinical recommendations remains to be seen.

2.3.1.2 Upadacitinib

Upadacitinib is a selective JAK1 inhibitor which has shown efficacy in rheumatoid arthritis. An international phase IIb/III randomized, double blind, placebo-controlled trial was

undertaken to assess upadacitinib as a treatment for axSpA[213]. This trial evaluated both efficacy and safety profile active radiographic axSpA with a primary endpoint of ASAS40 response at week 14. This was met by 52% of participants treated with upadacitinib compared to 26% in the placebo group ($p<0.001$). The treatment group also recorded a higher percentage of ASDAS low disease activity and ASDAS major improvement at week 14 compared to placebo. Additionally, significant differences in ASAS40 responses were noted between the two groups as early as week 2 which was maintained out to week 64.

The proportion of patients reporting adverse events were slightly higher in the upadacitinib group than placebo (62% vs 55%) with rise in creatine phosphokinase the most common adverse event. A rise in serum cholesterol was noted in the upadacitinib group but not in the placebo. These results have resulted in the approval of Upadacitinib for the treatment of both axSpA and psoriatic arthritis by the European Medical Agency (EMA)[214].

Table 2.2: Comparative ASAS outcomes in trials for Tofacitinib and Upadacitinib. **Note these are not head-to-head trials.

	Treatment	Placebo ASAS20	Treatment Group ASAS20	Treatment ASAS40	Placebo ASAS 40	*p value*
Tofacitinib	**2mg bd**	**41%**	**52%**	**42.3%**	**20%**	**<0.05**
	5mg bd		**81%**	**46.2%**		**<0.01**
	10mg bd		**56%**	**38.5%**		**<0.05**
Upadacitinib	**15mg od**			**52%**	**26%**	**<0.01**

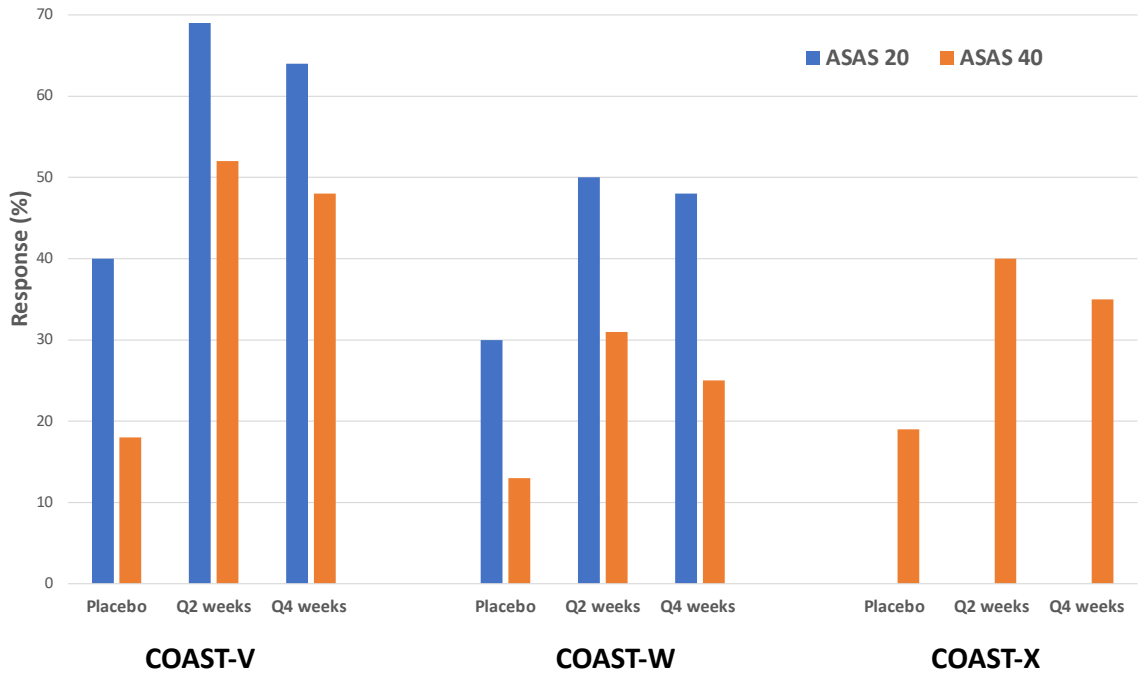
2.3.2 Anti IL 17

There is a growing body of evidence suggesting that IL-17 is one of the key cytokines in the pathogenesis of axial SpA [215]. As previously stated, secukinumab, a monoclonal antibody against IL-17A, has had market authorisation for AS treatment since 2016. Phase III studies have shown good efficacy and are described elsewhere in this review. Ixekizumab, another monoclonal antibody against IL-17A, has approval for the treatment of PsA. Three phase III studies have assessed the efficacy of Ixekizumab in axial SpA. The COAST-V study assessed the efficacy of Ixekizumab 80mg every 2 or 4 weeks in AS patients who were DMARD and TNF naïve compared to adalimumab or placebo (table 2)[216]. Fifty two percent of Ixekizumab 80mg patients achieved an ASAS40 response compared to placebo. The COAST-W study specifically assessed the efficacy of ixekizumab 80mg in patients who either failed or were intolerant to TNF blockers as first line therapy. Thirty one percent of patients treated with ixekizumab 80mg every 2 weeks exhibited an ASAS40 response at 16 weeks (figure 2.1). The COAST-X study was a phase

III study assessing the efficacy of ixekizumab 80mg given every 2 or 4 weeks in bDMARD naïve nr-axSpA [217]. Results demonstrated significant improvements in ASAS40 response in participants treated with ixekizumab at week 16 and 52 compared to placebo, regardless of frequency of ixekizumab dosing.

Based on the strong clinical response to Ixekizumab demonstrated in these trials, approval for treatment in axSpA, both radiographic and non-radiographic disease, was granted by the European Medicines Agency (EMA) in 2020[218].

Figure 2.1: Comparative ASAS response rates in clinical trials for Ixekizumab. **Note these are not head-to-head trials.



2.4 Treatments in Trials

2.4.1 Anti IL 17

2.4.1.1 Brodalumab

Brodalumab is a human monoclonal antibody against the interleukin-17 receptor A. It has previously been shown to be effective in the treatment of psoriasis leading to research in psoriatic arthritis. A phase II, randomized, double-blinded, placebo-controlled study published in 2014 examined the efficacy and safety profile of Brodalumab in psoriatic arthritis[219]. 168 patients were randomized into two treatments arms (brodalumab 140mg or 280mg) and one placebo group. Patients were followed to week 12, with an open label extension up to 5 years. Primary outcome was an ACR20 response at week 12 which was seen in 37% of patients in the

140mg dose group and 39%(p=0.03) in the 280mg dose group(p=0.02). Secondary outcomes were assessed in the extension period of the trial at week 24, showing ACR20 responses continued to increase and were highest in the 280mg group than the 140mg group (64% vs 51%). ACR50 and ACR70 response rates continued to improve through to week 52 in the 140mg group.

Following this a phase 3 trial, multi-center, randomized, double-blinded, placebo-controlled study was commenced in axSpA[220]. 159 patients were randomized into placebo group or brodalumab 210mg group and given treatment at week 1, 2 then every 2 weeks up to week 16. The primary outcome was ASAS40 at week 16, which was found to be higher in the brodalumab group than placebo group (43.8% vs 24.1%, p=0.018). Change in BASDAI and BASFI scores were also noted in the treatment group, it is unknow if this was statistically significant. Adverse events rate was comparable between the two groups, no suicidal attempts or ideation was noted during the trial period, which had previously been a concern during the drug's development for psoriasis.

2.4.1.2 Netakimab

Netakimab is a humanized monoclonal antibody targeting IL-17A. Results of a phase II, randomized, placebo-controlled trial focused on safety and pharmacokinetics in patients with active radiographic axSpA. Eighty-nine patients were randomized to receive 40, 80 or 120mg of subcutaneous netakimab or placebo up to week 12. Rates of ASAS 20 response in treatment groups(40/80/120mg) were: 73%, 82%, 91% vs 43% in placebo group. No dose dependent toxicity or serious adverse events were recorded[221].

These results led to the development of the phase III, double blinded, placebo controlled, randomized ASTERA trial. This 16-week observational study evaluated the effect of netakimab on patient reported outcomes in patients with radiographic axSpA up to 16 weeks. ASAS40 response rates at week 16 were superior in netakimab group compared to placebo: 40% vs 2.6% (p<0.0001)[222]. Results also demonstrated significant improvement in BASDAI, BASFI, WPAI (work productivity and activity impairment) response as compared to placebo at week 16 (p<0.0001) [223]. Further analysis of the ASTERA patients focused on spinal and sacroiliac inflammation as seen on MRI at baseline and week 16. Significant improvements with treatment in the Berlin spine score(p<0.0001) and SPARCC score(p<0.01) were found in the netakimab group as compared to placebo[224]. Plans for an extension trial to collect data up to 52 weeks are ongoing.

2.4.1.3 Bimekizumab

Bimekizumab is a monoclonal antibody targeting both IL-17A and Il-17F. While IL-17A alone is a well-recognised pro-inflammatory cytokine which can contribute to osteoclastogenesis

and angiogenesis, it has also been shown to work synergistically with IL-17F to promote an inflammatory response[225]. IL-17F is closest in structure to IL-17A and both signal through the same heterodimeric complex of IL-17 receptors A and C[226]. While IL-17A has a stronger affinity for these receptors, IL-17F is more frequently expressed in spondyloarthritis and psoriasis[227]. Thus, dual inhibition of both IL-17A and IL-17F has been strongly suspected to provide a greater level of clinical response than inhibition of IL-17A alone[228].

Initially trialled in psoriasis, recent trials focused on axSpA. A phase IIb, randomised, double-blind, placebo-controlled, dose ranging study was done on 303 patients with active axSpA to assess efficacy and safety[229]. Primary outcome was ASAS40 dose-response relationship at week 12 which was achieved ($p<0.01$) in this study. Significantly more bimekizumab patients achieved ASAS40 at week 12 than placebo across all doses($p<0.05$). Patients in the treatment arm also had greater reductions in their BASDAI and ASDAS-CRP than placebo($p<0.001$). Similar rates of adverse events were noted in treatment group and placebo.

Following this a phase IIb, randomised, double-blind, placebo-controlled, dose ranging study was carried out to assess impact of bimekizumab on quality of life and patient reported outcomes[230] in patients with active AS. This 48-week study included 303 patients with active AS randomised into treatment and placebo groups. BASDAI 50 at week 12 was achieved by 23.7% to 47.5% of patients in the treatment group versus 11.9% in placebo. All treatment dose groups also reported greater reductions in BASDAI, BASFI, ASQoL, and patient global assessment of disease activity (PGADA) as compared to placebo at week 12. Rates of adverse events were similar in placebo and treatment groups.

While head-to-head comparison trials have not been conducted between IL-17A inhibitors and dual IL-17A and IL-17F inhibitors to date, similar response rates to both have been observed as discussed here. However further studies in dual IL-17A and IL-17F inhibition in axSpA are needed.

2.4.2 Anti IL-23

2.4.2.1 Guselkumab

Guselkumab is an IgG1 monoclonal antibody that selectively binds to the p19 subunit of IL-23, resulting in inhibition of IL-23 signaling. Phase III trials have demonstrated Guselkumab's efficacy in psoriasis, leading to the development of trials in PsA of which results were previously published for 2 phase II trials. The randomized phase II trial with guselkumab in PsA patients showed significant improvement in composite indices of disease activity at week 24 as compared to placebo[231]. The other trial was a randomized, phase II, placebo-controlled trial which showed a significant decrease of RAPID3 scores in guselkumab group at week 24 compared to placebo[232]. Further pharmacodynamic studies have also demonstrated that treatment with

guselkumab result in rapid reduction in IL17A & IL17F. IL17F changes at weeks 4 and 16 was significantly associated with ACR20 responses at week 24, while IL17A change at week 4 and 16 was associated with PASI75 response at week 24 in the guselkumab group. More recently, results of the DISCOVER 2 trial were published, which was a phase III trial of guselkumab in the treatment of biologic naïve PsA patients[233]. This demonstrated superiority of guselkumab given every 4 or 8 weeks over placebo in achieving an ACR20 response at week 24. These results are promising however, there are yet to be any studies specifically evaluating the effect of guselkumab treatment in patients with spondyloarthritis.

2.4.2.2 Tildrakizumab

Tildrakizumab is an IL-23 inhibitor with an anti-p19mAb blocking mechanism. This has been shown to be of therapeutic benefit in psoriasis, which has led to trials in both PsA and axSpA. Both studies are randomized, double blinded, placebo-controlled phase IIa studies evaluating both efficacy and safe of Tildrakizumab. The axSpA trial's primary outcome is achieving a 40% improvement in a visual analogue scale score from baseline to 24 weeks with a secondary endpoint at 52 weeks[234]. The study is now completed, with preliminary results at week 24 indicating the treatment group failed to demonstrate superiority over placebo (74% vs 84%), however the full results of this study have yet to be published.

2.4.3 JAK Inhibitors

2.4.3.1 Filgotinib

Filgotinib is an oral selective JAK 1 inhibitor that has potentially therapeutic benefits in a number of autoimmune conditions. TORTUGA was the first randomized, placebo controlled, phase 2 study to examine the efficacy of filgotinib in patients with active radiographic ankylosing spondylitis[235]. This study recruited 116 adult AS patients with an inadequate response or intolerance to NSAIDs. Patients were required to have active AS at the time of study commencement for inclusion. The treatment arm received filgotinib 200mg once daily for a total of 12 weeks. The primary endpoint of change in ASDAS from baseline to week 12 was higher in the filgotinib group (-1.47) than in the placebo arm (-0.57) with a mean difference between groups of -0.87($p<0.001$). In the filgotinib group (n=58) versus placebo the following outcomes were achieved at week 12: ASAS 20 =76% vs 40%; ASAS 40 = 38% vs 19%; ASAS partial remission 12% vs 3%. Significant improvements in ASQoL, BASDAI, BASFI, BASMI, SPARCC spine & sacroiliac joint scores were noted in treatment group as compared to placebo.

The EQUATOR Trial was a randomized, double blinded, placebo controlled, phase 2 trial investigating efficacy and safety profile of filgotinib in patients with active psoriatic arthritis[236]. Those recruited had previously failed or shown intolerance of at least one conventional DMARD

prior to study commencement. The primary endpoint was ACR20 at week 16 which was reached by 80% of the treatment group and 33% of placebo group ($p<0.001$). The filgotinib group also demonstrated significantly higher rates of achieving secondary outcomes as compared to placebo: ACR50 =48% vs 15%; ACR70 23% vs 6%. No significant difference was detected in rates of adverse events.

The United States Food and Drug Administration (FDA) raised concerns regarding testicular toxicity in assessment of safety data from filgotinib trials. Since then Gilead, the pharmaceutical company, paused clinical trials of filgotinib[237].

2.5 Unsuccessful Treatments in AxSpA

2.5.1 Abatacept

Abatacept is a CTLA-4 immunoglobulin which has been shown to selectively modulate CD80 costimulatory signal needed for full T cell activation. A phase II, prospective, open label study was done in patients with active AS[238]. Primary outcome of ASAS40 at week 24 was seen in 13% of anti-TNF naïve patients and no patients in the anti-TNF failure group, with ASAS20 achieved by only 27% and 20% in the respective groups. At week 24 no significant change was detected in BASDAI or ASDAS in either group.

2.5.2 Tocilizumab

Tocilizumab is a humanised monoclonal antibody that binds to interleukin-6 receptors. BUILDER-1 was a two part, phase II/III trial assessing tocilizumab in patients with AS naïve to anti-TNF therapy[239]. Patients were randomised into tocilizumab 8mg/kg or placebo for 12 weeks. ASAS20 response rates at week 12 were similar between treatment and placebo groups ($p=0.28$), as was ASAS40 response rates ($p=0.27$). The BUILDER-2 trial was planned to be a phase III study on patients with inadequate response to anti-TNF treatment, however this was terminated due to failure of BUILDER-1 to achieve its primary endpoint.

2.5.3 Apremilast

A phase II, double blind, placebo controlled, single centre study was conducted in patients with active r-axSpA treated with an oral phosphodiesterase 4 inhibitor, apremilast[240]. Patients in the treatment arm achieved higher improvements in BASDAI, BASFI and BASMI scores at week 12, however results were not statistically significant. The POSTURE trial was then commenced which was a phase III, multicentre, randomised, double blind, placebo controlled, parallel group study evaluating apremilast in the treatment of active r-axSpA[241]. Treatment

group failed to achieve a superior ASAS 20 response rate at week 16 over placebo and the study was terminated.

2.5.4 Ustekinumab

This humanised monoclonal antibody against the p40 subunit of IL-12 and IL-23 was used in a proof of concept study in patients with active AS[242]. Sixty five percent of patients treated achieved ASAS40 response at week 24, with 75% achieving ASAS20. Three trials of ustekinumab were developed to evaluate efficacy in axSpA[243]. Due to the failure of the first study to achieve its primary endpoint of ASAS40 response at week 24 in the treatment group, studies 2 and 3 were discontinued.

2.5.5 Risankizumab

Risankizumab is a humanised monoclonal antibody against the p19 subunit of interleukin-23. A phase II, randomised, double blind, placebo-controlled study was commenced in active AS patients[244]. Treatment groups did not demonstrate significantly higher proportions of ASAS40 response over placebo leading to trial discontinuation.

2.6 Conclusion

Significant advances have been made in the treatment of axSpA. Improved understanding of the IL-17 pathway has led to the development of several medications including Secukinumab, which has been shown to improve patient outcomes in addition to decreasing radiographic progression. Two JAK inhibitors, Tofacitinib and Upadacitinib, have also demonstrated strong efficacy in the treatment of axSpA. However, use of this medication class has been shadowed by safety concerns. Ongoing drug development is focused on the IL-17/23 pathway and JAK inhibitors at present. As the evidence for these medications grow, treatment guidelines will eventually be adjusted to reflect the changing treatment options. This increased range of therapies provides clinicians with greater opportunity to treat axSpA as effectively as possible.

Chapter 3. Characterising the Ankylosing Spondylitis Registry of Ireland (ASRI)

Publications resulting from material contained within this chapter:

S Maguire, F O'Shea. The Same but Different? An Analysis of Late Onset Axial Spondyloarthropathy. *Journal of Clinical Rheumatology (JCR).* 2022 Jan; 28(1); 294-296; DOI: 10.1097/RHU.0000000000001700

S Maguire, G Fitzgerald, P Gallagher, F O'Shea. How Advances in Treatment of Axial Spondyloarthropathy Translate to Patient Outcomes: Data from the Ankylosing Spondylitis Registry of Ireland (ASRI). *Rheumatology International*. 2022 May; 42(5): 831-838. DOI: 10.1007/s00296-021-05067-z

(Full text of publications included in Appendix A)

3.1 National Registries: What are they and why do they matter?

A clinical registry is an "organizational system that uses observational study methods to collect uniform data to evaluate specified outcomes for a population defined by a particular disease or condition that serves a predetermined scientific, clinical or policy purpose" [245]. A registry allows the capturing of a large patient population over a predetermined geographic area to assess outcomes among other objectives. The aim of a clinical registry is to fulfil the following functions[246]:

1. Identify risk factors
2. Identify at risk groups of the population
3. Compare treatment options
4. Further characterize a disease and its subtypes
5. Determine the safety and incidence of adverse events of pharmacological treatments
6. Review the quality of care provided by institutions
7. Examine the cost effectiveness of treatment

This is achieved by systematic collection of large volumes of clinical data from a large pre-defined patient population. Defining this population involves establishment of inclusion and exclusion criteria to determine suitability for enrolment. Such criteria must be balanced to capture as many patients as possible to increase the power of findings generated from this data yet discerning enough so that results are "clean" or truly reflective of the population being studied.

Registries can be designed to be prospective, retrospective or cross-sectional depending on the purpose. Data captured within a registry should be detailed, consistent in quality and should be cross-checked when possible. This data should be standardized as much as possible to enable accurate statistical analysis and decrease the risk of data misinterpretation. Depending on ethics and design of the registry, information may be obtained from patients, medical records, other physicians and laboratory results.

Participation in clinical registries should be on a voluntary basis. Prior to patient enrolment informed consent should be obtained. Registry design should be reviewed and approved by local hospital ethics boards.

Registries have been implemented in many fields of medicine including orthopaedics, oncology and rheumatology. In rheumatology a number of earlier registries captured a broad range of diagnoses which would include predefined rheumatic diseases. Disease specific registries have become more common with registries for rheumatoid arthritis[247], psoriatic

arthritis[248], vasculitis[249] and axial spondyloarthritis[250]. There are also numerous registries centred around treatment such as biologic therapies[251,252].

3.2 How Advances in Treatment of Axial Spondyloarthritis Translate to Patient Outcomes: *Data from the Ankylosing Spondylitis Registry of Ireland (ASRI)*

3.2.1 Abstract

Introduction:

The Ankylosing Spondylitis Registry of Ireland (ASRI) captures both radiographic and non-radiographic axial spondyloarthritis (axSpA) in a large, well-characterised cohort. Data collection since 2013 has created a valuable resource for studies in therapeutics and burden of disease, following a period of rapid change in the field of axSpA.

Methods:

This is a cross-sectional study of registry data on 885 patients with confirmed axSpA as per the ASAS criteria for axSpA, as diagnosed by a Rheumatologist. Analysis was performed using IBM SPSS version 26. Patients were analysed on the basis of treatment categorised as: no medication, NSAIDs, biologics or combination therapy. Statistical significance was indicated by p-value of <0.05.

Results:

Currently 885 patients are enrolled in the ASRI, made up of 72.5% (642) males and 26.9% (238) females. Most of the cohort was categorized as radiographic axSpA 78.3% (693), with 21.7% (192) meeting criteria for non-radiographic disease. Overall, 40.6% (359) reported at least one comorbidity. Older age was associated with no medications compared to those on biologic therapy (50.3 vs 45, p=0.01). Lower levels of disease activity and higher quality of life were noted in those on biologics as compared to NSAIDs alone.

Conclusion:

This analysis provides detailed epidemiological data on axSpA from a large national registry. These results detail significant differences in prescribing patterns and impact on patient outcomes in axSpA. Ongoing development of registries provides a valuable insight into the real-world effects of axSpA.

3.2.2 Background

The Ankylosing Spondylitis Registry of Ireland (ASRI) was launched in 2013 as one of the first national registries for patients with rheumatic diseases in Ireland. The ASRI was developed primarily to characterise axSpA in a large homogenous population to allow characterisation of burden of disease, as well as determination of factors associated with poor outcomes. This was achieved by documentation of disease manifestations, prevalence of extra-articular manifestations (EAMs), medication usage, comorbidities, and detailed recording of disease activity via validated outcome measures.

The interval during which the ASRI has been collecting data follows a period of significant evolution of the field of axSpA. The concept of non-radiographic axSpA (nr-axSpA) was first included in the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA in 2009[2]. The expansion of classification criteria to recognise both nr-axSpA and radiographic axSpA (r-axSpA), previously called ankylosing spondylitis (AS), marked a considerable shift from more traditional phenotypes as captured by the modified New York criteria[253]. This triggered a period of re-evaluation of axSpA as a whole, as well as numerous comparative analyses of r-axSpA and nr-axSpA[254].

Another major area of change in axSpA is treatment, which is an area of significant advancement over the past two decades[255]. Previously limited to non-steroidal anti-inflammatories (NSAIDs) and corticosteroids, therapeutic options now include synthetic disease modifying anti-rheumatic drugs (sDMARDs) and biologics[256]. Biologic agents in particular have revolutionized management of axSpA leading to dramatic improvements of patient outcomes, quality of life and level of functional ability when commenced in the early stages of disease[257].

The data collected in the ASRI over the past eight years offers the opportunity to understand how these advances in axSpA have affected patient outcomes in a real-life cohort. The aim of this paper is to perform focused analysis on this large, well-characterized axSpA cohort to provide insight into patient outcomes. Specific analysis will focus on patterns of medication usage and burden of comorbidities in axSpA.

3.2.3 Methods

3.2.3.1 Patient population

Data for this analysis was captured via the Ankylosing Spondylitis Registry of Ireland (ASRI), a rich source of epidemiological data on axSpA in Ireland. This large national registry recruited patients from 12 Rheumatology centres, representing all major geographic regions of the country. Since being launched in 2013, 886 patients have been enrolled in the ASRI with recruitment ongoing in multiple centres. Our study included all participants with employment data enrolled in the ASRI since time of inception.

To be considered for enrolment in the ASRI participants were required to meet several inclusion criteria. All participants were diagnosed with axSpA by a Rheumatologist and meet the Assessment of Spondyloarthritis International Society (ASAS) criteria for axSpA at the time of enrolment. This allowed data collection on both radiographic and non-radiographic axSpA. In addition, all participants were over the age of 18 years, had full capacity and were fluent in English. All eligibility criteria were required at the time of enrolment in order to be included in the ASRI.

Written informed consent was obtained from each patient prior to enrolment. The consent process included discussion of the purpose of data collection, data protection and publication of studies using data from the ASRI. Patients were informed of their right to withdraw their data from the ASRI at any time and encouraged to discuss questions or concerns with the investigator prior to signing the consent declaration. Ethical approval was received from local hospital ethic boards at each site which contributed patients to the ASRI (appendix D). Each participating centre had a designated trained investigator who was responsible for local oversight.

3.2.3.2 Data Collection

Participation in the ASRI involved each participant attending a single clinical visit which was conducted by a trained investigator. This allowed for all data to be captured at a single time point. During the course of this visit patients completed a series of self-administered questionnaires including: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Function Index (BASFI), Ankylosing Spondylitis Quality of Life scale (ASQoL) and the Hospital Assessment Questionnaire (HAQ). All responses were recorded as numerical responses within a visual analogue scale with higher scores indicating greater severity or restriction. A clinical interview gathered details of time to diagnosis, symptom onset and family history. Medical records were reviewed for data on imaging, serology, treatment and disease manifestations.

For the analysis on medication exposure, participants were analysed on the basis of pharmacotherapy at any time specifically for axSpA. Treatment groups were defined as: no medication, NSAIDs, biologics and combination therapy. However, data regarding NSAIDs use only captured current use (including both regular and as needed dosing). As such, those in the "no medication" group may have previously been treated with NSAIDs but were not using any pharmacotherapy at the time of enrolment in the ASRI.

A focused clinical examination included capture of metrics to calculate a spinal mobility score including: tragus wall distance, chest expansion, cervical rotation, lateral lumbar flexion, modified Schober's test and intermalleolar distance.

Data was collected and recorded into an electronic database using pseudo-anonymisation of patient information. All data was stored in compliance with national GDPR legislation.

3.2.3.3 Outcome measures

The following validated outcome measures were collected:

- Bath AS Disease Activity Index (BASDAI)[115] – PRO assessing disease activity on a scale of 0-10
- Bath AS Functional Index (BASFI)[120] – PRO assessing functional status on a scale of 0-10
- Bath AS Metrology Index (BASMI)[124] – assesses spinal mobility on a scale of 0-10
- AS Quality of Life (ASQoL) score[127] – PRO assessing quality of life with a series of yes/no questions generating a total score of 0-18
- Health Assessment Questionnaire (HAQ)[131] – PRO assessing disability on a scale of 0-3.

3.2.3.4 Statistical Analysis

The data was analysed using IBM SPSS version 26. Categorical variables were documented as percentages with associated frequency counts. Normally distributed continuous variables were expressed as means with standard deviations (SD), while non-normally distributed continuous variables were expressed as a median with 25^{th} and 75^{th} centiles. Normality was assessed with a Shapiro-Wilk test of normality with $p>0.05$ indicating assumption of normality has not been violated. For medication exposure analysis patients were divided into four groups according to exposure to medications at any point in the disease course: (1) no treatment, (2) NSAIDs only, (3) biologics only (4) biologics and NSAIDs combined.

Analysis of medications and smoking status was carried out with a one-way analysis of variance (ANOVA) to test for statistical significance between groups. For continuous variables, differences between groups were tested for significance using an independent two tailed t-test. A chi^2 test for independence test for significance in categorical variables. A p-value of <0.05 was deemed significant.

3.2.4 Results

3.2.4.1 Baseline Demographics

At the time of analysis, 885 patients were currently enrolled in the ASRI composed of 72.5% (642) males and 26.9% (238) females. Average age of participants was 45.8 years [standard deviation (SD) 12.6; range 18-85] with median disease duration of 17.1 years (10, 28) (Table 3.1). The majority of the population enrolled in the ASRI was Caucasian (92.4%). Mean scores at time of entry were: BASDAI 4.0 (SD 2.4), BASFI 3.7 (SD 2.9), HAQ 0.53 (SD 0.52), ASQoL 6.5 (SD 5.5) and BASMI 4.0 (SD 2.1).

Most (78.3%, n=693) of the population consisted of r-axSpA, with 21.7% (192) meeting criteria for nr-axSpA. Of the available results, 90% were HLA-B27 positive.

Peripheral arthritis was seen in 30.3% (268), enthesitis in 17.3% (153), and dactylitis in 6.3% (56). A significant burden of extra-articular manifestations (EAMs) was recorded in this population with psoriasis in 16.5% (146), inflammatory bowel disease in 10.4% (92) and uveitis in 34.1% (302).

Table 3.1: Baseline characteristics of the ASRI population

	n = 885	%
Age *	45.8 (12.6)	
Disease duration	17.1 (10, 28)	
Age at symptom onset	23.9 (19, 32)	
Delay to diagnosis	5 (2, 12)	
Caucasian	819	92.4%
HLA B27+	610 (of 678 results)	90.0%
Male	642	72.5%
Female	238	26.9%
Enthesitis	153	17.3%
Arthritis	268	30.3%
Dactylitis	56	6.3%
Radiographic Sacroiliitis	693	78.3%
MRI sacroiliitis	398	45.0%
Extra-articular Manifestations:		
Uveitis	302	34.1%
Psoriasis	146	16.5%
Colitis	92	10.4%
Comorbidities:		
Ischaemic Heart Disease	33	3.7%
Cerebrovascular disease	14	1.6%
Hypertension	191	21.6%
Hyperlipidaemia	140	15.8%
Type II Diabetes	46	5.2%
Peptic Ulcer	55	6.2%
Tuberculosis	31	3.5%
Chronic Lung Disease	9	1.0%
Osteoporosis	46	5.2%
Depression	90	10.2%
Cancer	33	3.7%
Joint replacement surgery	33	3.7%
Spinal corrective surgery	11	1.2%

** Expressed in years as mean (standard deviation) or median (25th centile, 75th centile) as appropriate*

There was a high prevalence of comorbidities with 40.6% (359) recorded as having at least one comorbidity. Hypertension, hyperlipidaemia and depression were the most commonly reported comorbidities in this cohort (Table 3.1). These were also the most prevalent comorbidities in AxSpA patients with peripheral disease although hypertension (27% vs 19.4%, $p<0.01$) and hyperlipemia (19.5% vs 14.5%, $p<0.01$) were significantly more prevalent than in patients with axial disease alone. No other differences were noted in prevalence of comorbidities between participants with axial disease or those axial with peripheral involvement.

Alcohol consumption was reported in 71.4% (632) with mean consumption of 9.9 units per week over a mean duration of 22.1 years. Overall, 28.5% (252) of patients were current smokers with 28.4% (251) of patients identifying as ex-smokers. Mean pack year history was 13.4 for current smokers and 14.7 for ex-smokers. Current smokers were significantly younger than both non-smokers and ex-smokers (43.0 vs 45.1 vs 50.1, p<0.01).

3.2.4.2 Medication Exposure

Data on medication exposure was recorded in 882 participants. Treatment groups consisted of 10.7% (94) receiving no medication, 21.2% (187) NSAIDs only, 37.9% (334) biologics only and 31.2% (272) treated with both NSAIDs and biologics. Of note, the participants in the no medication group had no exposure to biologic agents. These patients were significantly older than either those on NSAIDs, biologics or combination therapy (50.3 vs 46.0 vs 45.0 vs 45.9, p=0.01).

Patients on NSAIDs were older at symptom onset than those on biologic therapy alone (28.1 vs 25.9, p<0.01) (Table 3.2). The cohort receiving no medication had the highest proportion of males at 80.9% compared to only 67.3% in the NSAID treatment group; this difference did not reach significance (p=0.16). However, the difference in prevalence of radiographic disease between these two groups was statistically significant (80% vs 68%, p<0.01).

Table 3.2: Baseline Demographics by Treatment Categories

	No Medication	**NSAIDs**	**Biologics**	**Combination Therapy**	***p value***
n	94	187	334	272	
Age*	50.3 (14)	46 (13.8)	45 (12.4)	45.9 (11.3)	***0.01***
Symptom onset	28.6 (11.6)	28.1 (12)	25.9 (9.9)	25.4 (9.8)	***0.01***
Disease duration	21.7 (15.1)	17.9 (13.2)	19.1 (11.7)	20 (11.3)	*0.10*
Delay to dx	9.49 (11.4)	8.72 (8.3)	7.34 (7.6)	7.65 (7.4)	*0.08*
Caucasian	88.3% (83)	87.7% (164)	91.6% (306)	89.7% (244)	*0.33*
Males	80.9% (76)	67.3% (126)	73.4% (245)	71.7% (195)	*0.16*
Females	19.1% (18)	31.6% (59)	26.6% (89)	26.1% (71)	*0.16*
HLA-B27+	84.8% *(56 of 66 results)*	84.8% *(128 of 151 results)*	91.8% *(223 of 243 results)*	90.0% *(198 of 220 results)*	*0.10*
r-axSpA	80.0% (75)	68.0% (127)	73.1% (244)	81.6% (222)	***<0.01***

Abbreviations: *NSAIDs -nonsteroidal anti-inflammatory drugs, Dx -diagnosis, HLA-B27 -human leukocyte antigen B27, r-axSpA -radiographic axial spondyloarthritis*
**Continuous variables expressed as means (standard deviation). Categorial variables expressed as %(n)*

Difference in BASDAI scores was significant between all groups, with patients on both biologics and NSAIDs noted to have the highest mean BASDAI while those on no medication had the lowest mean BASDAI (4.8 vs 3.4, p=0.01) (Table 3.3). However, patients on no medication

recorded significantly worse mean BASMI scores compared to those on NSAIDs (4.5 vs 3.7, p<0.01). Patients on biologics alone reported significantly better BASFI (3.2 vs 4.3, p<0.01), HAQ (0.42 vs 0.66, p<0.01) and ASQoL (5.2 vs 8.3, p<0.01) than those on combination therapy with biologics and NSAIDs.

Further analysis focused on patients on monotherapy with biologics alone or NSAIDs alone. Compared to those on NSAIDs, patients on biologics reported better BASDAI (3.4 vs 4.2, p=0.01), HAQ (0.42 vs 0.54, p<0.01) and ASQoL scores (5.2 vs 6.6, p<0.01).

Table 3.3: Breakdown of analysis of variance (ANOVA) on outcome measures. Treatment categories with statistically significant variation listed below each heading.

	No Medication	NSAIDs	Biologics	Combination Therapy	*p value*
BASDAI	**3.4**	**4.2**	**3.4**	**4.8**	***0.01***
	3.4	4.2			
	3.4			4.8	
		4.2	3.4		
			3.4	4.8	
BASFI	**3.3**	**3.8**	**3.2**	**4.3**	***<0.01***
	3.3			4.3	
			3.2	4.3	
HAQ	**0.47**	**0.54**	**0.42**	**0.66**	***<0.01***
	0.47			0.66	
			0.42	0.66	
ASQoL	**5.6**	**6.6**	**5.2**	**8.3**	***<0.01***
	5.6			8.3	
		6.6	5.2		
		6.6		8.3	
			5.2	8.3	
BASMI	**4.5**	**3.7**	**3.9**	**4.3**	***<0.01***
	4.5	3.7			

Abbreviations: *BASDAI -Bath Ankylosing Spondylitis Disease Activity Index; BASFI -Bath Ankylosing Spondylitis Functional Index; HAQ -Health Assessment Questionnaire; ASQoL -Ankylosing Spondylitis Quality of Life score; BASMI -Bath Ankylosing Spondylitis Metrology Index*

The majority of patients (97.6%, 326) in the ASRI on biologic agents were treated with TNF inhibitors, which was the first class of biologic agents approved for use in axSpA. Low numbers of participants on alternative biologic therapies prevented further subgroup analysis. Those with active disease (defined by BASDAI >4) averaged a higher mean number of previous biologics compared to those with inactive disease (1.09 vs 0.85, p=0.04).

3.2.5 Discussion

This is a large, well characterized cohort of patients with axSpA captured via a national registry following a period of significant change in the field of axSpA. The population within the ASRI was predominantly Caucasian, with a high prevalence of HLA-B27 positivity. Uveitis was the most commonly encountered EAM noted in 34.1%, while peripheral arthritis the most common articular manifestation reported in 30.3%. These findings are consistent with data from other national axSpA registries[258,259,47]. Although males made up a significant proportion of the cohort, 26.9% of the axSpA patients were female with a sex distribution of males to females of 3:1 in this population. In addition, 21.7% of patients overall met criteria for nr-axSpA as per the ASAS criteria for axSpA. The recognition of nr-axSpA is a significant contributor to the change in sex distribution, due to a higher prevalence of nr-axSpA in females[260]. AxSpA was previously thought to be a predominantly male disease with historical male to female ratios as high as 10:1[261] with more recent studies reporting this ratio to be close to 2-3:1[262]. Ongoing data collection via national registries, such as the ASRI, offers a unique opportunity to track the changing epidemiology of axSpA as the nonradiographic disease gains greater recognition.

The mean delay in diagnosis in the ASRI was 7.98 years, with an average age of symptom onset of 26.4 years. Other international cohorts have also reported similar results with a delay of 8.5 years in the United Kingdom[263], 4.9 years in France[264] and a mean time of 6.7 years from a systematic review on 64 axSpA studies[265]. This delay remains a particularly concerning result given the advancements in diagnostic imaging and recognition of the impact of early treatment initiation[266]. This is a challenge to axSpA management worldwide due to the increased risk of radiographic damage and disability associated with prolonged periods of uncontrolled inflammation[267,268]. Public health initiatives to increase clinician and public awareness of axSpA could aid in closing the gap between symptom onset and diagnosis.

The population in the ASRI reported a high prevalence of a number of comorbidities, with over 40% recording at least one comorbidity. Interestingly the most commonly reported comorbidities were hypertension (21.6%) and hyperlipidaemia (15.8%) with ischaemic heart disease reported in only 3.7% of the cohort. The low prevalence of ischaemic heart disease may reflect the relatively young mean age of the ASRI, but the high frequency of hypertension and hyperlipidaemia would be concerning for development of cardiovascular disease in the future. Studies on hypertension in axSpA have shown a higher prevalence in axSpA patients is independent of NSAID exposure[269]. Presence of comorbidities in axSpA has been associated with worse patient outcomes[270] and poorer response to treatment[271]. The presence of axSpA and one additional comorbidity causes the patient to be classified as multimorbid thus increasing the complexity of patient care, demand on healthcare resources and mortality risk[272,273].

Given the burden of comorbidities in this population, further analysis examined modifiable risk factors including smoking and alcohol consumption. A notable proportion of the cohort were either current smokers (28.5%) or ex-smokers (28.4%), with both groups reporting high mean pack year histories of 13.4 and 14.7 respectively. A similar prevalence of smoking has previously been reported in other international axSpA cohorts including 24% in the British Society of Rheumatology (BSR) biologics registry and 23% in the ASAS Comorbidities in Spondyloarthritis (COMOSPA) study[274,275]. In the short-term, smoking is concerning in axSpA due to association with poorer response to treatment and higher odds of persistent disease activity, resulting in increased prevalence of radiographic progression in the long-term[271]. Further research in this area has discovered that smokers are more likely to be employed in manual labour suggesting that mechanical strain could also be a factor in the observed outcomes[276]. Lastly, current smokers were significantly younger than the rest of the population suggesting a concerning social trend towards higher prevalence of smoking in younger patients. Given this information and the considerable associated risks of smoking in axSpA, smoking cessation must be actively encouraged in this population. Public health campaigns on smoking should be aimed at teenagers and young adults to advocate for tobacco avoidance from an early age.

The medication analysis illustrates how the identification and treatment of axSpA has evolved. The no-medication group was made up of patients who had never been on biologic therapy and were not taking NSAIDs at the time of enrolment. This cohort has the oldest average age and disease duration of all cohorts and is noted to have a number of characteristics typical of the more classical concept of ankylosing spondylitis (AS). This includes a high male to female ratio, the longest delay to diagnosis and the worst spinal structural damage as reflected by BASMI. Delay in diagnosis and lack of treatment have previously been shown to be associated with worse outcomes in axSpA[277,278], thus the emphasis on prompt recognition of symptoms in current guidelines and public health campaigns to improve time to diagnosis in axSpA[256,279]. An unexpected finding in this cohort was the low BASDAI scores, indicating a low level of disease activity similar to that observed in the biologic therapy cohort. This likely reflects disease which has burnt out and is no longer active. The severe residual restriction of spinal mobility in this cohort clearly illustrates the need for treatment in axSpA.

Since the development of biologic therapies for the management of axSpA, use has rapidly expanded due to their significant clinical benefit, reassuring safety profile and ease of use[280]. During this time the Assessment of Spondyloarthritis International Society (ASAS) released new classification criteria which introduced the concept of axSpA[2]. These changes are noted in the demographics of the biologic treatment cohort especially the shift in the sex distribution with a higher proportion of females affected. Despite averaging a similar disease

duration to those on no medication, the biologic group had a shorter delay to diagnosis. This means not only are these patients being identified earlier in their disease course, but they are also being promptly commenced on disease modifying treatment at an early stage. This is reflected in their patient outcomes which are on average among the lowest of all treatment categories. The benefits of biologic therapies in treatment of axSpA have been demonstrated in numerous clinical trials. However, the results presented here reflect the real-world experience of biologic agents in the management of axSpA.

Until the early 2000s, effective treatment options for axSpA were limited to NSAIDs. This medication class remains first line therapy in axSpA as per current American College of Rheumatology (ACR) and Spondyloarthritis Research and Treatment Network (SPARTAN) treatment guidelines[256]. Treatment in combination with physiotherapy and exercise can provide significant improvement in disease activity, quality of life and functional ability[154]. However, use of NSAIDs must be considered and limited where possible due to associated risks of chronic renal impairment and cardiovascular disease with long term use[281,282]. In patients with ongoing disease activity despite regular NSAID use, escalation of treatment to a biologic is required. The shorter disease duration noted in the NSAID cohort of the ASRI likely reflects patients at an earlier stage of their disease. Review of patient outcome scores reveal a higher level of disease activity, despite having the least limitation of spinal mobility overall. These results clearly depict the need for biologic therapy in axSpA, as if left untreated the persistent disease activity will eventually lead to further structural damage reflected in worsening BASMI scores over time.

Lastly, worse overall outcomes were noted in those on combination therapy, suggesting more resistant disease with suboptimal control thus the requirement for additional therapy. Unlike other forms of inflammatory arthritis, options for biologic therapies in axSpA remain limited. Currently available biologic therapies have resulted in improved disease control for many but not all axSpA patients, hence the need for ongoing research for alternative therapeutic options.

Further development of the ASRI has the potential to offer a number of insights into burden of disease and medication retention rates in axSpA as understanding of this complex disease continues to evolve. Eventually this information could be used to identify patients at high risk of persistent disease activity, medication failure and disability.

Limitations

Data on NSAID exposure was only available in terms of current use, however as NSAIDs are first line pharmacotherapy for axSpA and are commonly used analgesic agents the majority of patients with axSpA will have been exposed to this class of medication during the course of their disease. The ASRI is currently cross-sectional in design with patient data captured from a single clinical visit and chart review at the time. Plans are in place for development of longitudinal data in the form of structured clinical visits. This will allow the ASRI to capture the full effect of recent changes in classification and management of axSpA.

While there is a large volume of data captured within the ASRI for each patient, information on certain areas is limited. One example is data regarding current level of physical activity. Currently an abbreviated version of the International Physical Activity Questionnaire collects this information via four questions regarding frequency of stretching as well as vigorous, moderate or light physical activity on a weekly basis. While informative, this information does not provide insight into specific type of physical activity or duration. Similarly, for employment data information regarding employment status is captured however occupation type was not which precluded comparison analyses on this basis. One final limitation is the lack of data on overall socioeconomic status. These limitations were recognised during the following analyses of the ASRI and will be used to further improve the registry for future data collection.

3.2.6 Conclusion

The ASRI is a valuable source of epidemiological data on patients with axSpA. Analysis demonstrated a high prevalence of radiographic axSpA, with an overall male to female ratio of 3:1. Despite advances in diagnostic imaging axSpA patients continue to face a considerable delay in diagnosis. In addition, these patients reported a high burden of comorbidities with 40.6% reporting at least one comorbidity. Prevalence of smoking was high, with current smokers significantly younger than the rest of the cohort. Patients not on treatment were older, with longer duration of symptoms representing a cohort with established disease. Treatment with a biologic agent was associated with lower disease activity and improved quality of life compared to treatment with NSAIDs alone. Monitoring of axSpA patients diagnosed in the period following recent advancements in axSpA will demonstrate the full impact of these changes on patient outcomes. The ongoing development of registry data provides valuable insight into the real-world effects of axSpA.

3.3 The Same but Different? Analysis of Late Onset Axial Spondyloarthritis

3.3.1 Abstract

Objective

To examine late onset axial spondyloarthritis (axSpA) in a large well characterized cohort.

Methods

Patient registered in Ankylosing Spondylitis Registry of Ireland (ASRI) were analysed on the basis of age of symptom onset. Patients were divided into two groups with an age over 45 years old at symptoms onset categorized at late onset (LO). Outcome measures were compared between groups. Differences in incidence of HLA-B27, patterns of disease, imaging, extra-articular manifestations and medication usage was also tested for significance.

Results

In total 851 patients were included in the analysis with 6.3% (54) patients categorized as LO axSpA. Both groups had similar gender distribution, patterns of disease and rates of EAMs but a significant difference in age of symptom onset and delay to diagnosis. Patients with LO disease were found to have significantly higher BASFI, HAQ and ASQoL scores than typical onset disease. There is a trend towards worse BASDAI and BASMI scores in late onset axSpA, but this did not reach significance. LO patients had lower rates of biologic treatment use (50% vs 72%, $P<0.01$) with a trend toward higher rate of NSAID use (61.1% vs 54.2%, $p=0.2$).

Conclusion

Late onset disease occurs in up to 6.3% of patients with axSpA. These patients have similar patterns of disease and radiological findings consistent with classification criteria for axSpA. Despite having worse functional outcomes, patients have lower rates of biologic therapy treatment. Further research is needed to better understand and manage this cohort of axSpA patients.

3.3.2 Background

Axial spondyloarthritis (axSpA) has long been described as presenting in the third decade of life with the onset rarely occurring over the age of 45 years old[158]. Previous research[283-287] has shown there are a number of patients developing axSpA later in life. However, these studies have been limited to small numbers limiting the ability to detect patterns in disease.

Age of onset in axSpA has been examined in the setting of juvenile onset ankylosing spondylitis (JoAS) with studies showing JoAS presenting with different patterns of disease, although data on functional outcomes was divergent[288-290]. A period of extensive research on this topic culminated in a systematic review which confirmed variations in clinical presentation by age of onset and called for further research into genetics to better understand this variation in age of onset[291]. Currently JoAS is considered a subtype of axSpA with treatments pathways similar to those used in adults.

First described in a case series of ten patients in 1989[292], late onset axSpA has been slow to inspire further research. Calin et al published a letter to the editor in 1991 discussing a cohort of axSpA patients who developed the disease after the age of 35, highlighting the need for further research to better identify and treat such patients[287]. This study had a mean age of 38.7 years for late onset axSpA, which would meet current ASAS classification criteria for inflammatory back pain[42] and are not typical of patients with late onset axSpA in the current literature. However, this article highlighted that axSpA could develop later in life and the need to better identify and understand this subset of patients.

Large national registries, such as the ASRI, are an opportunity to further study this disease subtype in large numbers with greater power to detect differences between late and typical onset. The aim of this study was to examine prevalence and clinical characteristics of late onset axSpA in a large well characterized patient population.

3.3.3 Methods

Patients registered in ASRI were analysed on the basis of age of symptom onset using IBM SPSS version 26. Patients were divided into two groups with an age over 45 years at symptoms onset categorized at late onset. Mean BASMI, BASFI, BASDAI, HAQ, and ASQoL scores were compared between the two groups and tested for statistical significance using an independent two tailed t-test. Further analysis of differences in gender, HLA B27 status, imaging, medication use, and extra-articular manifestations (EAMs) was also performed using a chi-squared test for independence.

3.3.4 Results

A total of 851 patients with axSpA were included in the analysis, composed of 77.4% (659) males, 22.6%(192) females, mean age of 45.8 years [SD 12.6, range 18-85] and mean disease duration of 19.4 years (SD 12). Mean scores for patients of the ASRI were: ASQoL 6.5 (95% CI 6.1-6.7), HAQ 0.54 (95% CI 0.49-0.57), BASDAI 4.0 (95% CI 3.9-4.2), BASFI 3.7 (95% CI 3.5-3.9), and BASMI 4.0 (95% CI 3.9-4.2). Patient population was 93.7% (797) patients categorized as typical onset, while 6.3% (54) patients categorized as late onset (table 3.4). Difference in age of symptom onset between categories was significant (50.8 vs 22.8, 95% CI 25.8-30.4, $p<0.01$).

Table 3.4: Characteristics of Typical vs Late Onset axSpA Patients

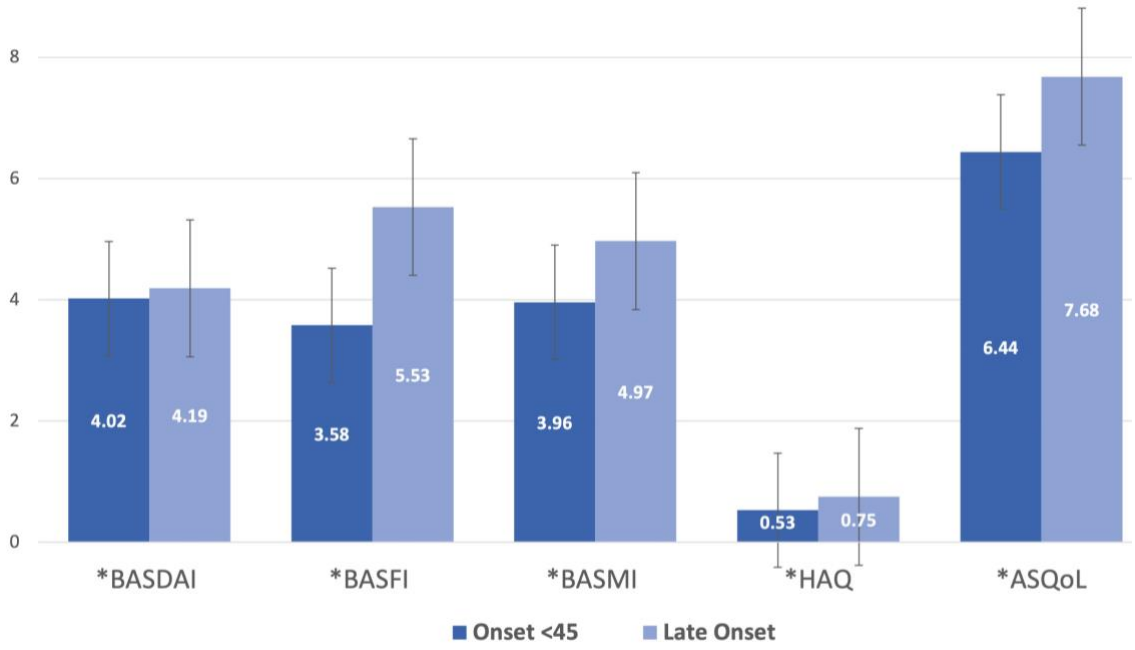
	Onset < 45 years (n=797)	Late Onset (n=54)	*p value*
Males (n=659)	77% (614)	83% (45)	0.19
Females (n=192)	23% (183)	16.6% (9)	
Age	44.6 (12)	62.9 (7.8)	**<0.01**
Age at symptom onset	22.8 (18, 30)	50.8 (48, 56)	**<0.01**
Delay to diagnosis (years)	6.0 (2, 12)	2.0 (1, 4)	**<0.01**
Disease duration (years)	17.8 (10, 29)	8.1 (5, 15)	**<0.01**
Caucasian	95% (758)	100% (54)	0.83
HLA-B27+ (n=580)	90.5% (554)	76.5% (26)	**<0.01**
Patterns of Disease			
Enthesitis (n=146)	16.9% (135)	20.4% (11)	0.45
Dactylitis (n=54)	6% (48)	11.1% (6)	0.21
Arthritis (n=256)	29.7% (237)	35.2% (19)	0.4
Imaging			
Radiographic sacroiliitis (n=668)	79% (628)	74% (40)	0.07
MRI Sacroiliitis (n=384)	45.3% (361)	42.6% (23)	0.69
EAMs			
Uveitis	28.5% (227)	24.1% (13)	0.07
IBD	9.9% (79)	14.8% (8)	0.32
Psoriasis	16.4% (131)	18.5% (10)	0.54
BASDAI	4.0 (2.5)	4.2 (2.2)	0.6
BASFI	3.6 (2.9)	5.5 (2.3)	**<0.01**
BASMI	4.0 (2.1)	5.0 (1.9)	0.12
HAQ	0.53 (0.5)	0.75 (0.6)	**<0.01**
ASQoL	6.4 (5.6)	7.7 (5.6)	**<0.01**
Treatment			
Biologics	69.1% (551)	48.1% (26)	**<0.01**
NSAIDs	54.2% (432)	61.1% (33)	0.2
Lifestyle Factors			
Smoker *(past & current)*	57.3% (457)	64.8% (35)	**0.01**
Alcohol consumption *(past & current)*	82% (654)	75.9% (41)	0.53

Abbreviations: *HLA-B27 -Human Leukocyte Antigen B 27, MRI -Magnetic Resonance Imaging, EAMs -extra articular manifestations, IBD -Inflammatory Bowel Disease, BASDAI -Bath Ankylosing Spondylitis Disease Activity Index, BASFI -Bath Ankylosing Spondylitis Functional Index, BASMI -Bath Ankylosing Spondylitis Metrology Index, HAQ -Hospital Assessment Questionnaire, ASQoL -Ankylosing Spondylitis Quality of Life questionnaire, NSAIDs -Non-Steroidal Anti-Inflammatory Drugs, CRP -C Reactive Protein, ESR -Erythrocyte Sedimentation Rate*

**Continuous variables expressed as means (standard deviation) or median (25th centile, 75th centile); Categorial variables expressed as %(n)*

Late onset patients had a shorter delay to diagnosis (2.0 vs 6.0 years, 95% CI -5.8 to -2.2, p<0.01) and disease duration (8.1 vs 17.8 years, 95% CI -13.2 to -6.6, p<0.01) than typical onset axSpA. Late onset axSpA patients were noted to have significantly higher mean BASFI (5.5 vs 3.6, 95% CI 1.1 to 2.7, p<0.01), HAQ (0.75 vs 0.53, 95% CI 0.1 to 0.4, p<0.01) and ASQoL scores (7.7 vs 6.4, 95% CI -0.3 to 2.8, p<0.01) (figure 3.1). They also had higher mean BASDAI (4.2 vs 4.0, 95% CI -0.5 to 0.8, p=0.6) and BASMI (5.0 vs 4.0, 95% CI 0.4 to 1.7, p=0.12) but this did not reach significance. Late onset patients had lower rates of HLA-B27 positivity (76.5% vs 91.2%, p<0.01).

Figure 3.1: Outcome Measures by Age of Symptom Onset, * indicates statistical significance at the level of p<0.01



No difference was detected between groups regarding gender distribution, ethnicity, patterns of disease, rates of EAMs, imaging or inflammatory markers. Late onset patients had higher rates of smoking (64.8% vs 57.3%, p=0.01) but similar rates of alcohol exposure (75.9% vs 82%, p=0.53).

The late onset axSpA patients had lower rates of biologic therapy use (50% vs 72%, p<0.01). They had a trend towards increased rate of NSAID usage (61.1% vs 54.2%, p=0.2) which was not significant.

3.3.5 Discussion

This analysis shows that late onset axSpA occurs in up to 6.3% of patients with axSpA, and the difference in the age of onset between typical axSpA and late axSpA is significant. Patients with late onset disease were noted to have similar patterns of disease, EAMs and radiological findings consistent with current classification criteria for axSpA. Less patients with late onset disease were HLA-B27 positive, the reason for this is unknown. The LO patients have worse mean functional outcomes, which could reflect the older age of symptom onset.

This study represents one of the largest cohorts of late onset axSpA published to date with 52 patients. Limited data has been previously presented on larger cohorts of up to 227 patients[293], but no full text publication is currently available for review. This detailed analysis of patterns of disease, radiological findings, EAMs and medication usage in late onset axSpA provides an insight for physicians managing this disease in clinical practice. The size of this cohort provides the power necessary for statistical significance to be detected between groups.

It is notable that patients with late onset axSpA in this study were treated less frequently with biologic agents and have a slightly higher rate of NSAID usage than patients with typical onset disease. Although the NSAID use differences did not reach significance, it is concerning that an older patient population would be using NSAIDs more often given the increased risk of cardiovascular and renal disease with age. The significantly lower rate of biologic use in the late onset patients is also interesting. EULAR guidelines on treatment of axSpA from 2016 recommend that biologic therapy should be considered in patients with active disease despite treatment[189]. Patients with late onset axSpA have worse mean functional outcomes with a trend towards increased disease activity, so why are they using biologic treatments less? Are they less likely to be offered this treatment? Or are they less suitable for such treatment? Do these patients prefer to not be on a biologic treatment? And if so, why? These questions are just a start to what needs to be examined to better understand variation in medication use in late onset axSpA.

Published literature on late onset axSpA, although limited was previously discussed in the form case series or case reports. Since 2012 this topic has received greater recognition with a number of countries publishing their experience with this cohort. The incidence of late onset axSpA of 6.3% in our axSpA patients is lower than that found in two Turkish studies 7.9% and 8.9%[285,293], and 9.7% in one Brazilian study[283]. Lower rates of 3.5% were reported in cohorts in Spain[286] and Taiwan[284].

Geographic variation should be considered when discussing these studies, given the known variation in HLA-B27 prevalence. Both Turkish studies found lower rates of HLA-B27 positivity in patients with late onset axSpA compared to typical onset, similar to findings of this study. Chen et al examined this in more detail, comparing rates of HLA-B27 positivity in juvenile,

adult and late onset axSpA and found higher rates of HLA-B27 to be associated with younger age of onset. The role of HLA-B27 in late onset axSpA has received limited discussion to date. Certain subtypes of HLA-B27 have been shown to be associated with older age at symptom onset[294], however the reason for this is unknown. Another possible genetic link with age of onset was proposed by Brophy et al who hypothesized age of onset is unrelated to the genetic susceptibility load as JoAS does not lead to worse outcomes[295]. They hypothesised that onset of symptoms could be related to timing of contact with an environmental trigger in a susceptible individual. Research is ongoing, but this hypothesis is yet to be validated.

Of the published data, outcomes in this cohort are conflicting. Chen et al and Montilla et al reported no difference in clinical or functional outcomes, while Bendahan et al reported higher disease activity and worse functional outcomes. Three studies[283,285,293] noted late onset patients had higher rates of sDMARD use and in two studies[293,283] higher rates of glucocorticoid use.

There are a number of possible contributing factors for these outcome variances. There is currently no clear definition of late onset axSpA, with studies independently defining what age qualifies as late onset. Of the studies discussed criteria for late onset ranges from over 40 to over 55 years of age at symptom onset, which could contribute to the variations in incidence noted. Establishment of criteria to define late onset disease would lead to more uniform populations for comparison. Limited cohort size is another issue, as this study is the first full publication with over 50 patients. Large registries from multiple countries would offer the opportunity to pool data to properly analyse late onset axSpA.

3.3.6 Conclusion

Late onset axSpA is a subtype of axSpA that is poorly understood but requires increased discussion. Additional registry studies into this subgroup would help to understand variations in medication usage and prescribing practices. Establishing criteria for late onset axSpA would lead to improved identification of these patients and allow for pooling of data from large national registries.

3.4 Summary of Findings

This chapter has outlined the need for clinical registries and the wealth of information that they can provide. Since inception in 2013, the ASRI has proven to be a valuable source of epidemiological data on axSpA in Ireland. This has provided valuable insights into patterns of disease, comorbidities, and medication usage. The large size of the ASRI has also created a prime opportunity to study and describe late onset axSpA, a less common subtype of axSpA.

As discussed in Chapter 2, the treatment of axSpA is evolving quickly with new classes of therapies approved for use in axSpA in recent years. The ongoing recruitment within the ASRI has created a prime opportunity to demonstrate changes in patient outcomes during this time of rapid treatment advancement. Continuous growth and development of the ASRI is ongoing, with plans to convert to longitudinal data in the near future. Careful maintenance of this resource will allow for further clinical research and improvements in clinical practice for Rheumatologists and patients with axSpA.

The following chapter focuses specifically on two issues which have been previously highlighted to be highly prevalent in patients with axSpA: unemployment and depression. This chapter will delve deeper into the data presented in the previous analyses to examine the impact of these issues for patients with axSpA.

Chapter 4. The Impact of Mental Health & Employment on Patient Outcomes in Axial Spondyloarthritis

Publications resulting from material contained within this chapter:

S Maguire, F Wilson, P Gallagher, F O'Shea. The Toll of Unemployment in Axial Spondyloarthropathy: High prevalence and negative impact on outcomes as captured in a national registry. *Scandinavian Journal of Rheumatology*. 2021 Nov 17; (1-4); DOI: 10.1080/03009742.2021.1992861

S Maguire, P Gallagher, F O'Shea. The Negative Impact of Depression in Women with Axial Spondyloarthropathy. *Joint Bone Spine*. 2021 Sept; 89 (1):105261. DOI: 10.1016/j.jbspin.2021.105261

S Maguire, P Gallagher, F O'Shea. The Negative Impact of Undiagnosed Depression in Axial Spondyloarthropathy. *Clinical & Experimental Rheumatology*. 2022 Mar; 40 (3): 669-670. DOI: 10.55563/clinexprheumatol/d6518k

S Maguire, F O'Shea. Social Isolation due to the COVID-19 Pandemic has led to Worse Outcomes in Females with Inflammatory Arthritis. *Irish Journal of Medical Science*. 2020 July; 190, 33-38. DOI: 10.1007/s11845-020-02307-2

(Full text of publications included in Appendix A)

4.1 Introduction

Risk factors for disease severity as reflected by worse patient outcomes in axial spondyloarthritis (axSpA) have been investigated extensively in published literature. Despite this, there is much that remains unexplained. In particular the impact of psychosocial factors related to disease such as mental health and unemployment. The two issues have significant potential to affect many aspects of an axSpA patient's management and experience of their disease. This includes the ability to engage with supportive services, access medication and travel to clinical appointments.

The analyses contained within this chapter go beyond detailing prevalence of unemployment and depression in an axSpA population to also examine the impact of these issues and how to identify those at risk. One of the aims of this chapter is to highlight the importance of recognition to create an opportunity for intervention.

4.2 The Toll of Unemployment in Axial Spondyloarthritis:
High Prevalence and Negative Impact on Outcomes Captured in a National Registry

4.2.1 Abstract

Objective

Persistent disease activity in axial spondyloarthritis (axSpA)can result in significant disability and affect ability to maintain employment. The aim of this study was to determine the prevalence of unemployment in axSpA and the impact on patient outcomes.

Methods

Data from the ASRI was cleaned, and information on employment, demographics and disease characteristics were extracted. Patients were analysed on the basis of employment and categorised as employed or unemployed. To test for statistical significance a two tailed t-test was used for continuous variables, while a chi-squared test for independence was used for categorical variables. A binomial logistic regression model was used to determine the effects of age, patient outcomes and disease duration on likelihood of unemployment.

Results

Employment status was available for 876 patients, with 759 eligible for inclusion in the analysis. Overall, 23.5% (178) of the population was unemployed, which is considerably higher than national averages of 6.2-13.1% during the same period. In addition, 24% (182) reported axSpA as a limitation in work ability. Unemployed patients reported significantly worse BASDAI (5.1 vs 3.6, $p<0.01$), BASMI (4.8 vs 3.4, $p<0.01$), BASFI (5.2 vs 3.0, $p<0.01$), HAQ (0.82 vs 0.40, $p<0.01$), and ASQoL scores (9.4 vs 5.4, $p<0.01$) compared to employed axSpA patients. A higher proportion of males were unemployed as compared to females (26.7% vs 14.6%, $p<0.01$). AxSpA males had 2.65 times higher odds than females to be unemployed (95% CI 1.5-4.8, $p<0.01$).

Conclusion

AxSpA patients report considerably higher levels of unemployment compared to the general population. These patients have worse quality of life, poorer levels of function and higher levels of disease activity compared to employed axSpA patients. Predictors of unemployment in axSpA were male sex, worse spinal mobility and greater functional limitation. Recognition of patients at risk of unemployment will improve the opportunity to offer intervention and maintain participation in the workforce.

4.2.2 Background

Rheumatic diseases such as inflammatory arthritis (IA) were historically associated with significant disability and deformity[296,297]. Consequently, many of these patients were unable to maintain employment and struggled with activities of daily living. Advances in imaging have increased detection of IA, while the advent of disease modifying anti-rheumatic drugs (DMARDs) and biologic agents have revolutionised treatment[298]. This has led to diagnosis and treatment initiation earlier in the course of the disease, resulting in improved outcomes[299]. Unfortunately, rheumatic diseases continue to be a considerable source of disability worldwide accounting for 4.8% of total disability globally in 2010 which increased to 5.5% in 2017 as per the Global Burden of Disease study[300].

Being able to actively participate in the workforce is a key indicator of functional ability and important to patients for a number of reasons. Employment is not only a source of income, but also allows for development of skills, socialisation and has been shown to positively impact mental well-being[301,302]. Both research and patient advocacy groups have placed a considerable emphasis on supporting patients with IA to maintain employment[303,304], however unemployment remains a challenge in this population.

For many years axial spondyloarthritis (axSpA) was associated with significant deformity and disability; issues which limited ability to maintain employment for many patients[305]. With advances in treatments and diagnostics, it would be expected that unemployment levels now would be similar to that of the general population.

The aim of this study was to examine the prevalence of unemployment in axSpA and quantify the impact on burden of disease, level of function and quality of life.

4.2.3 Methods

4.2.3.1 Patient population

Data for this analysis was captured via the Ankylosing Spondylitis Registry of Ireland (ASRI). This large national registry recruits patients with axSpA from Rheumatology centres across the country. Full details on patient population including eligibility criteria and data captured as part of this registry are discussed at length in Chapter 3: Methods under "Patient Population".

4.2.3.2 Outcomes & Assessments

Full discussion of outcomes captured within the ASRI are included in Chapter 3: Methods under "Data Collection" and "Outcome Measures."

Current employment status was recorded at time of enrolment with all participants categorised into one of ten options. To simplify data for comparison analysis, this categorisation was then simplified into employed or unemployed. Employed included all patients with employment status listed as: full-time, part-time, homemaker, and student. Unemployed included all participants with the following employment status recorded: looking for work, disabled, and unemployment. Participants who were retired or on sick leave were excluded from the analysis.

4.2.3.3 Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) version 26 was used for statistical analysis and data processing. Patients were analysed on the basis of employment and categorised as employed or unemployed. A series of comparison analysis was carried out to assess variation between employed and unemployed axSpA patients. This included comparison of baseline demographics, patterns of disease, medication usage, patient outcomes and comorbidities. A two tailed t-test was used to test for significance in differences between means of continuous variables between employed and unemployed patients. For categorical variables a chi-squared test of independence was used to determine statistical significance. An alpha level of $p < 0.05$ was deemed significant.

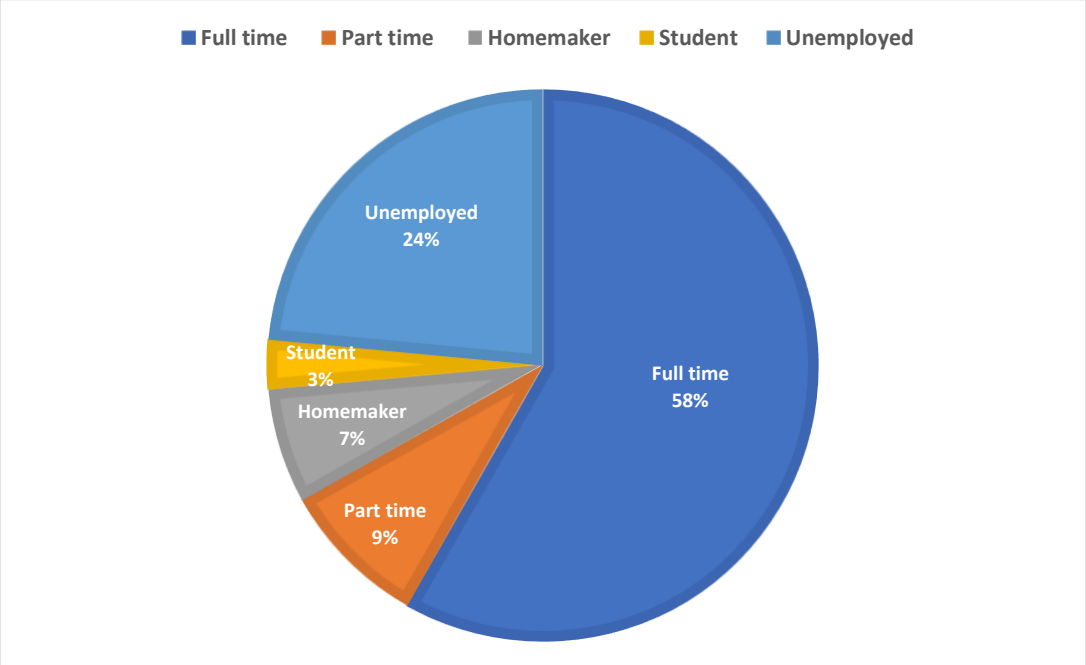
A binomial logistic regression model was constructed to capture the effect of age, sex, disease duration and patient outcome scores on likelihood of unemployment. Results were expressed as odds ratios (OR) with 95% confidence intervals (95% CI) and p values to indicate level of statistical significance. For each statistical test in this analysis all appropriate assumptions were met.

4.2.4 Results

At the time of analysis 886 patients were enrolled in the ASRI with data on employment status available for 876 participants, of whom 759 were eligible for inclusion in the analysis. The patient population was made up of 73% (554) males and 27% (205) females with 91% (690) identifying as Caucasian. Mean age was 45.9 years (SD 12.6, range 18-85) with median disease duration of 17.1 years (9.5, 27.8) and median delay to diagnosis of 5 years (2, 12). Mean scores for the ASRI population were BASDAI 4.0 (95% CI 3.9-4.2), BASMI 4.0 (95% CI 3.9-4.2), BASFI 3.7 (95% CI 3.5-3.9), HAQ 0.53 (95% CI 0.49-0.56), ASQoL 6.6 (95% CI 6.1-6.8). Overall axSpA females were noted to have worse BASDAI (4.5 vs 3.8, $p<0.01$) HAQ (0.56 vs 0.47, $p=0.04$) and ASQoL (7.4 vs 6.0, $p<0.01$) scores compared to males. Although females recorded better BASMI scores (3.3 vs 3.9, $p<0.01$) than axSpA males.

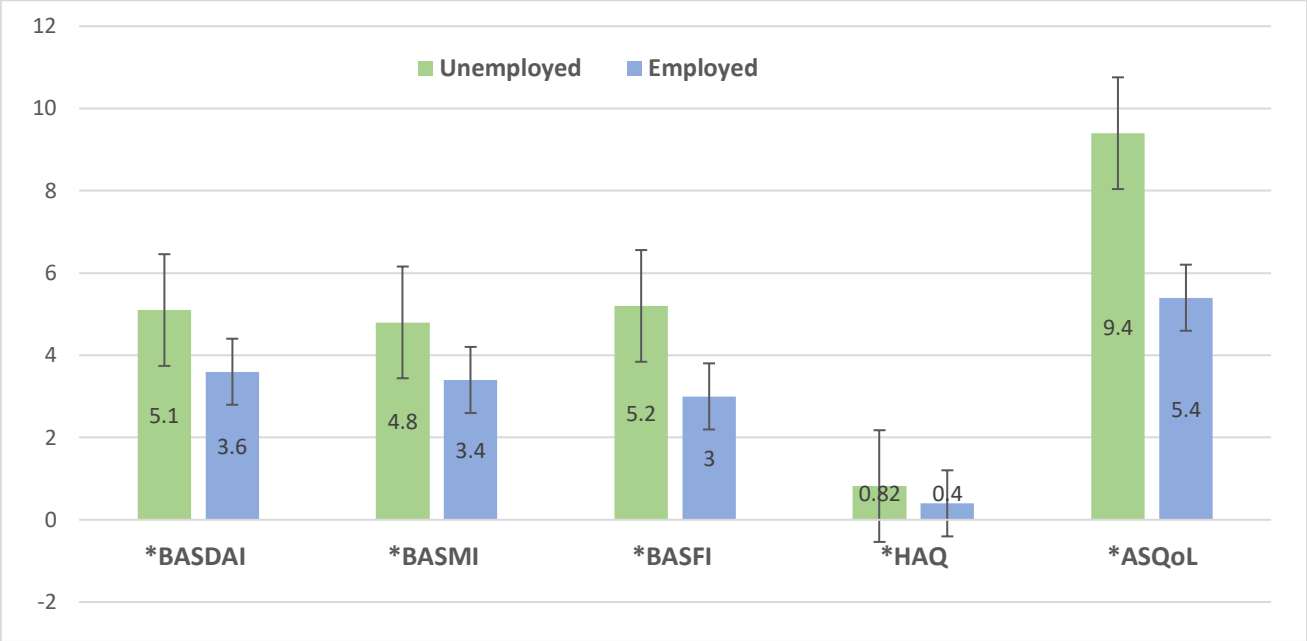
Unemployment rate in the ASRI population was 23.5% (178) at the time of analysis (figure 4.1). In total, 24% (182) of patients reported their employment had been affected by axSpA resulting in unemployment, disability or part-time employment. Limitation of employment due to disease was observed in similar frequencies in both males and females (25.8% vs 20.3%, $p=0.08$).

Figure 4.1: Employment status of axSpA patients in the ASRI



Unemployed axSpA patients had significantly worse ASQoL (9.4 vs 5.4, 95% CI 3.1-4.9, p<0.01), HAQ (0.82 vs 0.40, 95% CI 0.34-0.50, p<0.01), BASDAI (5.1 vs 3.6, 95% CI 1.1-1.9, p<0.01), BASFI scores (5.2 vs 3.0, 95% CI 1.8-2.8, p<0.01) and BASMI (4.8 vs 3.4, 95% CI 1.0-1.8, p<0.01) (figure 4.2) as compared to those who were employed. These differences were significant at the p<0.01 level across all outcomes.

Figure 4.2: Comparison of mean outcomes on the basis of employment, all differences were statistically significant at the p<0.01 level (as indicated by *)



No significant differences were noted in patterns of disease, prevalence of extra-articular manifestations or radiographic findings between the two groups (table 4.1). However, unemployment was more frequently encountered in axSpA males than females (26.7% vs 14.6%, p<0.01).

A significantly higher proportion of the unemployed patients were active smokers (38.1% vs 26.2%, p<0.01) than unemployed patients. Current alcohol consumption displayed a trend to occur more commonly in employed patients than unemployed (74.1 vs 65.1, p=0.05) which did not reach statistical significance.

Table 4.1: Characteristics of the employed versus unemployed cohort in the ASRI

	Unemployed	Employed	*p value*
n*	23.5% (178)	76.5% (581)	
Males	83.1% (148)	70% (406)	***<0.01***
Females	16.9% (30)	30.1% (175)	
Age	46.2 (10)	42.5 (10.7)	***<0.01***
Disease duration	18.4 (9.4, 27.4)	17.1 (9.6, 28)	***0.02***
Delay to diagnosis	5 (2,10)	6 (2, 12)	*1*
Symptom onset age	22.6 (19, 33)	25.6 (18, 30)	*0.08*
Caucasian	93.3% (166)	524 (91.2% (524)	*0.25*
HLA-B27 +	90.3% (121 of 134)	90.1% (414 of 457)	*0.92*
r-axSpA	80% (142)	73.8% (429)	*0.11*
nr-axSpA	20.2% (36)	26.2% (152)	*0.11*
Arthritis	31.5% (56)	28.1% (163)	*0.68*
Enthesitis	20.2% (36)	15.8% (92)	*0.38*
Dactylitis	7.3% (13)	6% (35)	*0.67*
Psoriasis	17.4% (31)	16.5% (96)	*0.78*
Uveitis	34.8% (62)	34.1% (198)	*0.53*
Colitis	6% (11)	10.2% (59)	*0.21*
NSAIDs	49.4% (88)	51.8% (301)	*0.59*
csDMARDs	25.2% (45)	22% (128)	*0.39*
bDMARDs	74.7% (133)	67.5% (392)	*0.14*
CRP	7.4 (11.2)	6.9 (13)	*0.62*
ESR	17.2 (18)	14.8 (17)	*0.24*

Abbreviations: *HLA-B27 -human leukocyte antigen B27; MRI -magnetic resonance imaging; NSAIDs -non-steroidal anti-inflammatory medications; csDMARDS – conventional synthetic disease modifying anti-rheumatic drugs; bDMARDs -biologic disease modifying anti-rheumatic drugs; CRP -C reactive protein; ESR -erythrocyte sedimentation rate*
**Categorical variables expressed as % (n), continuous variables expressed as mean (standard deviation) or median (25th centile, 75th centile)*

Medication use was similar in both employed and unemployed patients. However, there was a trend towards increased use of biologic therapies in the unemployed patients (74.7% vs 67.5%, p=0.14) but this did not reach statistical significance.

Prevalence of a number of comorbidities was also assessed, with no significant difference detected in prevalence of ischaemic heart disease (4.2% vs 3.5%, p=0.68), cerebrovascular disease (2.1% vs 1.3%, p=0.55) or diabetes (4.8% vs 5.4%, p=0.71) between

unemployed and employed participants. However, unemployed patients had a significantly higher prevalence of depression compared to employed patients (16.4% vs 8.7%, p<0.01).

A binomial logistic regression was performed to determine the effects of sex, disease duration and patient outcomes on likelihood of unemployment in patients with axSpA. The model was statistically significant x^2 (8) =109.75, p<0.001. The model correctly classified 79% of cases overall. Of the nine predictor variables only three were statistically significant: male sex, BASMI and HAQ (table 4.2). AxSpA males had 2.65 times higher odds than females to be unemployed (95% CI 1.46-4.83, p<0.01). Increasing HAQ and BASMI scores were found to be associated with a higher likelihood of unemployment, while increasing age was associated with a lower likelihood of unemployment. The area under the ROC curve was 0.776 (95% CI 0.729 to 0.823) which indicated an acceptable level of discrimination for a model.

Table 4.2: Prediction model for risk of unemployment in AxSpA

	Odds Ratio	**95% CI**	*p value*
Male sex	2.65	1.46 - 4.83	**<0.01**
Age	1.01	0.98 – 1.03	0.62
Delay to diagnosis	0.99	0.96 - 1.02	0.46
Disease duration	1.00	0.98 - 1.03	0.75
BASDAI	1.04	0.90 - 1.20	0.62
BASMI	1.19	1.02 - 1.33	**0.02**
BASFI	1.03	0.93 - 1.13	0.61
HAQ	2.18	1.13 – 4.19	**0.02**
ASQoL	1.07	1.00 - 1.14	0.05

Abbreviations: *CI -confidence interval; BASDAI -Bath Ankylosing Spondylitis Disease Activity Index; BASMI -Bath Ankylosing Spondylitis Metrology Index; BASFI -Bath Ankylosing Spondylitis Functional Index; HAQ -Health Assessment Questionnaire; ASQoL -Ankylosing Spondylitis Quality of Life questionnaire*

4.2.5 Discussion

This analysis demonstrates the very high prevalence (23.5%) of unemployment in patients with axSpA. National unemployment during the same period (2013-2019) was noticeably lower with a range of 6.2% to 13.1%[306-308], even when compared to the peak of unemployment at 20.4% in 2020 due to the COVID-19 pandemic[309]. Compared to other axSpA cohorts, the prevalence of unemployment in our cohort was above the reported prevalence in Spain of 20.1%[310], but lower than in Argentina with 26.2%[311] and 30% in the United Kingdom[312]. These results indicate the high levels of unemployment in axSpA is an issue extending beyond Ireland and affecting axSpA patients globally. By comparison, literature in psoriatic arthritis suggests a high level of unemployment (20-50%)[313] with a similar range reported in rheumatoid arthritis (32%-50%)[314]. Thus, the high prevalence of unemployment in patients with axSpA, while alarming, also extends other forms of inflammatory arthritis.

Another concerning finding was that 24% of patients reporting their employment had been affected or limited by their disease. Similar results were found in an Italian axSpA cohort with 21% reporting work restriction due to axSpA[315]. The loss or limitation of work productivity in such a large proportion of the cohort represents significant financial loss for axSpA patients, families and dependents. Lower socioeconomic status has previously been found to be associated with worse health outcomes in axSpA using the ASAS health index[316]. This has also been associated with a higher prevalence of depressive symptoms and worse overall psychological well-being[317]. This is supported by the significantly higher prevalence of depression found in the unemployed patients in this study (16.4% vs 8.7%, $p<0.01$).

AxSpA patients who were unemployed were found to have significantly worse outcomes across all measures captured in this analysis as compared to those who were employed. This included higher levels of disease activity, worse functional abilities, greater limitation of spinal mobility and worse overall quality of life. This was supported by results of the prediction model which found an increased likelihood of unemployment in patients with worse BASMI (OR 1.19, 95% CI 1.02-1.33) and HAQ scores (OR 2.18, 95% CI 1.13-4.19). Perhaps as a reflection of these findings, there was a trend towards increased use of biologic agents in this group (74.7% vs 67.5%, $p=0.14$) which did not reach statistical significance. This could indicate patients with persistent disease activity thus the increased requirement for biologic therapy and negative impact on outcome measures. However, given the proven efficacy of biologic therapy in axSpA it is also surprising to see worse outcomes in a cohort with a high prevalence of biologic use. Development of additional research capturing longitudinal data is required to determine if a causal relationship between disease activity and employment exists.

Male sex was found to be the most significant variable associated with an increased likelihood of unemployment (OR 2.65, 95% CI 1.46-4.83, p<0.01). This is supported by the higher proportion of males who were unemployed as compared to females (26.7% vs 14.6%, p<0.01). Worse spinal mobility as captured by the BASMI was also associated with an increased likelihood of unemployment (OR 1.19, 95% CI 1.02-1.33). As males have significantly worse BASMI scores on average compared to axSpA females (3.92 vs 3.32, p<0.01), this could explain the higher levels of unemployment observed in axSpA males. Worse HAQ scores were also associated with a significantly increased likelihood of unemployment (OR 2.18, 95% CI 1.13-4.19) in axSpA. Both BASMI and HAQ scores are routinely recorded in each Rheumatology consultation for axSpA patients. Monitoring these scores for worsening trends could help to identify patients at risk of employment loss and trigger prompt intervention from a multidisciplinary team.

Limitation of work productivity is often a precursor to job loss and unemployment. This concept, while difficult to quantify and monitor, can have a significant effect on a patient's overall wellbeing and is important to capture. Tools are being developed to identify those at risk of impaired productivity due to axSpA, which can help clinicians to recognise such patients and allow intervention[318]. The Work Productivity and Activity Impairment questionnaire in AS (WPAI: SpA) was developed specifically for axSpA patients to capture both employment and productivity[319]. The simplicity of this self-administered questionnaire allows for regular monitoring as part of routine care for axSpA patients. The arthritis specific Work Productivity Survey (WPS) is another validated tool to assess productivity, with questions designed to assess limitations both at home and work[320]. Regular use of tools such as these, as part of regular axSpA monitoring would allow valuable insights into participation in the workforce and impact of disease on functional ability.

Work instability is a mismatch between an individual's abilities and demands of a job. This frequently proceeds work disability and can be detected via the AS Work Instability Scale (AS-WIS) which is in both radiographic and non-radiographic axSpA[321]. This allows for early recognition of patients prior to progression to disability or job loss. Such patients can significantly benefit from prompt input from occupational therapists and physiotherapists to optimise work conditions and environments, in addition to optimising disease control. The European League Against Rheumatism (EULAR) recently released guidance on study design and reporting of work participation in patients with inflammatory arthritis[322]. Adherence to these guidelines could improve the quality of data on work participation and allow for more thorough comparison analysis between studies.

The two main strengths of this study were the large size of the patient population studied and the detailed patient characteristics captured within the ASRI to support the analysis. Both the employed and unemployed cohort were adequately powered to detect differences

without individual results disproportionally skewing overall proportions. All data was collected by trained investigators ensuring reliability of data collection. Data was gathered from multiple centres allowing for accurate representation of the true axSpA patient population of Ireland. Lastly, the inclusion of a prediction model identified risk factors for unemployment, which has significant clinical implications.

4.2.5.1 Limitations

The main limitation of this study is the cross-sectional nature of the data from the ASRI. This prevented the ability to detect causal relationships, especially the impact of persistent disease activity on employment status. Data was collected over an eight-year period, during which time national unemployment rates varied by year. However, national unemployment rates remained significantly lower than the unemployment rates observed from patients in the ASRI. The lack of data on occupation type prevented analysis of association between employment status and specific occupations. The ASRI is in the process of developing longitudinal data and expanding collection on employment to include more detailed data collection on occupation type. This will allow future studies to study impact of specific occupations and risk of unemployment in patients with axSpA.

4.2.6 Conclusion

Prevalence of unemployment in axSpA remains notably higher than nationally reported averages from the general population. Despite a high uptake of biologic therapy in this group, these patients have higher levels of disease activity, poorer levels of function and worse quality of life compared to employed axSpA patients. A large proportion of axSpA patients also reported work limitations due to their disease. Predictors of unemployment were male sex, worse spinal mobility and greater functional limitation. In males, higher average BASMI scores were a significant contributing factor to the higher rates of unemployment observed. Prompt intervention for patients with worsening scores would provide an opportunity for occupational supports and prevent progression to unemployment. In addition, increased use of tools to identify patients at risk for work instability or work disability will allow for rapid recognition and intervention to keep these patients active members of the workforce.

4.3 Depression in Axial Spondyloarthritis:

Negative Impact on Patient Outcomes & High Prevalence of Undiagnosed Depression

4.3.1 Abstract

Objective

To capture the prevalence of depression and undiagnosed depression in axial spondyloarthritis (axSpA) and to analyse the effects of depression on patient outcomes.

Methods

This two-stage study initially assessed the prevalence of depression in a large well characterised axSpA cohort as captured in the Ankylosing Spondylitis Registry of Ireland (ASRI). Outcomes were analysed on the basis of presence of underlying depression. The second stage was a period of prospective screening of a cohort of axSpA patients for undiagnosed depression using the Patient Health Questionnaire 9 (PHQ-9) and the Hospital Anxiety and Depression Score for Depression (HADS-D) surveys. IBM SPSS version 26 was used for data analysis. Differences between cohorts were tested for statistical significance using independent t-tests, chi^2 tests for independence and Fisher's exact test depending on the variable assessed. A p-value of <0.05 was deemed significant.

Results

Prevalence of depression within this axSpA cohort was 10.1%. These patients had significantly worse outcome measures compared to those without depression. When analysed on the basis of sex, axSpA females with depression reported significantly worse outcomes compared to males with depression. In the screening for undiagnosed depression 9.9% of patients had abnormal HADS-D scores and 23.9% moderate to severe PHQ-9 scores. Abnormal scores were associated with worse BASDAI and ASQoL results.

Conclusion

Depression is a prevalent comorbidity in axSpA and has a significant effect on outcome measures of disease. This is especially notable in females with axSpA. Active screening for depression could aid in identification of this co-morbidity.

4.3.2 Background

Mental health issues such as depression, are a source of considerable disability which can affect all aspects of life. The World Health Organisation (WHO) has projected that depression will be the leading cause of severe disability worldwide by 2030[323]. True prevalence of depression is suspected to be underestimated as this diagnosis can persist undetected in a significant proportion of the population[324]. Reasons for this are multifactorial but include issues such as societal stigma, under recognition of symptoms and limited or lack of access to appropriate services[325]. Depression can often complicate chronic disease which results in worsening of underlying disease and decline in quality of life[326]. Understanding and recognising the impact of depression in chronic inflammatory arthritis could result in improved patient outcomes.

Other forms of inflammatory arthritis have been shown to have higher prevalence of depression as compared to the general population[327]. In rheumatoid arthritis (RA) depression has been shown to be associated with increased fatigue[328], disability[329] and higher healthcare costs[330]. Presence of depression has even been shown to be associated with increased mortality[331]. Psoriatic arthritis (PsA) also has an increased prevalence of depression than the general population[332] but the relationship between disease manifestations and comorbid depression is poorly understood[333].

Although advances in imaging and improved understanding of the course of disease have led to improved recognition of axial spondyloarthritis (axSpA), many patients continue to face a considerable delay in diagnosis. A recent study reported an average time from symptom onset to diagnosis of 8.2 years[334] this represents a period of uncontrolled disease activity which can result in chronic pain and disability. These issues are recognised risk factors for depression. There is strong evidence that axSpA patients have an increased prevalence of a number of comorbidities[335] including depression[336-338]. Furthermore, a diagnosis of depression has been shown to be associated with a younger age, increased disease activity and lower levels of exercise[317,339].

Changing classification criteria and terminology have resulted in the bulk of this research being focused on ankylosing spondylitis (AS) as highlighted in a recent review[340]. Evaluating depression in axSpA as a whole is important for a number of reasons. Females are more likely to have non-radiographic axSpA (nr-axSpA) than radiographic axSpA (r-axSpA) or ankylosing spondylitis[341]. In addition, female sex is associated with a significantly higher prevalence of depression in the general population[342]. Significant variations in patterns of disease and reporting of outcome measures have also been reported between sexes[20]. For these reasons,

further analysis on depression in axSpA is needed to further characterise how depression affects females with axSpA.

The aim of this analysis was to assess prevalence and effect of confirmed depression and undiagnosed depression in axSpA. This study also aims to assess depression in axSpA on the basis of sex, an area that has received limited attention in current published research.

4.3.3 Methods

This analysis examined depression and the effects on axSpA in two approaches. The first examined the prevalence of diagnosed depression in a large, well characterised cohort from a national registry (the ASRI). The second part of the study was a prospectively screened cohort of axSpA patients for undiagnosed depression with no previous diagnosis of depression.

Written informed consent was obtained from participants prior to patient enrolment in the ASRI. Informed consent was also obtained prior to participants taking part in the screening study. Ethical approval was received from the St James' & Tallaght Hospital Joint Ethics committee prior to commencement of both studies. Ethical approval was also obtained from local hospital ethics boards at each site which contributed patients to the ASRI. Additionally, a designated trained investigator at each site was responsible for local oversight and data collection.

4.3.3.1 Patient Population

Confirmed Depression

Data for this analysis was captured via the Ankylosing Spondylitis Registry of Ireland (ASRI). This large national registry recruits patients with axSpA from Rheumatology centres across the country. Full details on patient population including eligibility criteria and data captured as part of this registry are discussed at length in Chapter 3: Methods under "Patient Population".

Prevalence of depression was captured using data extracted from the Ankylosing Spondylitis Registry of Ireland (ASRI). In addition to data on other comorbidities, a diagnosis of depression is captured at time of enrolment into the ASRI. This diagnosis must have been made by a clinician, with presence of depression confirmed via review of medical records.

Full discussion of additional outcomes captured within the ASRI are included in Chapter 3: Methods under "Data Collection" and "Outcome Measures."

Screening for Undiagnosed Depression

AxSpA patients attending the Rheumatology department in St James' Hospital between February and October 2020 were invited to take a self-administered survey which included the

Patient Health Questionnaire 9 (PHQ-9) and the Hospital Anxiety and Depression Scale for Depression (HADS-D). These two scores are validated tools to screening for the presence of undiagnosed depression in Psychiatry[343]. Both tools have previously functioned well in studies on mental health issues in rheumatic disease[344,345]. Scores from the HADS-D yielded a numerical result which was then categorised as normal, borderline or abnormal. Abnormal scores (greater than 11) are considered clinically significant and suggestive of underlying depression[346]. PHQ-9 numerical results were categorised as normal, mild, moderate, moderate/severe or severe. Moderate scores (greater than 10) have previously shown good sensitivity and specificity in detecting undiagnosed depression. Patients with a known diagnosis of depression were excluded from participation. In addition to baseline demographics, patient outcomes from the clinic visit were also recorded.

4.3.3.2 Statistical Analysis

Data analysis was performed using IBM SPSS version 26. Continuous variables were recorded as means with standard deviations or medians with 25th and 75th centiles as appropriate, categorical variables were recorded as frequencies with percentages. Distribution of data was assessed with the Shapiro Wilk test for normality. Data was analysed for statistical significance using independent t-tests for continuous variables and a chi^2 test for independence or Fisher's exact test for categorical variables. In the initial depression analysis patients were analysed on the presence of an underlying diagnosis of depression. A multivariate analysis was run with a two-way multivariate analysis of variance (MANOVA) to assess the impact of sex and depression on patient outcome scores. For the screening analysis a one-way analysis of variance analysis (ANOVA) was used to determine significance of variation in outcomes between patient outcomes as determined by the HADs-D and PHQ-9. A hierarchical multiple regression analysis was performed to determine if the addition of HADs-D scores and PHQ-9 scores (considered individually) improved prediction of BASDAI and ASQoL by assessment of adjusted R^2. Final models retained variables which significantly improved overall fit. All necessary assumptions were met for each statistical test. A p-value of alpha <0.05 was deemed significant.

4.3.4 Results

4.3.4.1 Depression in the ASRI

At the time of data extraction 877 patients were enrolled in the ASRI and included in this analysis. This was made up of 73.4% (644) males and 21% (184) females. Average age of participants was 45.9 years (standard deviation [SD] 12.6, range 18-73), with median disease duration of 17.1 years (9.5, 27.8) and median delay to diagnosis of 5 years (2, 12). Mean outcome measures of the ASRI were: BASDAI 4.0 (95% CI 3.8-4.2), BASFI 3.7 (95% CI 3.5-3.9), BASMI 4.0 (95% CI 3.8-4.2), ASQoL 6.5 (95% CI 6.1-7.0) and HAQ 0.54 (95% CI 0.51-0.59). The majority of the patients were Caucasian at 91.1% (799), with a high prevalence of HLA-B27 positivity 89.9% (595 of 662 available results).

Patients were compared on the presence of a diagnosis of depression. Overall, 10.1% (89 participants) of the population captured in the ASRI had been previously diagnosed with depression. This population was made up of 70.1% (63) males and 25.8% (23) females, with a similar sex distribution in both cohorts (table 4.3).

Table 4.3: Comparison of characteristics of patients with depression to those without depression

	Depression % (n)	No Depression % (n)	*p value*
n	10.1% (89)	88.5% (776)	
Males	70.1% (63)	74.6% (579)	0.34
Females	25.8% (23)	20.7% (161)	0.34
Age	47.5 (9.9) *	45.7 (12.9)	0.2
Age at symptom onset	22.8 (18, 32)	24.1 (19, 32)	0.27
Delay to dx (years)	8.0 (3, 12)	5 (2, 11)	0.11
Disease duration (years)	23.5 (13, 30)	16.7 (9, 27)	**0.02**
Caucasian	96.6% (86)	91.6% (711)	0.06
HLA-B27+	91.4% (64)	89.7% (529)	0.64
r-axSpA	80.9% (72)	77.7% (603)	0.47
nr-axSpA	19.1% (17)	22.2% (173)	0.49
Articular Manifestations			
Arthritis	41.6% (37)	29.3% (227)	**0.01**
Enthesitis	25.8% (23)	29% (125)	**0.02**
Dactylitis	5.6% (5)	6.3% (49)	0.83
EAMs			
Psoriasis	23.6% (21)	15.5% (120)	**0.04**
Uveitis	33.7% (30)	34% (264)	0.96
Colitis	13.5% (12)	10.2% (79)	0.28
Medications			
NSAIDs	61.8% (55)	49.6% (385)	**0.02**
DMARDs	18% (16)	18.9% (147)	0.86
Biologics	71.9% (64)	67.5% (524)	0.35
anti-TNF	69.7% (62)	67.2% (522)	0.55

Abbreviations: Dx -diagnosis, HLA-B27 -human leukocyte antigen 27, r-axSpA -radiographic axSpA, nr-axSpA -non-radiographic axSpA, NSAID -non-steroidal anti-inflammatory drug, DMARD -disease modifying antirheumatic drug, anti-TNF -anti tumour necrosis factor
*Continuous variables expressed as: Mean (Standard Deviation) or median (25th centile, 75th centile), Categorical variables expressed as: %(n)

Patients with depression reported a longer average disease duration (23.5 vs 16.7 years, 95% CI 0.4-5.9, p=0.02) than those without, however all other baseline demographics were similar in both groups. There was a significantly higher prevalence of arthritis (41.6% vs 29.3%, p=0.01) and psoriasis (23.6% vs 15.5%, p=0.04) noted in patients with depression, although enthesitis was more prevalent in those without depression (25.8% vs 29%, p=0.02). Medication usage was similar regardless of diagnosis of depression with the exception of NSAID use which was more frequent in patients with depression (61.8% vs 49.6%, p=0.02).

Overall, patients with depression had significantly worse scores in all outcome measures captured in this analysis compared to those without depression: BASDAI 5.2 vs 3.9, 95% CI 0.8-

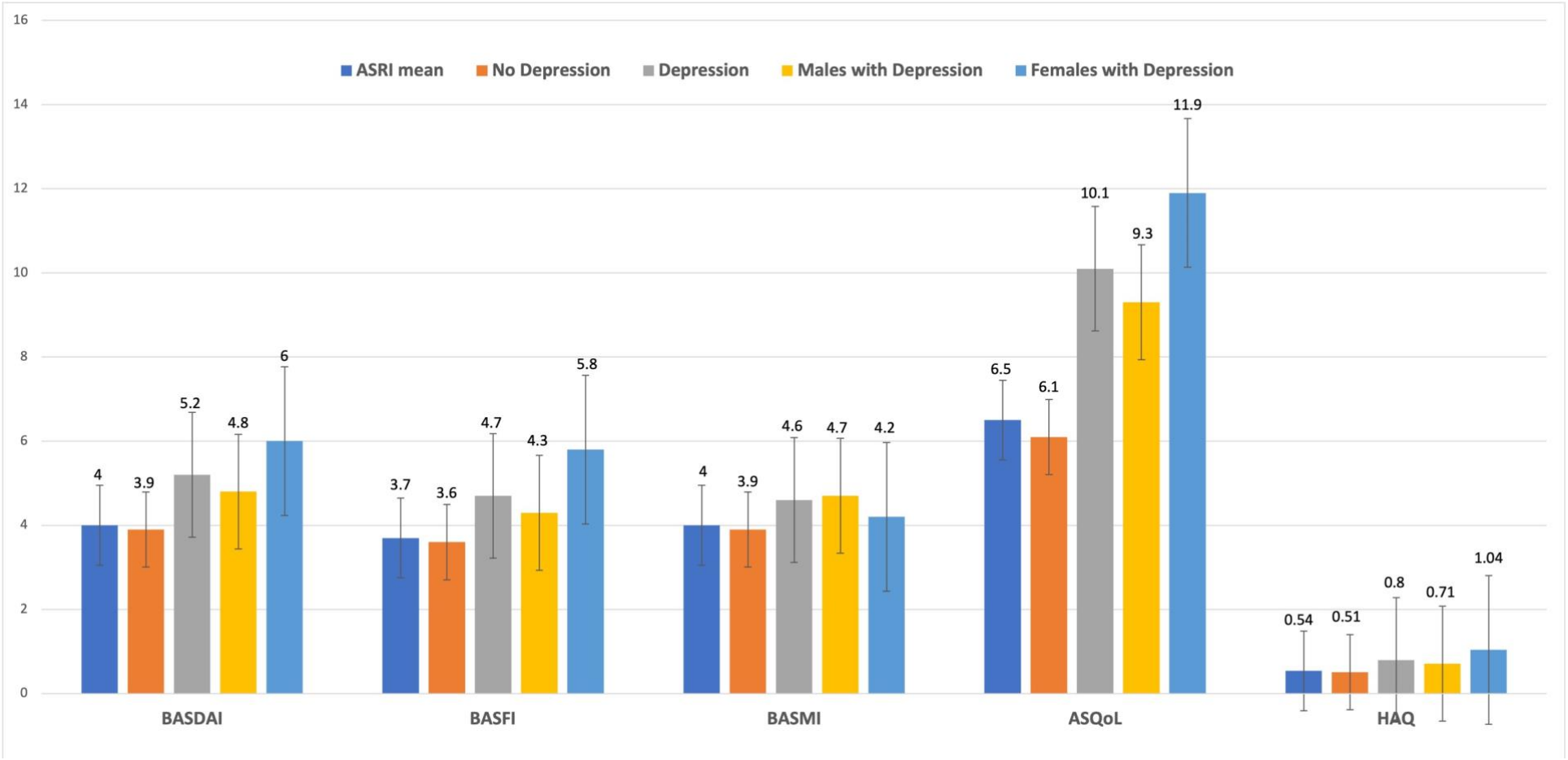
1.8, p<0.01; BASFI 4.7 vs 3.6, 95% CI 0.7-1.8, p<0.01; BASMI 4.6 vs 3.9, 95% CI 0.1-1.2, p=0.02; ASQoL 10.1 vs 6.1, 95% CI 2.9-5.2, p<0.01; HAQ 0.8 vs 0.51, 95% CI 0.2-0.4, p<0.01. Additionally, the depression cohort had higher rates of active smoking (44.9% vs 27.3%), while non-smokers were more commonly encountered in the cohort without depression (27% vs 43.9%). Current alcohol consumption was higher in the non-depression cohort (73.7% vs 58.4%), however higher rates of previous alcohol intake were noted in the depression cohort (22.5% vs 8.6%) compared to the non-depression cohort (table 4.4).

Table 4.4: Prevalence of smoking and alcohol exposure on the basis of underlying diagnosis of depression

	Depression	No Depression	*p value*
Smoking			<0.01
Current	44.9% (40)	27.3% (212)	
Past	28.1% (25)	28.7% (223)	
Non-smoker	27% (24)	43.9% (341)	
Alcohol intake			<0.01
Current	58.4% (52)	73.7% (572)	
Past	22.5% (20)	8.6% (67)	
None	19.1% (17)	17.7% (137)	

Further analysis of patients with depression was carried out on the basis of sex. Males and females with depression in this cohort were found to have similar baseline demographics, patterns of disease, radiographic findings, medication usage, prevalence of smoking and alcohol use. However, females with depression recorded significantly worse mean BASDAI (6.0 vs 4.8, 95% CI 0.1-2.3, p=0.03), BASFI (5.8 vs 4.3, 95% CI 0.3-2.8, p=0.02) and HAQ (1.04 vs 0.71, 95% CI 0.1-0.6, p=0.01) compared to males (figure 4.3). Depressed females also recorded worse mean ASQoL (11.9 vs 9.3, 95% CI -0.2 to 5.5, p=0.05) but lower mean BASMI (4.2 vs 4.7, 95% CI -1.7 to 0.7, p=0.41) compared to males, but these results did not reach significance.

Figure 4.3: Summary of outcome measures by presence of depression and depression within each sex



Abbreviations: *ASRI -Ankylosing Spondylitis Registry of Ireland; BASDAI -Bath Ankylosing Spondylitis Disease Activity Index; BASFI -Bath Ankylosing Spondylitis Function Index; BASMI -Bath Ankylosing Spondylitis Metrology Index; ASQoL -Ankylosing Spondylitis Quality of Life scale; HAQ -Hospital Assessment Questionnaire*

Multivariate analysis to assess the effects of depression and sex on patient outcome scores was then carried out. The interaction effect of sex and depression on the combined outcome scores was not statistically significant (F=1.26, Wilk's lambda =0.99, p=0.28). A follow up univariate two-way ANOVA was run, and the main effect of gender and depression considered. There was a statistically significant effect on outcome scores from both gender (F=5.43, Wilk's lambda =0.96, p<0.01) and depression (F=7.58, Wilk's lambda =0.94, p<0.01).

Within sex the main effects interaction was significant for BASDAI (F=10, p<0.01), BASFI (F=5.5, p<0.01), HAQ (F=9.5, p<0.01) and ASQoL (F=5.5, p=0.02) but did not reach significance for BASMI (F=3.5, p=0.06). There was also a statistically significant main effect of depression for all included outcome measures (p<0.01 for all). A Tukey pairwise comparison was run for the differences in mean outcome scores between males and females considering the presence of depression (table 4.5).

Table 4.5: Effects of depression and sex on patient outcome scores

Depression vs No Depression

		Mean Difference (95% CI)	p value
BASDAI	Females	1.9 (0.7, 3.0)	<0.01
	Males	1.1 (0.4, 1.8)	<0.01
BASFI	Females	2.1 (0.7, 3.)	<0.01
	Males	0.9 (0.1, 1.7)	0.03
HAQ	Females	0.6 (0.3, 0.9)	<0.01
	Males	0.2 (0.1, 0.4)	0.01
ASQoL	Females	5.6 (2.8, 8.3)	<0.01
	Males	3.6 (1.9, 5.2)	<0.01
BASMI	Females	0.8 (-0.3, 1.8)	0.14
	Males	0.6 (0.01, 1.2)	0.05

Females vs Males

		Mean Difference (95% CI)	p value
BASDAI	No depression	0.7 (0.2, 1.2)	<0.01
	Depression	1.5 (0.2, 2.7)	0.02
BASFI	No depression	0.3 (-0.2, 0.9)	0.24
	Depression	1.5 (0.1, 3.0)	0.04
HAQ	No depression	0.1 (-0.1, 0.2)	0.26
	Depression	0.4 (0.1, 0.7)	<0.01
ASQoL	No depression	1.0 (-0.2, 2.0)	0.12
	Depression	2.9 (-0.7, 5.9)	0.06
BASMI	No depression	-0.7 (-1.1, -0.2)	<0.01
	Depression	-0.5 (-1.6, 0.6)	0.39

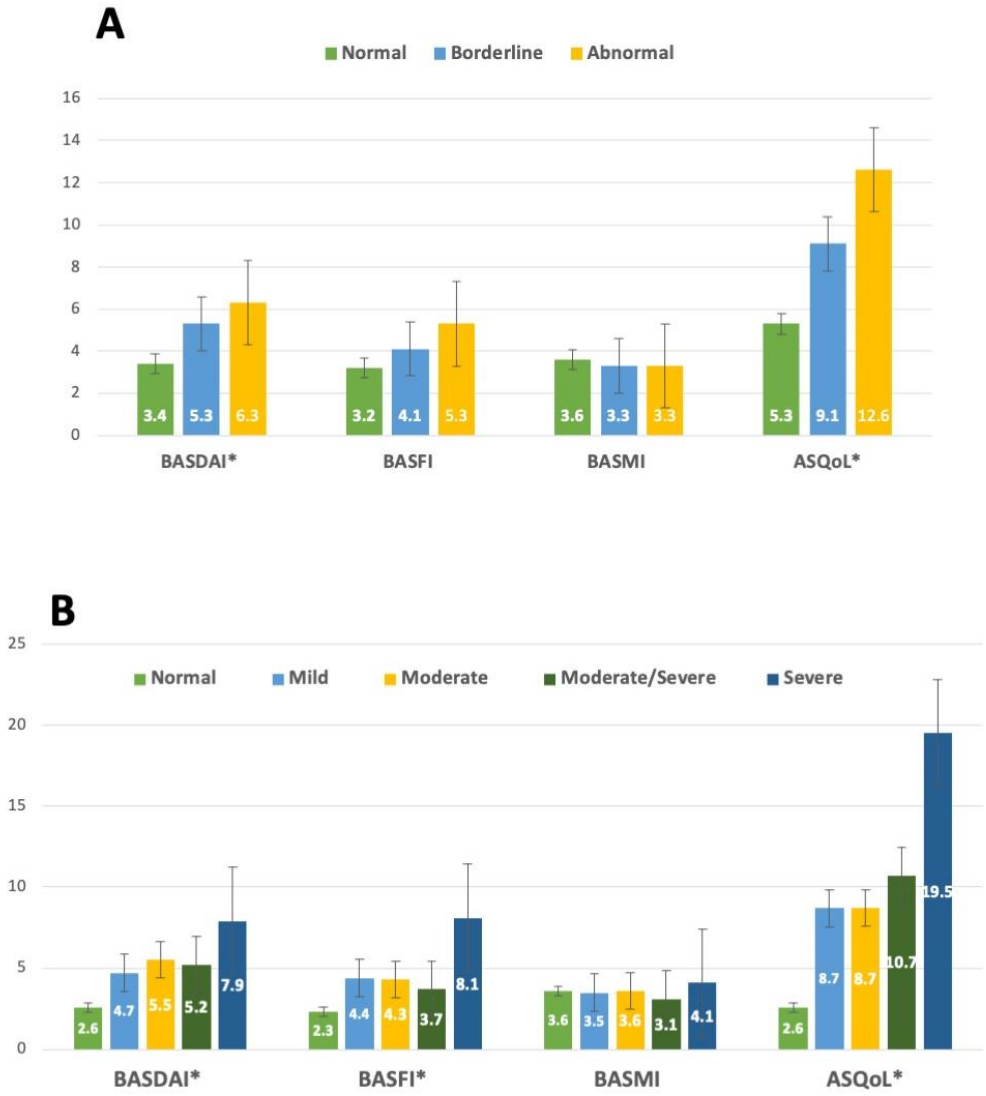
Abbreviations: *BASDAI -Bath Ankylosing Spondylitis Disease Activity Index, BASFI - Bath Ankylosing Spondylitis Functional Index, HAQ -Hospital Assessment Questionnaire, ASQoL -Ankylosing Spondylitis Quality of Life scale, BASMI -Bath Ankylosing Spondylitis Spinal Metrology Index*

4.3.4.2 Screening for Undiagnosed Depression

In total, 71 axSpA patients took part in the survey. The population was 70.4% (50) males and 29.5% (21) females, with an average age 47.9 years (SD 15.4, range 20-78) and median disease duration 15 years (8, 32). Mean scores for participants were: BASDAI 4.1 (SD 2.3), BASFI 3.6 (SD 2.5), BASMI 3.5 (SD 1.8), and ASQoL 6.7 (SD 5.2). Overall, seven (9.9%) participants recorded abnormal HADS-D scores, while 17 (23.9%) recorded moderate to severe PHQ-9 scores indicative of underlying depression. AxSpA females had higher mean HADS-D scores (7.5 vs 4.8, p=0.01) than males, with abnormal scores in 19% (4) of females and 6% (3) of males. No significant differences were found in PHQ-9 scores between genders.

Analysis revealed significantly worse BASDAI (6.3 vs 3.4, 95% CI 1.2-4.5, p<0.01) and ASQoL scores (12.6 vs 5.23, 95% CI 3.7-11, p<0.01) in axSpA patients with abnormal compared to normal HADS-D scores (figure 4.4). No significant differences were noted in BASFI, BASMI or baseline demographics. A similar pattern was noted on analysis of PHQ-9 scores, with significantly worse BASDAI (7.9 vs 2.56, 95% CI 3.0-7.8, p<0.01), BASFI (8.1 vs 2.3, 95% CI 2.6-8.8, p<0.01) and ASQoL (19.5 vs 2.6, 95% CI 12.9-19.8, p<0.01) noted in those scoring as severe compared to normal. No significant differences were detected in BASMI scores or baseline demographics.

Figure 4.4: Patient outcomes by classification with (A) HADS-D score and (B) PHQ-9 score, *indicates statistically significant differences between classification categories at the p<0.05 level



Abbreviations: *BASDAI -Bath Ankylosing Spondylitis Disease Activity Index; BASFI -Bath Ankylosing Spondylitis Function Index; BASMI -Bath Ankylosing Spondylitis Metrology Index; ASQoL -Ankylosing Spondylitis Quality of Life scale; HAQ -Hospital Assessment Questionnaire*

Hierarchical multiple regression models made up of sex, age, BASFI, BASMI and HADS-D or PHQ-9 score to predict BASDAI and ASQoL were statistically significant. (Table 4.6). In each model the addition of HADS-D score or PHQ-9 scores led to a statistically significant increase in adjusted R^2.

Table 4.6: Hierarchical multiple regression predicting BASDAI and ASQoL from: age, sex, BASFI, BASMI and either HADS-D scores or PHQ-9 scores

	BASDAI	ASQoL
Age	0.01 (-0.26, 0.05)	-0.01 (-0.07, 0.06)
Sex	0.13 (-0.87, 1.11)	-0.29 (-2.07, 1.49)
BASFI	0.56 (0.31, 0.81)	1.8 (1.34, 2.25)
BASMI	-0.14 (-0.52, 0.25)	-0.57 (-1.26, 0.13)
HADS-D score	1.05 (0.35, 1.75)	1.7 (0.43, 2.98)
Adjusted R^2	54.2%	70.9%
R^2 change with HADS-D score	8.5	4.3
p value	<0.01	<0.01
	BASDAI	**ASQoL**
Age	0.01 (-0.03, 0.05)	-0.002 (-0.06, 0.06)
Sex	0.37 (-0.62, 1.36)	-0.13 (-1.65, 1.38)
BASFI	0.52 (0.23, 0.81)	1.43 (0.98, 1.87)
BASMI	-0.15 (-0.56, 0.26)	-0.35 (-0.96, 0.28)
PHQ-9 score	0.60 (0.04, 1.16)	2.03 (1.18, 2.88)
Adjusted R^2	50.1%	77.8%
R^2 change with PHQ-9 score	4.8	10.4
p value	<0.01	<0.01

Abbreviations: *BASDAI -Bath Ankylosing Spondylitis Disease Activity Index; Ankylosing Spondylitis Quality of Life Questionnaire; BASFI -Bath Ankylosing Spondylitis Functional Index; BASMI -Bath Ankylosing Spondylitis Metrology Index; PHQ-9 -Patient Health Questionnaire 9*

4.3.5 Discussion

This analysis was unique in capturing depression prevalence and subsequent impact in axSpA via two approaches and perspectives. Analysis of outcomes from the ASRI allowed for calculation of prevalence of depression and its effects in a large axSpA cohort. Additional prospective screening for undiagnosed depression demonstrated the under recognition of this condition in an axSpA cohort and the significant impact it can have on all aspects of a patient's life.

Depression is a commonly encountered comorbidity in patients with axSpA affecting 10.1% of the ASRI cohort. These patients were found to have significantly worse levels of all outcome measures captured in this analysis. Depressed patients were more likely to be smokers, consistent with the large body of current research on this topic[347]. It was interesting to find current alcohol intake was more commonly encountered in the non-depression cohort, with higher rates of past alcohol intake noted in the depression cohort. The reason for this is unknown but given the known association between alcoholism and depression[348], this could indicate recovery from previous alcohol addiction.

Analysis of the effects of depression between sexes revealed similar prevalence of depression between males and females in our cohort. However, axSpA females with depression recorded significantly worse scores of disease activity and function as detailed in figure 1. In the prospectively screened cohort, axSpA females also recorded significantly worse mean HADS-D scores, yielding a higher prevalence of borderline and abnormal scores compared to axSpA males. These results raise concerns around the high prevalence of undiagnosed depression in axSpA females and the impact on disease control.

There has been significant research into the prevalence of depression in ankylosing spondylitis, with fewer studies on axSpA. Despite this, the true prevalence of depression in axSpA remains difficult to capture, as illustrated in a meta-analysis which reported a prevalence range of 11% to 64%, with pooled prevalence of moderate depression of 15%[340]. Reasons for this variation are multifactorial but include variation in diagnostic criteria, use of diagnostic tools, socioeconomic status and sampling methods.

Of the prospectively screened cohort, a high percentage of axSpA patients recorded high HADS-D and PHQ-9 scores suggestive of undiagnosed depression. Abnormal PHQ-9 scores were more commonly encountered than elevated HADS-D scores (23.9% vs 9.9%), with greater significance detected in variation of outcome measures between patient groups as determined by their PHQ-9 scores. It is notable that axSpA females recorded significantly worse mean HADS-D scores than males. Elevated PHQ-9 scores and HADS-D scores were encountered more frequently in patients with worse BASDAI and ASQoL scores. This indicates that these axSpA patients have significantly worse disease activity and quality of life compared to patients with

normal scores. These findings would suggest that clinicians treating axSpA should consider mental health and potentially consider screening for depression in this population. Our results are supported by those in the Atlas study which determined a higher percentage of axSpA patients were at risk of mental health disorders[349], with higher levels of disease activity identified as a significant risk factor. These findings would suggest that clinicians treating axSpA should consider mental health and potentially consider screening for depression in this population. Furthermore, future management strategies in axSpA would benefit from considering the psychosocial influences of the disease experience when assessing patient outcomes.

Use of self-administered surveys, such as the PHQ-9 and the HADS, are quick and effective options for rapidly screening axSpA patients in a busy Rheumatology department. These tools have demonstrated reliability in patients with other rheumatic diseases[350,351] as well as non-rheumatology patients with chronic medical conditions[352,353]. The HADS-D is especially sensitive for detecting emotional distress but does not capture somatic symptoms, while the PHQ-9 is based on the Diagnostic and Statistical Manual of Mental Disorders(DSM) IV criteria for depression with strong psychometric properties[354]. Use of these tools in combination can aid in detection of both somatic and psychological symptoms concerning for the presence of undiagnosed depression.

During the course of this study our investigators found use of these surveys often prompted discussions with the physicians about the importance of monitoring mental health. Given the considerable societal stigma surrounding mental health issues, use of such tools could help to break down barriers to these essential conversations and improve health literacy for our patients.

The relationship between disease activity and depression symptoms is complex to interpret. Patients with active disease could experience greater levels of functional impairment and lower quality of life increasing their risk of developing depression. However, patients with depression may also experience worse quality of life causing functional limitations and increased reporting of symptoms. Webers et al[344] suggested that mastery, the extent to which a person feels in control of major life issues including disease, plays a key role in depression in axSpA. Further collaborative research between Rheumatology, Psychiatry and Psychology is needed to fully understand this relationship.

4.3.5.1 Limitations

In patients with confirmed depression, diagnosis was made by a relevant treating physician, with confirmation obtained from medical records. As such we were unable to examine criteria used to make this diagnosis to ensure standardisation across the cohort. Information on severity of depression, subtype of depression, age at diagnosis or duration of depression and details of depression treatment were not included in the data collection of the ASRI. Thus, further sub-analyses could not be carried out to examine the impact of these factors on patient outcomes in axSpA.

4.3.6 Conclusion

Depression is a prevalent comorbidity in axSpA as captured within the patient population of the ASRI. AxSpA patients with depression have significantly worse outcome measures reflecting a greater burden of disease and worse quality of life. A high percentage of axSpA patients recorded high HADS-D and PHQ-9 scores suggestive of undiagnosed depression. The effects of depression are especially notable in females with axSpA, in addition axSpA females may have a higher prevalence of undiagnosed depression compared to axSpA males. The impact of this prevalent mental health issue cannot be understated. Clinicians treating axSpA should consider screening for depression in this population.

4.4 Social Isolation due to the COVID-19 Pandemic has led to Worse Outcomes in Females with Inflammatory Arthritis

4.4.1 Abstract

Background

Prolonged social isolation as a result of the COVID-19 global pandemic has been a source of considerable psychological distress for many people. This can manifest in many ways and if left undetected can impact negatively on general health. It is essential to understand the impact of these conditions on inflammatory arthritis (IA) patients, especially axial spondyloarthritis (axSpA). The aim of this study is to capture the level of psychological distress for patients with IA following prolonged social isolation.

Methods

A survey was sent to patients with a confirmed diagnosis of IA, including axSpA. This captured changes in sleep, mood, disease activity, employment and general health since the beginning of the social isolation period. A PHQ-4 (Patient Health Questionnaire) was included to determine level of psychological distress. Initial analysis included all patients with IA, with a subgroup analysis performed on only axSpA patients.

Results

Females with IA reported significantly higher rates of decline in general health (40% vs 16%, p=0.01), mood disturbance (43.4% vs 26%, p=0.03) and increased disease activity (50% vs 16%, p=0.01) compared to males. No significant difference was noted between genders in the mean PHQ-4 scores (4.80 vs 3.44, p=0.10). However, females demonstrated a non-significant trend toward increased rates of moderate to severe psychological distress (40% vs 30%, p=0.13). Subgroup analysis of patients with axSpA found high rates of moderate to severe distress in both sexes.

Conclusion

Females with IA reported significantly higher rates of decline in general health, mood disturbance, and increased disease activity during the period of social isolation. This was reflected in a trend towards greater levels of psychological distress.

4.4.2 Background

Quarantine and social isolation are public health measures used to contain and prevent the spread of an infectious disease[355]. Throughout human history, a number of infectious diseases have required periods of quarantine to prevent widespread illness and death. Use of these measures were first described in Venice due to the Black Plague, with more recently mandated quarantines for the severe acute respiratory syndrome (SARS) and Ebola outbreaks[356]. The Coronavirus 2019 (COVID-19) pandemic is unprecedented in many ways, with almost 4 billion of the world's population required to live in social isolation. In Ireland, and much of the European Union, social isolation had gone on for over three months at the time of this study. Although restrictions were slowly being lifted, it was expected that social distancing and normal life as we know it will not be able to resume until a vaccine is widely available.

This prolonged period of social isolation has affected multiple aspects of everyday living. These disruptions have the potential for far-reaching effects if not identified and addressed promptly. During this time a number of households are under significant financial strain, without childcare, working from home and managing remote education for children. These new challenges in addition to concerns around COVID-19 infection and transmission could lead to significant psychological distress.

Given the setting of a global pandemic, some distress is to be anticipated. However, cases of extreme psychological distress, if left unrecognised, can impact both general health in addition to significantly affecting long-term mental health. It is essential to identify patients at high risk of developing severe psychological distress and address the triggers when possible.

Inflammatory arthritis (IA) refers to systemic autoimmune mediated diseases affecting the joints. Patients with this type of diagnosis commonly require lifelong medication to decrease inflammation, manage symptoms and prevent progression of disease. Regular exercise and stretching is also an essential component of management. Patients with axial spondyloarthritis (axSpA) have been previously shown to have increased rates of depression[338] and there is a trend towards higher levels of disease activity in patients with depression[344]. For this reason, it is essential to understand the impact of the COVID-19 pandemic on axSpA patients, in order to address their needs and concerns in the months to come.

The aim of this study is to capture the level of psychological distress for patients with inflammatory arthritis and understand how this is affecting their disease and general health.

4.4.3 Methods

4.4.3.1 Study Design

A survey was distributed in May 2020, to patients attending the department of Rheumatology in St James' Hospital. Eligible patients were over the age of 18, fluent in English and had a confirmed diagnosis of inflammatory arthritis including axSpA. Participation was voluntary. Results of the survey were analysed on the basis of sex and diagnosis.

The survey captured information on changes in sleep, mood, disease activity, exercise, employment and general health since the beginning of the social isolation period. Changes were quantified as improved, no change or worsened.

A PHQ-4 (Patient Health Questionnaire) was included to determine level of psychological distress. This four-question tool generates a numerical result corresponding with the following levels of psychological distress: 0-2 = none, 3-5 = mild, 6-8 =moderate, 9-12 = severe. To capture the level of social interaction patients were asked if they were in isolation with other people or alone. For patients who were employed, they were asked if they were working remotely or on site.

4.4.3.2 Data Analysis

Analysis was performed using IBM SPSS version 26. Distribution of data was assessed with a Shapiro-Wilk's test for normality. Categorical variables were expressed as frequencies with percentages, while categorical variables were expressed as means with standard deviations (SD) or medians with 25th and 75th centiles depending on normality of distribution. An independent sample t-test was used to test for significance in differences of means between groups, including age and PHQ-4 scores. A chi^2 test for independence was used to test categorical variables. A p value of <0.05 was deemed significant. PHQ-4 scores were tested by mean overall scores and prevalence of each category between comparison groups.

4.4.4 Results

In total, 88 completed surveys were returned, of these 80 contained data on sex and were included in this analysis. Patients were 37.5% (30) females and 62.5% (50) males with a mean age of 50.7 (SD 13.7) years (table 1). Population was predominantly axSpA patients 73.8% (59) with 26.3% (21) patients with inflammatory arthritis, 50% (40) were currently employed and of this, 47.5% (19) of patients were working from home. Of the 54.5% (48) of patients who were unemployed 35% (17) had become unemployed since the Covid-19 imposed shutdowns began. Median PHQ-4 score was 3 (0, 7), corresponding with a level of mild psychological distress. Analysis of patients by diagnosis revealed no significant differences in outcome measures between IA and axSpA. Patients with IA were noted to be older than axSpA patients (57.9 vs 48.3 years, p=0.02).

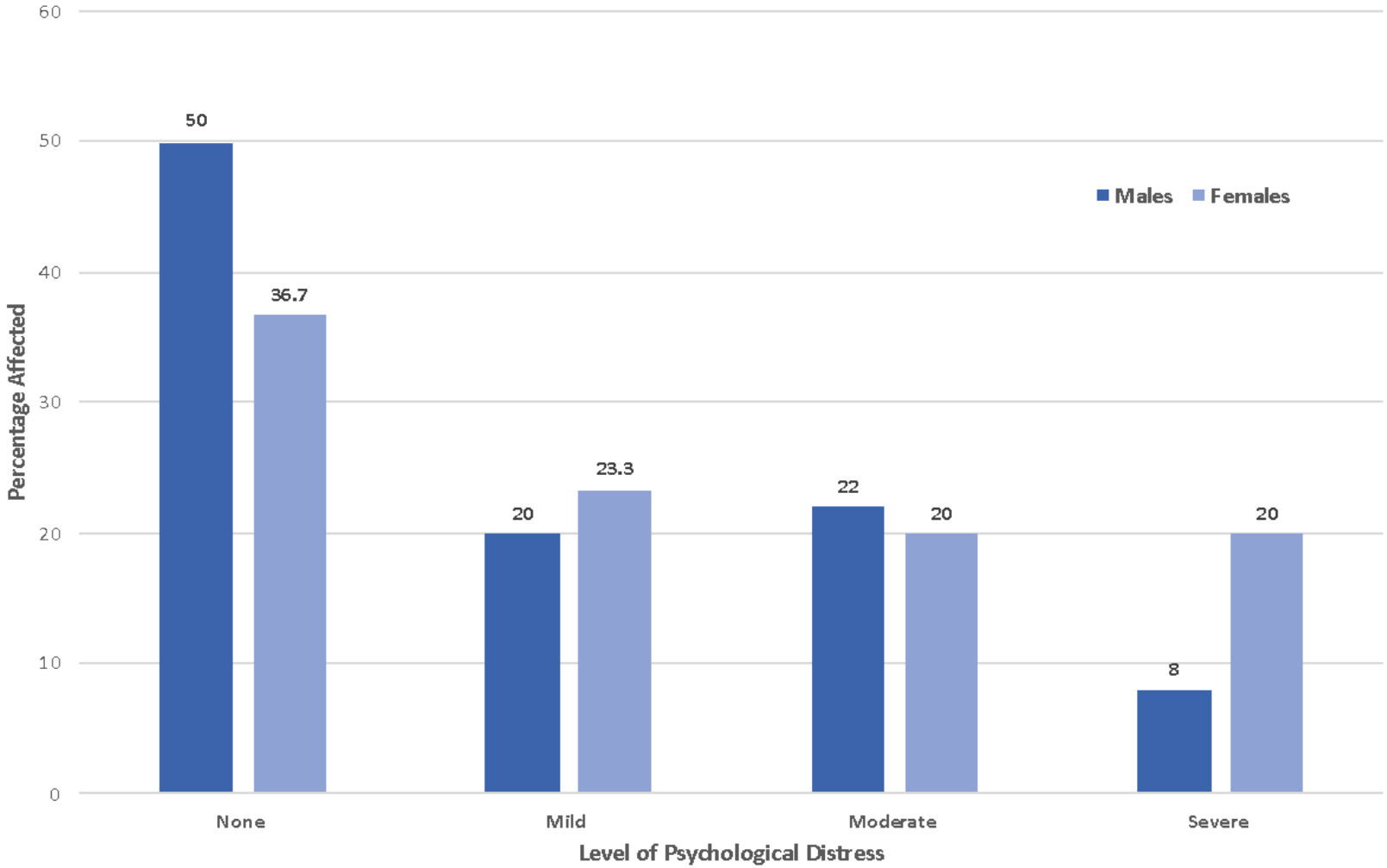
Eighty responses contained data on sex. Overall, females reported significantly higher rates of mood disturbance (43.4% vs 26%, p=0.03) and increased disease activity (50% vs 16%, p=0.01) compared to males (table 4.7). Females also reported high rates of decline in general health (40% vs 16%, p=0.01). No differences were detected in sleep quality or weekly exercise. Similar rates of employment were noted in both groups.

Table 4.7: Overall Outcomes by Sex

	Males	Females	*p-value*
n	62.5% (50)	37.5% (30)	
Age	50.1 (14.8)	50.5 (11.7)	0.91
General Health			**0.01**
Improved	20% (10)	30% (9)	
No change	64% (32)	30% (9)	
Worsened	16% (8)	40% (12)	
Sleep Quality			0.2
Improved	12% (6)	10% (3)	
No change	68% (34)	43.4% (13)	
Worsened	20% (10)	43.4% (13)	
Mood			**0.03**
Improved	8% (4)	26.7% (8)	
No change	64% (32)	30% (9)	
Worsened	26% (13)	43.4% (13)	
Disease Activity			**0.01**
Improved	10% (5)	20% (6)	
No change	70% (35)	30% (9)	
Worsened	16% (8)	50% (15)	
Weekly Exercise			0.26
Increased	26% (13)	43.4% (13)	
No change	44% (22)	33.3% (10)	
Decreased	30% (15)	23.3% (7)	
Self-Isolation Companions			0.16
Alone	22% (11)	10% (3)	
Family or Partner	76% (38)	90% (27)	
Currently Employed			0.55
Yes	42% (21)	53.3% (16)	
No	58% (29)	46.7% (14)	
Unemployed due to COVID-19	22% (11)	16.7% (5)	0.49
Work Location			0.54
Home	16% (8)	33.3% (10)	
On site	20% (10)	13.3% (4)	
Other	4% (2)	6.7% (2)	
Engagement with patient support group	4% (2)	3.3% (1)	0.25

No significant difference was detected in mean PHQ-4 scores or distribution or level of psychological distress, however females demonstrated a non-significant trend towards higher rates of severe distress (20% vs 8%, p=0.13) (figure 4.5).

Figure 4.5: Prevalence of PHQ-4 Outcomes by Sex



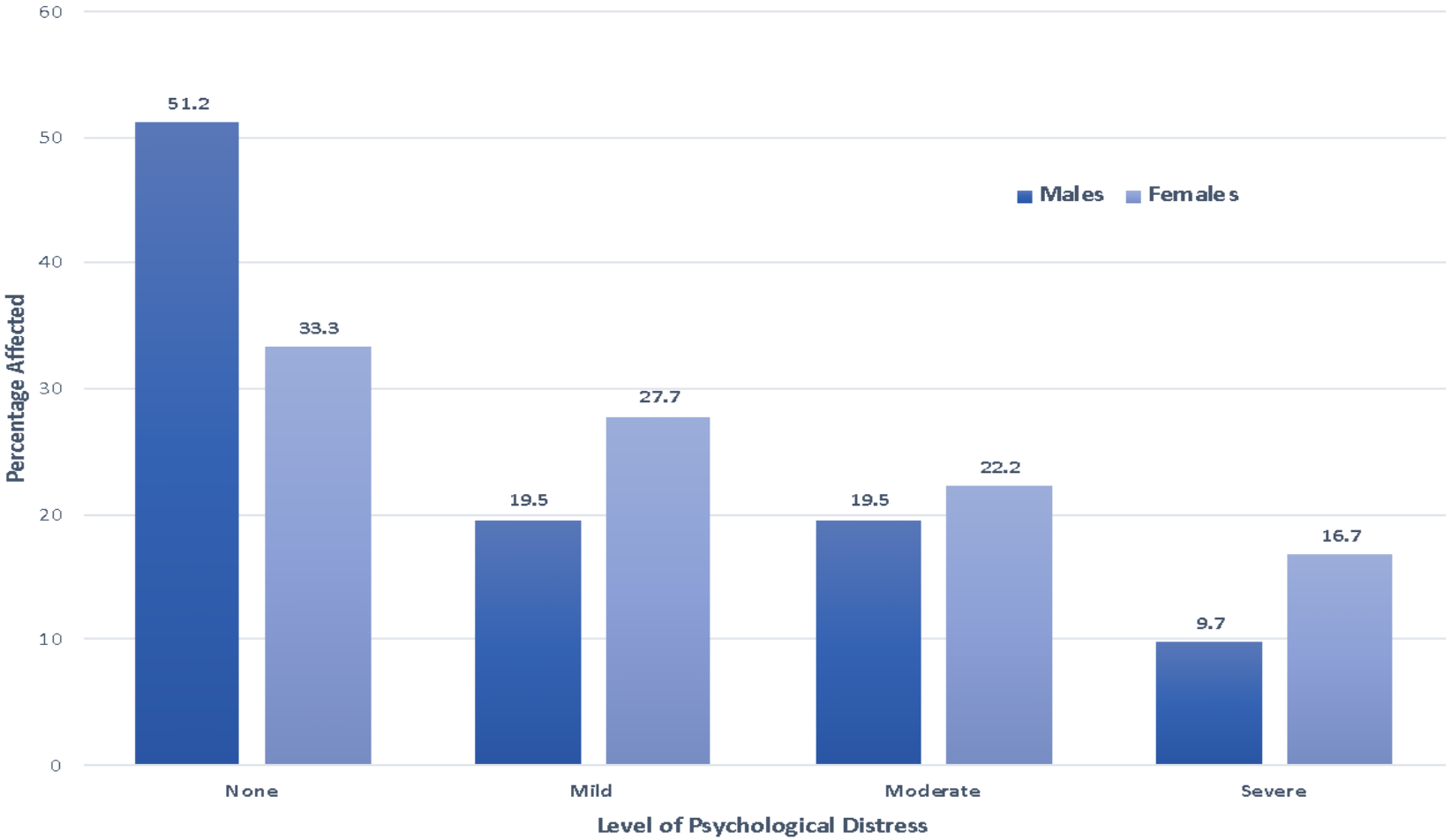
Further analysis focused on axSpA patients alone on the basis of sex. Of the 59 axSpA patients included in the analysis, 30.5% (18) were female and 69.5% (41) male (table 4.8). AxSpA females had higher rates of decline in general health (50% vs 17.1%, p=0.02) and increased disease activity (50% vs 17%, p=0.04) compared to axSpA males. Although axSpA females had increased rates of mood disturbance (44.4% vs 26.8%, p=0.1) this did not reach significance.

Table 4.8: Outcomes in AxSpA by Sex

	Males	Females	*p-value*
n	69.5% (41)	30.5% (18)	
Age	49.6 (15)	45.6 (10.7)	0.36
General Health			**0.02**
Improved	19.5% (8)	27.7% (5)	
No change	63.4% (26)	22.2% (4)	
Worsened	17.1% (7)	50% (9)	
Sleep Quality			0.18
Improved	9.7% (4)	16.7% (3)	
No change	70.1% (29)	38.9% (7)	
Worsened	19.5% (8)	44.4% (8)	
Mood			0.1
Improved	7.3% (3)	27.7% (5)	
No change	63.4% (26)	27.7% (5)	
Worsened	26.8% (11)	44.4% (8)	
Disease Activity			**0.04**
Improved	7.3% (3)	22.2% (4)	
No change	73.2% (30)	27.7% (5)	
Worsened	17.1% (7)	50% (9)	
Weekly Exercise			0.26
Increased	22% (9)	44.4% (8)	
No change	46.3% (19)	27.7% (5)	
Decreased	31.7% (13)	27.7% (5)	
Self-Isolation Companions			0.09
Alone	22% (9)	5.6% (1)	
Family or Partner	75.6% (31)	94.4% (17)	
Currently Employed			0.73
Yes	46.3% (19)	55.6% (10)	
No	53.7% (22)	44.4% (8)	
Unemployed due to covid-19	19.5% (8)	27.7% (5)	0.13
Work Location			0.54
Home	17.1% (7)	38.9% (7)	
On site	22% (9)	11.1% (2)	
Other	4.9% (2)	5.6% (1)	
Engagement with patient support group	2.4% (1)	5.6% (1)	0.75

No significant difference was noted in mean PHQ-4 scores (4.78 vs 3.44, p=0.18) or level of psychological distress, but axSpA females demonstrated a non-significant trend towards higher rates of psychological distress than males (figure 4.6).

Figure 4.6: Prevalence of PHQ-4 Outcomes in AxSpA by Sex



4.4.5 Discussion

The COVID-19 global pandemic led to an abrupt and prolonged period of social isolation to stem spread of the virus. This analysis demonstrates the significant effect of these lifestyle changes on patients with inflammatory arthritis. Use of the PHQ-4 allowed for quantification of the level of psychological distress during this time with over 59% of patients surveyed reporting some level of distress. Females reported high levels of decline in general health, mood disturbance and increased disease activity. This is reflected in higher mean PHQ-4 scores and increased rates of moderate to severe psychological distress in females compared to males. Subgroup analysis of the axSpA patients alone demonstrated similar findings but did not reach significance in variation of mood disturbance. These results are similar to a Spanish study which reported 37% of patients with rheumatic disease experienced an increase in disease activity while 75% developed a mood disorder during lockdown[357]. Of note, incidence of COVID-19 in patients with RMDs was observed to be lower than that of the general population in the early stages of the pandemics which was suspected to be secondary to high levels of social isolation[358,359].

Previous studies have shown prolonged social isolation can lead to decreased work performance and increased risk of mental health disorders[360]. Addressing the issues identified in this analysis will require considerable time, education and energy from clinicians. Recognising those most affected is only the first step in aiding recovery. The WHO has encouraged healthcare workers to be familiar with resources available to support patients requiring psychosocial support[361]. Encouraging regular exercise[362], increased reliance on digital communication[363] and social integration[66] are strategies proposed to decrease psychological distress under current restrictions.

It is unclear why disease activity and general health outcomes are worse in females than males. One potential contributing factor is the increased rates of females working from home, while males more commonly worked on site. Females also reported higher rates of sleep disturbance which did not reach significance but could be contributory. Discussion with individual patients to identify potential causes of distress would provide further insight into this issue.

As this study was conducted via mail survey with an overall response rate of 44%, a potential limitation of the study was nonresponse bias. However, the sample respondent groups were highly representative of both patient populations surveyed in terms of age and gender, which has been shown to decrease the risk of nonresponse bias[364,365].

4.4.6 Conclusion

This analysis demonstrates that the impact of the pandemic extends beyond physical wellbeing and disease activity. Prompt recognition of psychological distress and other effects of prolonged social isolation will help in managing patients going forward.

4.5 Summary of Findings

Unemployment is alarmingly common in patients with known axSpA. This is a cause for concern not only for economic purposes but also in terms of disease control, as unemployed patients reported significantly higher levels of disease activity, poorer levels of functional ability and worse overall quality of life. Men were more frequently unemployed than women, although a large proportion of both sexes reported work limitations due to their disease.

The studies on depression and mental health also revealed clear differences in men and women with axSpA. Depression was very prevalent in the ASRI population and was associated with worse patient reported outcome measures. However, depression was noted to have a greater impact on outcomes in women with axSpA. Results of the screening study would also suggest that the prevalence of undiagnosed depression is higher in axSpA women compared to men.

The final study in this chapter was undertaken during the initial wave of the COVID-19 pandemic in Ireland. This clearly demonstrated that while there was a trend for women with axSpA to be more frequently employed, they also suffered higher levels of psychological distress during this time. This was associated with worsening of their disease activity and general health during this time.

These studies clearly demonstrate significant sex differences between men and women with axSpA. To evaluate this further the following chapter examines these differences directly as well as examining how tools to capture disease activity perform in both sexes.

Chapter 5. Worse Scores but Similar Patterns of Disease Activity: Interpreting Outcomes in Women with Axial Spondyloarthritis

Publication resulting from material contained within this chapter:

S Maguire, F Wilson, P Gallagher, F O'Shea. Worse Scores but Similar Patterns of Disease Activity: Interpreting Outcomes in Women with Axial Spondyloarthropathy. *Scandinavian Journal of Rheumatology.* 2022 Jan; 1-8. DOI: 10.1080/03009742.2021.2007609

(Full manuscript in Appendix A)

5.1 Abstract

Objective

The aim of this study was to examine trends in patient outcomes in axSpA to understand the impact of sex in reporting of disease activity in axSpA.

Methods

Data was extracted from the Ankylosing Spondylitis Registry of Ireland (ASRI), a registry of patients with axSpA in Ireland. Patients were analysed on the basis of sex, with a series of comparison analyses performed.

Results

Overall, 886 participants were enrolled in the ASRI, composed of 26.2% (232) females and 72.6% (644) males. Females recorded significantly worse BASDAI (4.6 vs 3.8, $p<0.01$) and ASQoL (7.5 vs 6.1, $p<0.01$) compared to males. There was a stronger correlation in BASFI and BASMI in females ($r_s= 0.619$, $p<0.01$) compared to males ($r_s =0.572$, $p<0.01$]. Analysis of the BASDAI revealed the higher total scores in females compared to males was not due to any single component, but rather worse scores in all 6 components of the BASDAI combined. Furthermore, ranking of components by severity between sexes revealed identical ranking in 4 of the 6 components of the BASDAI.

Conclusion

Women with axSpA reported significantly worse outcome scores compared to men, however a similar pattern of disease activity as captured by the BASDAI was noted in men and women. Limitation of spinal mobility in women with axSpA corresponded with a greater impairment in functional ability. Further evaluation of disease monitoring tools are required to ensure disease activity is accurately captured in men and women with axSpA.

5.2 Background

The findings of the previous chapter highlight the notable differences between men and women with axial spondyloarthritis (axSpA). In chapter 4 this was noted in the context of employment and mental health. However, these differences led us to question how else the patient experience and burden of disease in axSpA varies between sexes. To thoroughly explore this critical issue, this chapter contains a dedicated analysis examining sex differences in axSpA.

There has been a considerable shift in sex distribution of axSpA over time. Historically described as strongly male predominant disease with male to female sex ratios reported as high as 10:1[366], more recent studies have reported ratios closer to 2-3:1[261]. One of the major factors contributing to this dramatic shift is the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA which recognised not only r-axSpA, also referred to as ankylosing spondylitis (AS), but also nr-axSpA[2]. While initially believed to represent an early stage of disease, longitudinal studies have demonstrated that only 10-40% of nr-axSpA will advance to r-axSpA over time[367]. As women with axSpA are more likely to have non-radiographic disease[262], the formal recognition of nr-axSpA allowed these women to have not only a diagnosis of their condition but also to be eligible for treatment previously reserved for r-axSpA only.

Despite evolution of classification and epidemiology of axSpA, much of what is known about axSpA is based on research of men with AS[20]. As a result, there remains a considerable underrepresentation of axSpA in women in published research. Combined with the under-recognition of the disease in women[368,369], there is a significant need for increased awareness and focused research on the sex-specific impact and disease manifestations of axSpA[370]. Detailed analysis and characterisation of axSpA in women is the first step in optimising management and outcomes in this significant proportion of the population.

The aim of this study is to carry out a focused analysis of disease activity, reporting of disease and impact of disease in women compared to men with axSpA. This sex-based analysis goes beyond summary comparisons, to capture how axSpA affects women, examine the relationship between functional ability and spinal mobility and to highlight directions for future research.

5.3 Patients & Methods

5.3.1 Patient Population

Data for this analysis was captured via the Ankylosing Spondylitis Registry of Ireland (ASRI). This large national registry recruits patients with axSpA from Rheumatology centres across the country. Full details on patient population including eligibility criteria and data captured within this registry are discussed at length in Chapter 3: Methods under "Patient Population".

5.3.2 Outcomes & Assessments

Full discussion of outcomes captured within the ASRI are included in Chapter 3: Methods under "Data Collection" and "Outcome Measures."

5.3.3 Statistical Analysis

Data was extracted from the ASRI and cleaned to allow for analysis. A series of descriptive comparison analyses were carried out on all participants captured in the ASRI stratified on the basis of sex. A Shapiro Wilk's test was used to assess normality of distribution for all included variables. Categorical variables were expressed as frequencies with percentages, while continuous variables were expressed as means with standard deviations (SD) or median with 25th and 75th centiles as appropriate. Differences between continuous variables in the two groups was tested for significance using an independent two tailed t-test or a Mann Whitney U test. A chi-squared test for independence assessed for statistical significance in differences of categorical variables between sexes.

Focused analysis of the BASDAI involved comparison of mean total score and mean component scores between sexes. In addition to statistical testing for significance of differences, components were ranked by average scores within each sex with average component scores plotted in a spider chart for visualization of results.

For the correlation analysis, data from patients with both BASFI and BASMI scores were included. Variables were assessed with a Shapiro-Wilk's test for normal distribution in addition to visual inspection of a scatter plot to determine presence of a monotonic relationship between the two variables. Once established, a Spearman's rank-order correlation was run between the two PROs. Records were then split by sex and a Spearman's rank-order correlation was undertaken to assess strength of correlation of scores within each sex. An alpha level of $p < 0.05$ was deemed significant. IBM SPSS version 26 was used to carry out all statistical analyses in this study.

5.4 Results

At the time of data extraction 886 participants were enrolled in the ASRI. The patient population was 26.2% (232) females, 72.6% (644) males, with mean age of 45.9 years (standard deviation [SD] 12.6, range 18-85), median disease duration of 17.1 years (9.5, 27.8) and median delay to diagnosis of 5 years (2, 12). Mean scores for the ASRI population were: ASQoL 6.5(95% CI 6.1-7.0), HAQ 0.53(95% CI 0.55-0.6), BASDAI 4.0(95% CI 3.8-4.2), BASFI 3.7(95% CI 3.5-3.9), BASMI 4.0 (95% CI 3.9-4.2). The majority of the population was Caucasian (90.2%), with a high prevalence of HLA-B27 positivity (88.7%).

5.4.1 Clinical Characteristics & Burden of Disease

No significant differences were noted in average delay to diagnosis (females vs males: 5 vs 6; 95% CI -2.0, 0.5; p=0.24) or age at symptom onset (24.2 vs 23.7; 95% CI -2.5, 1.0; p=0.41) between sexes (Table 5.1). Radiographic axSpA was more commonly encountered in males than females (78.1% vs 70.7%, p=0.02), while non-radiographic axSpA was significantly more prevalent in females (21.9% vs 29.3%, p=0.02).

Table 5.1: Analysis of patient characteristics on the basis of sex*

	Females	Males	p value
n	26.2% (232)	72.6% (644)	
Age	43.8 (11.7)	46.5 (12.8)	**0.01**
Delay to diagnosis	5 (2, 13)	6 (2, 12)	0.64
Symptom onset age	24.2 (19, 30)	23.7 (19, 33)	0.41
Disease duration	15.8 (9, 25)	17.2 (10, 29)	0.06
Caucasian	78% (181)	96% (618)	**<0.01**
HLA-B27+	72.2% (164 of 227)	89.9% (438 of 487)	0.68
r-axSpA	70.7% (164)	78.1% (503)	**0.02**
nr-axSpA	29.3% (68)	21.9% (141)	**0.02**
Patterns of Disease			
Peripheral Arthritis	36.2% (84)	28.3% (182)	0.08
Enthesitis	18.5% (43)	16.9% (109)	0.56
Dactylitis	9.9% (23)	5% (32)	**0.01**
EAMs			
Psoriasis	17.2% (40)	16.1% (104)	0.21
Uveitis	40.5% (94)	35.7% (203)	**0.01**
Colitis	17.2% (40)	7.9% (51)	**<0.01**
Medications			
NSAIDs	55.6% (129)	49.4% (318)	0.2
DMARDs	22.4% (52)	23.9% (154)	0.29
Biologics	66.8% (155)	68.2% (439)	0.81
Current ESR	12 (6, 22)	9 (4, 19)	**0.04**
Current CRP	2.4 (1, 8)	3.0 (1, 8)	0.46
Patient Outcomes			
BASDAI	4.6 (2.5)	3.8 (2.4)	**<0.01**
BASFI	3.9 (2.6)	3.6 (3)	0.32
BASMI	3.6 (2)	4.2 (2.1)	**<0.01**
HAQ	0.50 (0.3, 0.9)	0.37 (0.0, 0.8)	0.05
ASQoL	7.5 (5.7)	6.1 (5.5)	**<0.01**

*Results displayed as %(n) for categorical variables, mean (standard deviation) or median (25th centile, 75th centile) as appropriate

Abbreviations: *HLA-B27 -human leukocyte antigen B27, r-axSpA -radiographic axSpA, nr-axSpA -non-radiographic axSpA, EAMs -extra-articular manifestations, NSAIDs -non-steroidal anti-inflammatories, DMARDs -disease modifying anti-rheumatic drugs, ESR -erythrocyte sedimentation rate, CRP -C reactive protein, BASDAI -Bath Ankylosing Spondylitis Disease Activity Index, BASFI -Bath Ankylosing Spondylitis Functional Index, BASMI -Bath Ankylosing Spondylitis Spinal Metrology Index, HAQ -Hospital Assessment Questionnaire, ASQoL -Ankylosing Spondylitis Quality of Life questionnaire*

In terms of articular manifestations, females were found to have a significantly higher prevalence of dactylitis (9.9% vs 5%, p=0.01) and a trend towards an increased prevalence of peripheral arthritis (36.2% vs 28.3%, p=0.08). For extra-articular manifestations (EAMs) females reported significantly higher prevalence of both uveitis (40.5% vs 35.7%, p=0.01) and colitis (17.2% vs 7.9, p<0.01) compared to males.

Analysis of medication usage revealed no significant difference in terms of use of NSAIDs (55.6% vs 49.4%, p=0.02) or DMARDs (22.4% vs 23.9%, p=0.29). A high proportion of the total population were prescribed biologic agents (67.9%) with no differences detected between female and male participants (66.8% vs 68.2%, p=0.81).

In terms of previously failed biologic therapies, females were noted to have a higher prevalence of failing multiple biologic agents compared to males with axSpA (11.6% vs 7.2%, p=0.03). The range of failed biologic agents was also wider in axSpA females (0 to 6) compared to males (0 to 4). However, the median number of failed biologic agents was one for both sexes.

Female patients recorded significantly higher ASQoL (7.5 vs 6.1; 95% CI 0.6, 2.2; p <0.01) and BASDAI (4.6 vs. 3.8; 95% CI 0.4, 1.1; p <0.01) scores compared to axSpA males (Table 2). They also recorded trends towards worse mean HAQ (0.5 vs 0.37; 95% CI -0.002, 0.2; p=0.05), and BASFI score (3.9 vs 3.6; 95% CI -0.2, 0.7; p=0.32) but these differences were not significant. Spinal mobility as captured in the BASMI was significantly less impaired in females than males (3.6 vs 4.2; 95% CI -0.9, -0.2; p<0.01).

5.4.2 BASDAI Analysis

Females with axSpA reported worse mean total BASDAI (4.6 vs 3.8; 95% CI 0.4, 1.1; p<0.01), compared to males. Within the BASDAI, females scored significantly worse than males across all components (Fatigue: 5.6 vs 4.5, 95% CI 0.6-1.5, p<0.01; Spinal pain: 5.5 vs 4.6, 95% CI 0.4-1.4, p<0.01; Other pain: 3.8 vs 3.2, 95% CI 0.2-1.1, p=0.01; Discomfort: 4.1 vs 3.3, 95% CI 0.3-1.2, p<0.01; EMS: 4.6 vs 3.9, 95% CI 0.1-0.2, p=0.01), with the exception of duration of EMS which demonstrated a non-significant trend towards higher average scores in females (3.5 vs 3.12, 95% CI 0.9 to -0.03, p=0.07) (Table 5.2).

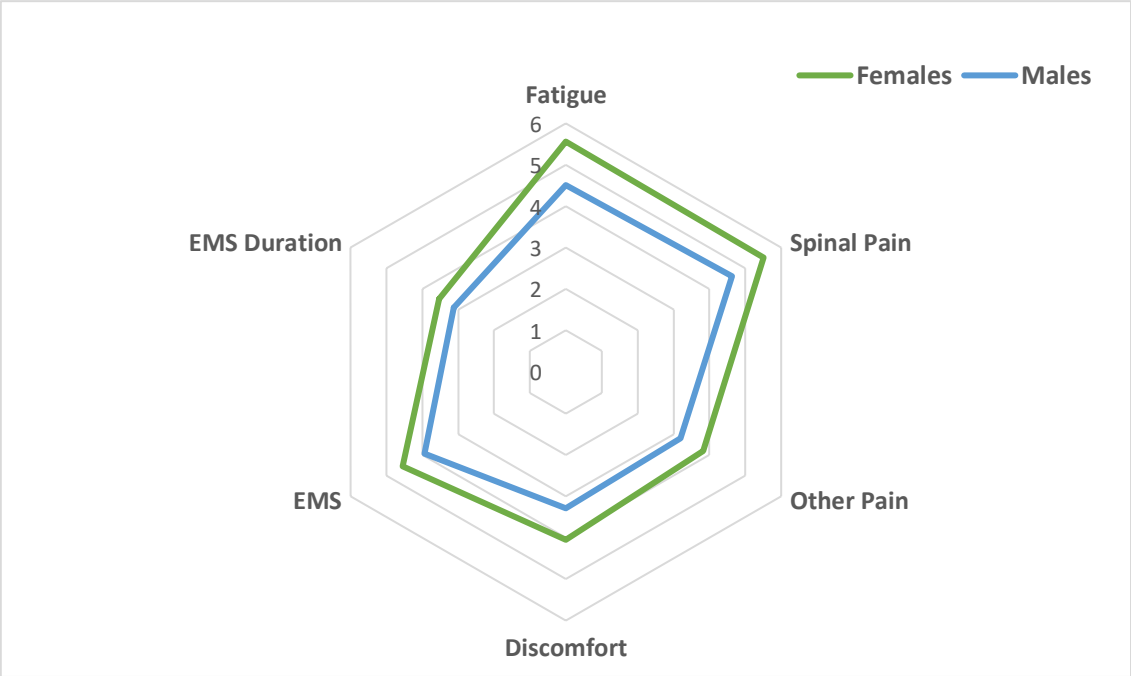
Table 5.2: Breakdown of BASDAI total and component scores by sex, with ranking of average component scores by severity within each sex

	Females	Males	*p value*
Mean Scores			
BASDAI total	4.6	3.8	**<0.01**
1 -Fatigue	5.6	4.5	<0.01
2 -Spinal Pain	5.5	4.6	<0.01
3 -Other Pain	3.8	3.2	0.01
4 -Discomfort	4.1	3.3	<0.01
5 -EMS	4.6	3.9	0.01
6 -EMS Duration	3.5	3.1	0.07
Ranking by Severity			
1- most severe	Fatigue	Spinal pain	
2	Spinal pain	Fatigue	
3	EMS	EMS	
4	Discomfort	Discomfort	
5	Other pain	Other pain	
6 -least severe	EMS Duration	EMS Duration	

Abbreviations: BASDAI -Bath Ankylosing Spondylitis Disease Activity Index, EMS - early morning stiffness

Ranking of the BASDAI components by mean scores in order of overall severity revealed identical ranking in both sexes for four of the six components of the BASDAI, with the only variation observed in the component ranked as the most severe. In males this was spinal pain, while for females it was fatigue. Plotting of average component scores for each sex revealed a similar pattern in disease activity (Figure 5.1).

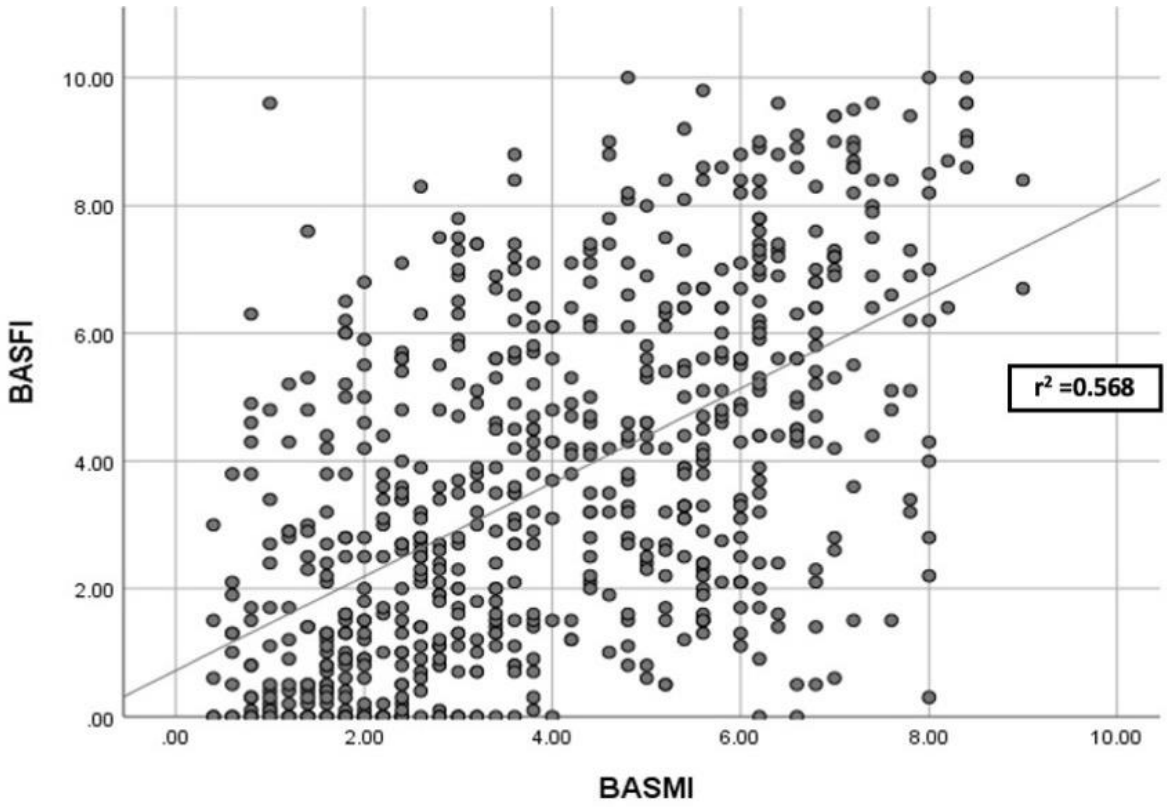
Figure 5.1: Mean BASDAI Component score plotted by sex



5.4.3 Spinal Mobility & Function

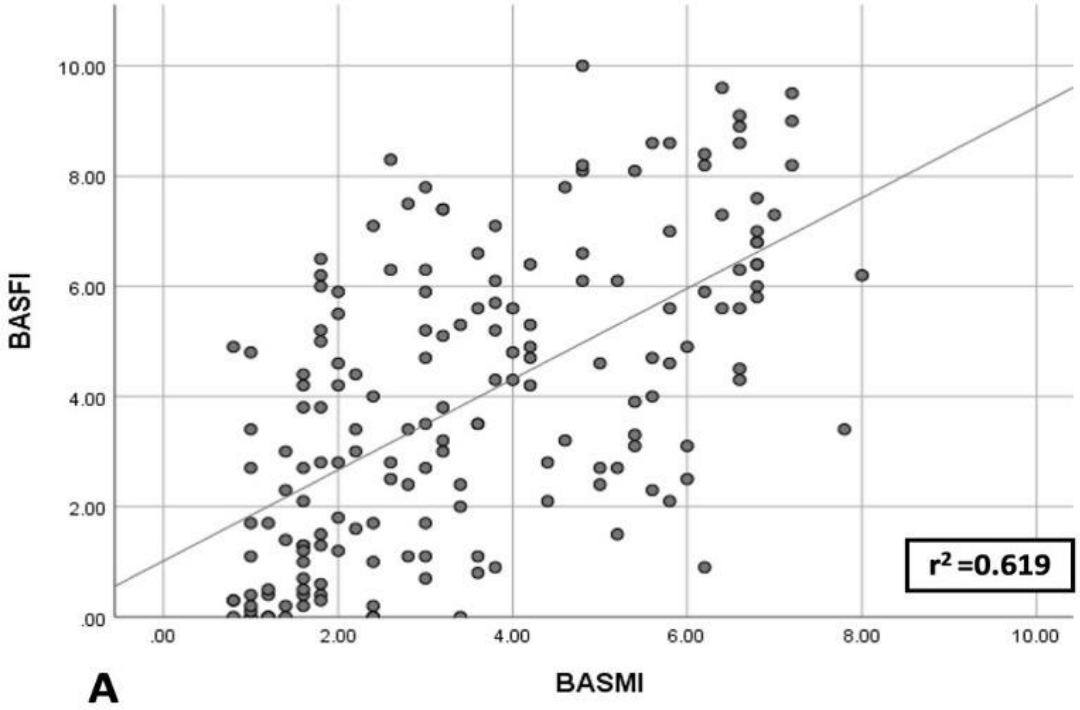
Data on both BASMI and BASFI scores were available on 680 patients, which were included in the analysis. Variables were not normally distributed as assessed by Shapiro-Wilk's test ($p<0.01$). The relationship between the two measures was monotonic (as the BASFI score increases, so too does the BASMI score), as determined by visual inspection of the scatterplot (Figure 5.2).

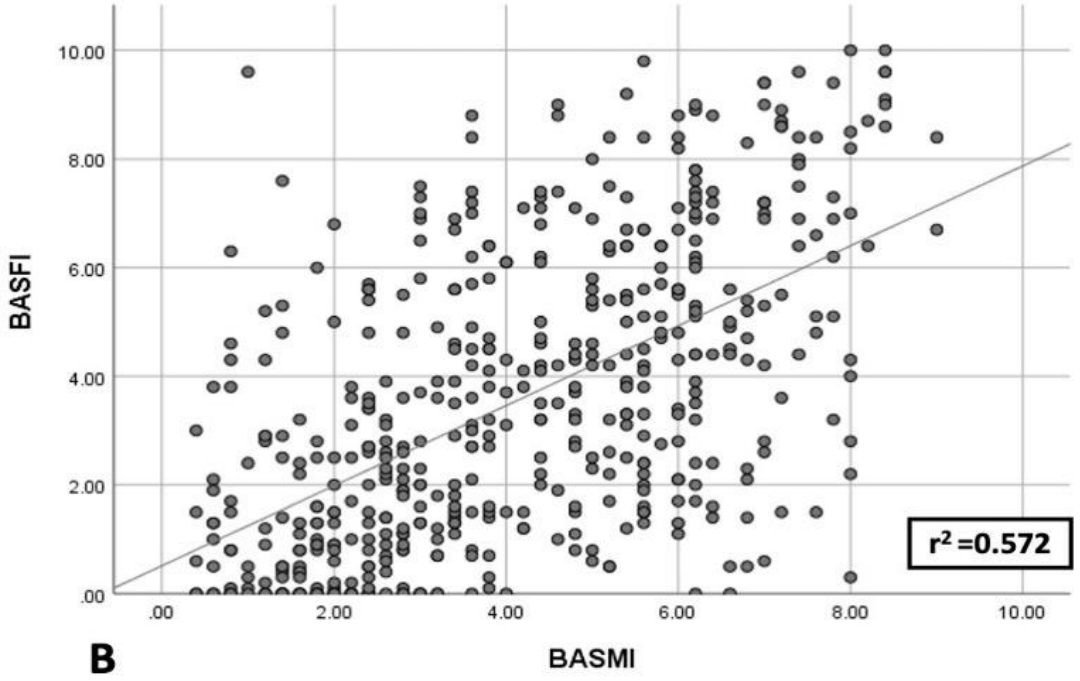
Figure 5.2: Correlation between BASFI and BASMI



There was a statistically significant, strong positive correlation between BASMI and BASFI scores in axSpA patients, $r_s(678) = 0.568$, $p<0.01$ based on calculations by Spearman's rank-order correlation. A Spearman's rank-order correlation analysis following splitting of records by sex showed the correlation becomes stronger if assessed within each sex (Females $r_s(144) = 0.619$, $p<0.01$; Males $r_s(509) = 0.572$, $p<0.01$) and has a slightly stronger association with in females(Figure 5.3).

Figure 5.3: Correlation between BASFI and BASMI in (A) Females and (B) Males





The prevalence of a number of comorbidities was also compared between sexes (Table 5.3). The only significant differences were a lower prevalence of ischaemic cardiac disease in females (0.9% vs 4.7%, p=0.02) and a higher prevalence of chronic lung disease (3.4% vs 0.5%,

p<0.01). No other differences were detected in prevalence of comorbidities between axSpA males and females, however for certain comorbidities actual numbers were small which limited ability to detect significance of differences.

Table 5.3: Difference in prevalence of comorbidities between males and females with axSpA

	Females	**Males**	***p value***
HTN	19% (44)	22.7% (146)	0.34
Hyperlipidaemia	14.7% (34)	16.5% (106)	0.56
IHD	0.9% (2)	4.7% (30)	**0.02**
Cerebrovascular Disease	0.4% (1)	1.9% (12)	0.21
Joint replacement	2.6% (6)	3.9% (25)	0.06
MSK surgery	1.7% (4)	2% (13)	0.05
Depression	12.1% (28)	9.8% (63)	0.44
Osteoporosis	6% (14)	5% (32)	0.58
Type II Diabetes	4.7% (11)	5.4% (35)	0.64
Cancer	4.7% (11)	3.4% (22)	0.46
Chronic Lung Disease	3.4% (8)	0.5% (3)	**<0.01**

Abbreviations: *HTN -Hypertension, IHD -Ischemic Heart Disease, MSK -Musculoskeletal*

5.5 Discussion

This analysis of real-world data from a large cohort of axSpA patients captured in the ASRI outlines the significant burden of disease in women with axSpA. This is reflected by worse patient reported outcomes, with a higher prevalence of a number of articular and extra-articular manifestations noted in axSpA women compared to men. The analysis contained within this study provides valuable insight into the impact of axSpA and how this varies between men and women.

5.5.1 Patient Outcomes in the ASRI

Overall, women with axSpA reported significantly worse disease activity and greater impairment of their quality of life compared to men, captured via worse average BASDAI and ASQoL scores. There were also non-significant trends toward worse HAQ (0.5 vs 0.37, p=0.05) and BASFI (3.9 vs 3.7, p=0.21), representing greater impairment of function. However, women recorded significantly better spinal mobility captured via the BASMI (3.6 vs 4.2, p<0.01) with a lower proportion classified as radiographic axSpA (72% vs 80.1%, p=0.01) than males with axSpA. These findings are supported by studies in other large international axSpA cohorts which reported similar differences between sexes[371-374].

5.5.2 Insights from the BASDAI

Women with axSpA recorded significantly worse total BASDAI scores compared to men, consistent with results from other large axSpA cohorts[372-376]. Further focused analysis of the individual components of the BASDAI demonstrated that this was due to worse scores across all six components of the BASDAI in women, and not driven by higher scores in any single component. Ranking of mean component scores in order of severity between sexes revealed identical ranking of four of the six BASDAI components. The main difference observed in this ranking was the symptom ranked as the most severe within each sex, which was spinal pain in men and fatigue in women. However, when examining the mean scores for these two components within each sex, minimal difference is noted (Males: spinal pain 4.6, fatigue 4.5; Females: fatigue 5.6, spinal pain 5.5). This suggests that despite differences in total scores, the overall pattern of disease activity, as captured by the BASDAI, is strikingly similar in both men and women.

The question of why women with axSpA record worse PROs including the BASDAI still remains. The findings of our analysis demonstrated axSpA women had a significantly higher burden of a number of articular and extra-articular manifestations. For articular manifestations this included a significantly higher prevalence of dactylitis (9.9% vs 5%, p=0.01) with a trend towards an increased prevalence of peripheral arthritis (36.2% vs 28.3%, p=0.08) compared to

men. Women also recorded a higher prevalence of all extra-articular manifestations (EAMs) which was significant in both uveitis (40.5% vs 35.7%, p=0.01) and inflammatory colitis (17.2% vs 7.9%, p<0.01). This could explain the higher average scores across a number of items within the BASDAI, with a greater burden of inflammatory symptoms potentially contributing to increased severity of fatigue observed in axSpA women. Of interest, a previous study examined the topography of pain reporting in axSpA and reporting of symptoms in the BASDAI[377]. This revealed that level of pain corresponded with BASDAI total scores in men, while in women level of pain was linked to assessment of peripheral and axial symptoms when considered separately. These findings recommended sex specific approaches when considering results of the BASDAI.

The elegance of the BASDAI is in the simplicity of the design, allowing both ease of use for patients and ease of interpretation for clinicians. It is one of the most commonly used outcome measures in clinical practice for monitoring disease activity in axSpA. For this reason, it is essential to ensure the wealth of information captured within this tool is interpreted in a way that adequately reflects the clinical picture in both men and women with axSpA.

5.5.3 Spinal Mobility & Function

It has been well established that men with axSpA tend to have greater limitation of spinal mobility as captured in the BASMI[378,83,379] although this finding seems contradictory to the worse outcomes observed in women with the disease. It stands to reason that level of function would have a strong positive correlation with spinal mobility in axSpA[380], in clinical terms, patients with greater limitation of spinal mobility are likely to have increased level of functional impairment and vice versa. The results of this analysis by sex indicate this correlation is more significant if compared separately within each sex and is notably stronger in females.

Men with axSpA have been previously shown to have a greater prevalence of radiographic disease and a worse severity of radiographic disease over time[381,382]. It would be expected that this would result in greater impact on functional ability, however males in the ASRI demonstrated a non-significant trend towards better BASFI scores compared to females (3.63 vs 3.86, p=0.32). The stronger correlation noted in axSpA women in our study indicates that as the level of spinal mobility worsens, a larger change is observed in deterioration of functional ability compared to men. In practical terms, deterioration of spinal mobility appears to have less of an impact on restriction of function in axSpA men compared to women. Why this variation occurs is not immediately apparent, however research and advancements in motion capture technology may offer further insights[383].

5.5.4 Quantifying Disease Activity in AxSpA

Previous studies have proposed that higher prevalence of centralised sensitization[374] and fibromyalgia[384] in women could be significant contributors to the differences detected in patient outcomes as both can lead to chronic widespread pain (CWP). Although these issues are more common in women in the general population, they are clinical diagnoses of exclusion once other possible differential diagnoses have been out ruled[385,386]. The importance of thorough investigation of CWP was highlighted in an Israeli study of known fibromyalgia patients which found 10.2% met ASAS criteria for axSpA while up to 25% had imaging findings suggestive of inflammatory disease[387]. In patients with a known underlying axSpA, distinguishing between disease activity and CWP can be quite difficult[388,389]. To further complicate this diagnostic dilemma, symptoms of inflammatory pain can vary by sex with women more likely to describe widespread pain while men report back pain[390]. However, it is crucial to ensure adequate treatment of axSpA prior to attributing symptoms to CWP.

Recent increased use of the Ankylosing Spondylitis Disease Activity Score (ASDAS) has demonstrated less variation between sexes[391,392] when assessing disease activity in axSpA. A meta-analysis examining performances of the ASDAS and BASDAI concluded that the ASDAS may not be sensitive enough in the detection of active peripheral disease[393]. As peripheral involvement is more common in females with axSpA[261], this introduces a significant sex bias. The ASDAS has proven to be a remarkable tool in detecting disease activity and even in predicting response to biologic therapies in males with axSpA[394]. However, given the known variation of patterns of disease activity between sexes axSpA, is it time to reconsider our evaluation of disease activity in females with axSpA?

As suggested by the experience with the ASDAS, differences in reporting of disease activity could be due to the methods used to capture this information. Tools such as the BASDAI and BASFI were developed and validated for ankylosing spondylitis (AS) in predominantly male cohorts[115,395]. This analysis demonstrates that although women record worse overall scores, the overall pattern of disease activity is quite similar between sexes. Development of sex specific scores indicative of active disease could help to better compare scores between men and women. Additionally, evaluation of outcome measures regarding their ability to capture burden of articular and extra-articular manifestations in both sexes may provide further insights into the variation in outcomes observed between sexes.

5.5.5 Usage in AxSpA Women

Despite higher prevalence of a number of disease manifestations and worse PROs noted in women with axSpA, medication usage was statistically similar between both sexes. This remained consistent across all classes of medications assessed including: NSAIDs (55.6% vs 49.4%, p=0.2), DMARDs (22.4% vs 23.9%, p=0.29) and biologic therapies (66.8% vs 68.2%, p=0.81). Current treatment guidelines recommend use of DMARDs for peripheral articular manifestations with escalation to biologic therapy if needed[159]. This pattern of medication usage is not unique to the ASRI with similarities in frequency of DMARD and biologic agent usage in men and women observed in other large cohort studies[371,372]. A recent publication examining medication usage before and after the recognition of nr-axSpA found no change in use of DMARDs or biologics between males and females[396]. This raises the question: are women with axSpA less likely to be offered treatment? If so, why? Could it be that women's symptoms are less likely to be considered inflammatory and thus less responsive to treatment? Most importantly are women with axSpA being under treated?

5.5.6 The Effect of Hormones in AxSpA

One of the most obvious but least understood causes for variations between men and women is hormonal differences[262]. Oestrogens have previously been proven to inhibit production of tumour necrosis factor alpha (TNF ∝) and decrease differentiation of Th17 cells[397], both of which have significant effects on the inflammatory pathway. However, studies examining the effect of female sex hormone supplementation have failed to show any effect on outcomes in axSpA[398]. Additionally, we must consider the significant hormonal shifts the female body undergoes over the course of a lifetime and how this affects disease activity. This includes menstruation, pregnancy and menopause, as data suggests the overall effects of hormones are related to concentration[399]. Studies on disease activity during pregnancy in axSpA vary widely, but a high prevalence of active disease during pregnancy with a peak of disease activity in the second trimester has been reported[400]. Research on menstrual variation of activity disease is incredibly limited, however one study reported an inverse relationship between oestrogen level and erythrocyte sedimentation rate[401]. Further research into the effect of sex hormones in axSpA has the potential to offer significant insight into observed variations in outcomes between sexes and could potentially lead to improved management of axSpA in women.

5.5.7 Limitations

Data used for the analysis contained within this study was cross-sectional in nature due to the current design of the ASRI. As such, it was not possible to comment on disease progression over time or treatment response. Plans to collect longitudinal data for the ASRI are in place and will further enrich this valuable epidemiological resource. Secondly, at the time of analysis ASDAS results were not available for a large proportion of the ASRI population. This prevented comparison analysis of performance of the ASDAS and the BASDAI in our population. This has been studied in detail in numerous axSpA populations previously, thus sex specific patterns in reporting of ASDAS are well established as discussed above.

5.6 Conclusion

In this large registry-based study of axSpA, women had a higher prevalence of a number of articular and extra-articular manifestations compared to men. In addition, they reported significantly worse disease activity and quality of life. However, the overall pattern of disease activity as captured by the BASDAI was similar in both men and women. Despite better mean spinal mobility overall compared to axSpA men, limitation of spinal mobility in axSpA women corresponded with a greater impairment in functional ability. These results would suggest further evaluation of the tools and outcome measures currently used to monitor disease activity are needed to accurately assess the burden of axSpA in women. Additionally, further studies are required to examine the impact of significant hormonal changes on disease activity and disease progression in axSpA women.

Improved understanding of the patient experience and disease manifestations for women with axSpA is critical to optimising outcomes in this large proportion of the axSpA patient population. Further research to understand factors associated with these sex differences is needed to improve outcomes for women with axSpA. Physical size and body proportions are obviously different between men and women in the general population. The following chapter will examine anthropometrics in the context of sex and patient outcomes to further build on understanding of axSpA in women.

Chapter 6. Central Obesity in Axial Spondyloarthritis: the Missing Link to Understanding Worse Outcomes in Women?

Publications resulting from material contained within this chapter:

S Maguire, F Wilson, P Gallagher, F O'Shea. "Central Obesity in Axial Spondyloarthritis: the Missing Link to Understanding Worse Outcomes in Women?" 2022 Mar; 49 (3); DOI: 10.3899/jrheum.211062. Epub ahead of print.

(Full manuscript available in Appendix A)

6.1 Abstract

Objective

To determine i) the prevalence of central obesity in axSpA and its impact on disease related outcomes and ii) how/if this differs between sexes.

Methods

Data was extracted from the Ankylosing Spondylitis Registry of Ireland (ASRI) for analysis. Patients with physical measurements for calculation of anthropometric measures were included. Body mass index (BMI) and waist to hip ratio (WtHpR) were used to compare classification of obesity. Comparison analyses based on sex and presence of central obesity were carried out. Multivariate analysis examined the impact of these factors on patient reported outcome: BASDAI, BASFI, ASQoL and HAQ.

Results

753 patients were included in the analysis made up of 27.6% (208) females and 71.4% (538) males. 29.6% (223) patients were obese based on BMI, while 41.3% (311) were centrally obese as per WtHpR. The prevalence of central obesity was significantly higher in axSpA females (71.6% vs 29.9%, $p<0.01$) compared to males. Central obesity had a clear impact on patient reported outcomes, regardless of sex. Presence of central obesity was associated with significantly worse mean BASFI ($p<0.01$), HAQ ($p<0.01$) and ASQoL scores ($p=0.01$). There was also a non-significant trend towards worse BASDAI scores ($p=0.07$).

Conclusion

There is a high prevalence of central obesity as assessed by WtHpR in axSpA, most notably in females with axSpA. This modifiable comorbidity was significantly associated with worse quality of life, greater impairment of functional ability with a trend towards worse disease activity. Regular use of the WtHpR to screen for central obesity as part of an axSpA assessment would provide an opportunity for prompt identification and intervention for at-risk patients.

6.2 Background

The previous chapter outlines the numerous differences in burden of disease and patient outcomes between men and women with axial spondyloarthritis (axSpA). Given the known variation in body composition between sexes, this chapter will explore how these differences in physical measurements or anthropometrics are associated with differences in patient outcomes.

Worldwide prevalence of obesity has been steadily increasing[402,403], despite numerous public health campaigns to increase public awareness. Obesity is known to be associated with an increased risk of all-cause mortality[404] and was previously found to be the second most common preventable cause of death in the United States[405]. As the prevalence of this health issue surges, so too do the frequencies of associated complications such as type II diabetes and cardiovascular disease which have a significant impact on patients' overall quality of life and demand on the healthcare system[406].

This rising prevalence is especially concerning in axial spondyloarthritis (axSpA), as it has been shown to be associated with higher levels of disease activity[407,408,183] and decreased response to treatment[409,185]. Presence of obesity has even been linked to new syndesmophyte formation and enthesitis in both peripheral and axial joints[184]. This is related to adipose tissue secretion of proinflammatory cytokines, called adipocytokines, which in high concentrations can promote a persistent systemic inflammatory state[410]. Serum levels of adipocytokines are directly related to body fat content with elevated levels contributing to the development of metabolic disorders including insulin resistance and accelerated atherosclerosis[411]. Despite the established negative impact of obesity in axSpA, it remains a frequently encountered comorbidity with a reported prevalence of 14-27%[196,271,412,270].

Presence of obesity is commonly determined by calculation of body mass index (BMI). However, additional anthropometric scores have been developed to move beyond weight excess and focus on capturing prevalence of abdominal or central obesity. The waist to hip ratio (WtHpR) is a validated measure to screen for central obesity in the general population[413]. Central deposition of adipose tissue is associated with increased risk of cardiovascular disease, type II diabetes and premature death[414-417]. Typically, central obesity is more often found in males due to deposition of visceral fat, while females are more prone to gluteal-femoral subcutaneous fat deposition[418]. During menopause there is a shift towards more central fat deposition, which increases further in the post-menopausal period[419,420].

The aim of this study was to capture the prevalence of central obesity in a large cohort of patients with axSpA and assess how this affects disease related outcomes. This analysis will also examine how this differs between men and women with axSpA, as well as compare strength of association between anthropometric measures.

6.3 Methods

6.3.1 Patient Population

Data for the analysis was extracted from the Ankylosing Spondylitis Registry of Ireland (ASRI), a rich source of epidemiological data on axSpA in Ireland. This large national registry recruits patients with axSpA from Rheumatology centres across the country. Full details on patient population including eligibility criteria and data captured within this registry are discussed at length in Chapter 3: Methods under "Patient Population".

6.3.2 Outcomes & Assessments

Full discussion of outcomes captured within the ASRI are included in Chapter 3: Methods under "Data Collection" and "Outcome Measures."

Participants were analysed on the basis of sex and presence of obesity as defined by body mass index (BMI) and waist to hip ratio (WtHpR). Obesity was defined by BMI, calculated as weight in kilograms divided by height in meters squared, with a result of greater than 30 categorised as obese as per the Centre for Disease Control (CDC) definitions[421]. Central obesity was assessed by WtHpR and defined as per the World Health Organisation (WHO) guidelines[422] (table 6.1).

Table 6.1*:* Waist to Hip Ratio (WtHpR) definitions for classification of central obesity as per the WHO[422]

	Males	Females
Normal	< 0.9	< 0.8
Overweight	0.9-0.99	0.8-0.84
Obese	≥ 1.0	≥ 0.85

6.3.3 Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) version 26 was used for statistical analysis and data processing. Comparison analyses determined variation in prevalence of obesity as captured by WtHpR and BMI. Further analyses focused on variation in prevalence of these measures within each sex. Categorical variables were recorded as frequencies with percentages, with a chi^2 test for independence or a Fischer's exact test used to test for statistical significance. Numerical variables were recorded as means with standard deviations (SD) or median with 25th and 75th centile as appropriate within each group. An independent t-test or Mann Whitney U test used to test for statistical significance of differences between groups. A Shapiro-Wilk's test was carried out on all included variables to determine normality of the distribution. To assess the relationship between WtHpR and BMI, a Spearman's rank order correlation was run as variables

were not normally distributed. Scatterplots were constructed to visualise presence of a monotonic relationship for each analysis.

A two-way multivariate analysis of variance (MANOVA) assessed the impact of sex (males versus females) and central obesity (as determined by WtHpR) on patient reported outcomes (PRO) (BASDAI, BASFI, ASQoL and HAQ). An alpha level of <0.05 was deemed significant. A binary logistic regression model examined the effects of age, sex (male or female), axSpA classification (radiographic vs non-radiographic), BASDAI, BASFI and BASMI on the likelihood of presence of central obesity. A Bonferroni correction was applied to determine p value for level of statistical significance of linearity. All necessary assumptions for each statistical test were met.

6.4 Results

At the time of data extraction, physical measurements were available on 753 participants enrolled in the ASRI made up of 88.4% (666) Caucasians with 27.6% (208) females and 71.4% (538) males (Table 6.2). The mean age was 45.6 years (SD 12.6, range 18-85) with a mean disease duration of 17.1 years (10, 28). Of the total population 75.2% (556) were classified as r-axSpA while 24.8% (187) were nr-axSpA. Results of HLA-B27 status was available in 598 participants, of which 88.6% (530) were positive. Mean scores were as follows: BASDAI 4.1 (95% CI: 3.9 - 4.3), BASFI 3.7 (95% CI: 3.5 - 3.8), BASMI 4.0 (95% CI: 3.4 - 4.5), HAQ 0.53 (95% CI: 0.5 - 0.6), ASQoL 6.7 (95% CI: 6.3 - 7.1), ASDAS 2.4 (95% CI: 2.0 - 2.7). In terms of anthropometric measurements, mean BMI was 28.2 (SD 6.3) and mean WtHpR was 0.941 (SD 0.104).

Table 6.2: Characteristics of participants, including comparison by sex and presence of central obesity as detected by the WtHpR

	Total	Females	Males	*p value*	No Central Obesity	Central Obesity	*p value*
n	753	208	538		442	311	
Age	45.6 (12.6)*	43.6 (12)	46.1 (12.7)	***0.03***	43.7 (12.3)	48.6 (12.6)	***<0.01***
Age of Onset	26.8 (10.9)	24.2 (19, 30)	23.7 (19, 33)	*0.22*	23.1 (18, 32)	26.1 (20, 36)	***<0.01***
Disease duration	17.1 (10, 28)	15.6 (8, 25)	16.5 (9, 27)	*0.25*	15.5 (9, 35)	17.2 (9, 40)	*0.06*
Delay to dx	5 (2, 12)	5 (2, 13)	5 (2, 12)	*0.85*	5 (2, 11)	5.5 (2, 12)	*0.73*
HLA-B27 +	88.6% *(530 of 598)*	89.3% *(150 of 168)*	89.8% *(380 of 423)*	*0.8*	87.6% *(324 of 370)*	90.4% *(206 of 228)*	***<0.01***
Caucasian	88.4% (666)	72.6% (151)	95.7% (515)	***<0.01***	92.8% (410)	82.3% (256)	***<0.01***
r-axSpA	75.2% (566)	69.7% (145)	78.3% (421)	***0.02***	73.5% (325)	77.5% (241)	*0.21*
nr-axSpA	24.8% (187)	30.3% (63)	21.7% (117)	***0.03***	26.5% (117)	22.5% (70)	*0.34*

**Continuous variables expressed as mean (standard deviation) or median (25th, 75h centile) as appropriate; Categorical variables expressed as %(n)*
Abbreviations: *Dx -diagnosis, HLA-B27 -human leukocyte antigen B27, r-axSpA -radiographic axial spondyloarthritis, nr-axSpA -non radiographic axial spondyloarthritis*

In total 29.6% (223) patients were obese based on BMI results, while 41.2% (310) were centrally obese as per the WtHpR. Comparison analysis on the basis of sex revealed no significant variation in mean BMI (27.9 vs 28.3, p=0.44) or prevalence of obesity as assessed by BMI (29.8% vs 29.6%, p=0.21) between females and males (Table 6.3). Normal weight was the most common classification by BMI in females, while overweight was the most common classification in males.

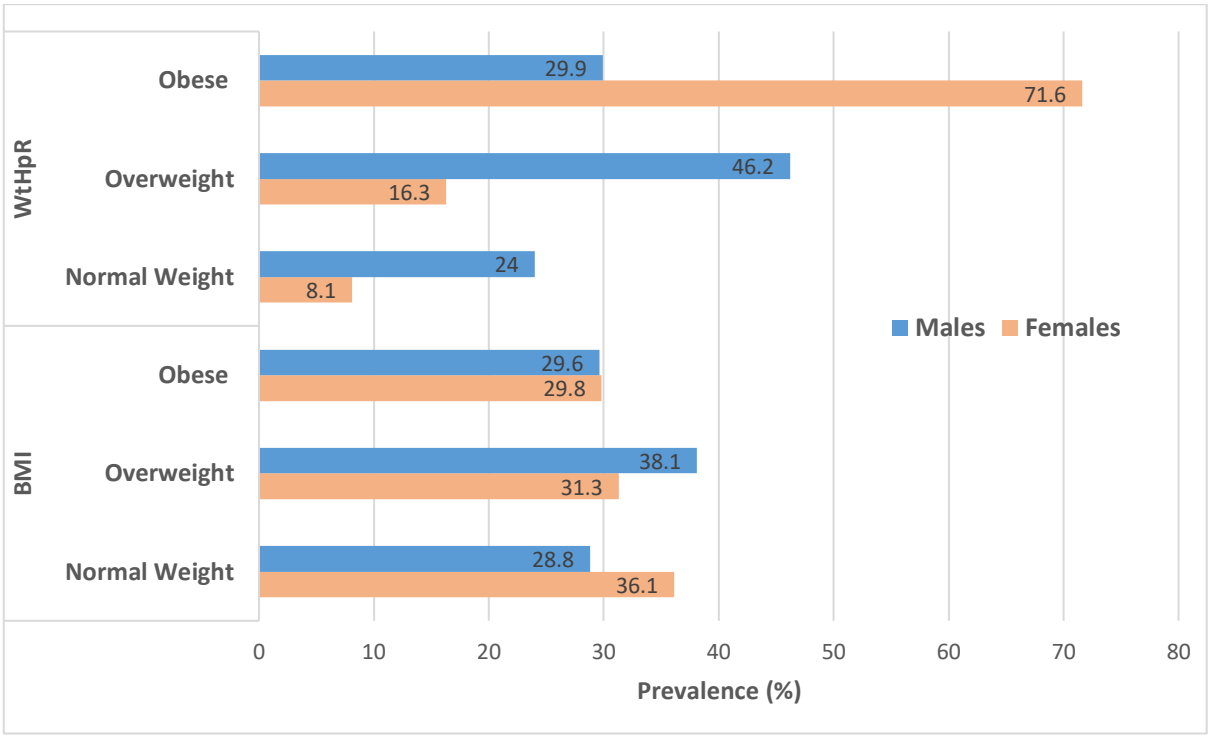
Table 6.3: Assessment of anthropometric measures by sex

	Females	**Males**	***p-value***
n	208	538	
Weight (kg)	75.1 (18)*	84.9 (15.4)	**<0.01**
BMI	27.9 (6.7)	28.3 (6.2)	0.44
Underweight	2.9% (6)	0.9% (5)	0.21
Normal Weight	36.1% (75)	28.8% (155)	
Overweight	31.3% (65)	38.1% (205)	
Obese	29.8% (62)	29.6% (159)	
Waist Circumference (cm)	91.3 (16.8)	97.6 (17.2)	**<0.01**
Hip Circumference (cm)	101.8 (14.6)	102.1 (15.5)	0.78
Waist to Hip Ratio	0.897 (0.1)	0.956 (0.09)	**<0.01**
Normal Weight	8.1% (25)	24% (129)	**<0.01**
Overweight	16.3% (34)	46.1% (248)	
Obese	71.6% (149)	29.9% (161)	
Height (cm)	164.3 (8.5)	172.6 (17.4)	**<0.01**

**Continuous variables expressed as mean (standard deviation), categorical variables expressed as percentages (frequency counts)*
***Abbreviations**: kg -kilogram, BMI -body mass index, cm -centimetres*

Analysis of WtHpR revealed higher mean ratios in males compared to females (0.956 vs 0.897, p<0.01). Further analysis of classification by WtHpR revealed the prevalence of central obesity was significantly higher in females compared to males (71.6% vs 29.9%, p<0.01) (Figure 6.1). Assessment of WtHpR results revealed obesity to be the most common classification in females affecting 71.6% (149), while for males, overweight was the most common classification affecting 46.1% (248). Furthermore, only 12% (25) of females were classified as normal weight as per the WtHpR.

Figure 6.1: Weight classification by WtHpR (waist to hip ratio) and BMI (Body Mass Index) by sex



Analysis of average PROs revealed significantly worse ASQoL (7.7 vs 6.1, p<0.01), BASFI (4.2 vs 3.3, p<0.01), HAQ (0.63 vs 0.45, p<0.01) and BASDAI scores (4.4 vs 3.9, p=0.01) observed in those with central obesity compared to those without. As there was a higher proportion of females in the central obesity cohort, further analyses were carried out to determine if sex was a contributing factor in the differences observed.

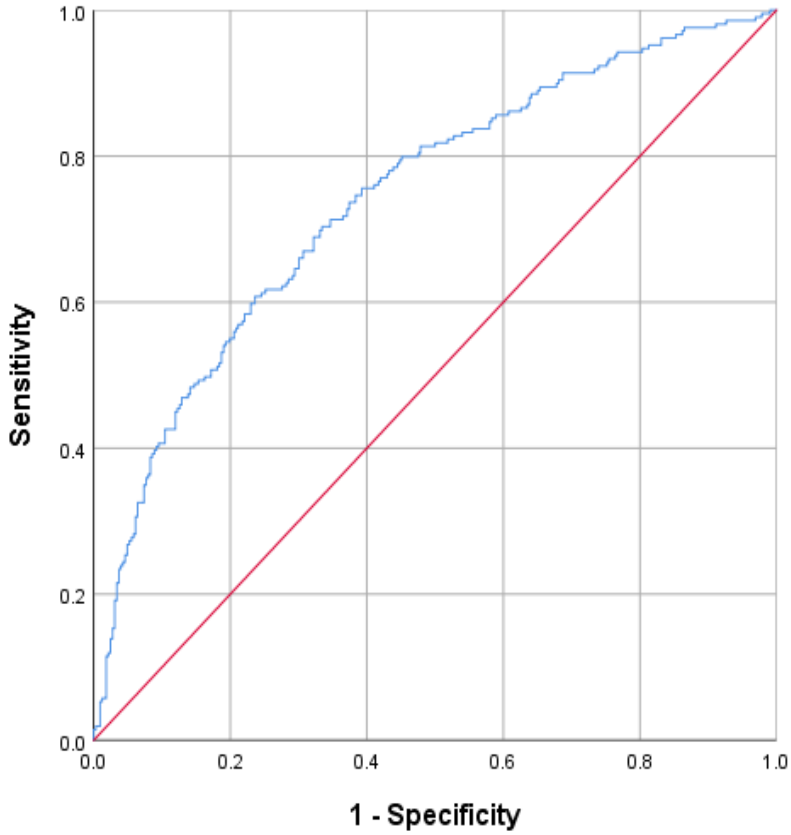
To examine this further, a multivariate analysis was carried out to determine the effect of sex and central obesity on PROs, including the BASDAI, BASFI, ASQoL and HAQ. This analysis did not detect a significant interaction effect between sex and central obesity (F=0.5, Wilk's lambda =0.997, p=0.74). However, there was a significant main effect of both sex (F=3.99, p<0.01) and central obesity (5.68, p<0.01) on PROs when assessed individually.

A follow up univariate two-way ANOVA found a significant main effect of central obesity on several PROs. There was a significant main effect of central obesity on a number of PROs. This included ASQoL (F=7.87, p=0.01), BASFI (F=19.45, p<0.01) and HAQ (F=12.25, p<0.01), with a non-significant trend detected for BASDAI scores (F=3.63, p=0.07). Follow up analysis of PROs between centrally obese participants compared to normal weight participants revealed the following average differences: ASQoL 2.0 (95% CI 3.3- 0.7, p<0.01), BASFI 1.4 (95% CI 2.0 – 0.8, p<0.01), HAQ 0.24 (95% CI 0.4 – 0.1, p<0.01) and BASDAI 0.7 (95% CI 1.2 – 0.1, p=0.02). For ASQoL, HAQ and BASFI these differences remained significant, though lesser in magnitude, even when comparing those classified as overweight compared to centrally obese participants.

There was a statistically significant positive relationship between BMI and WtHpR in axSpA patients (r_s =0.456, p<0.01). When assessed within each sex, the strength of this correlation was found to be stronger in males with axSpA (r_s =0.538, p<0.01) but weaker in axSpA females (r_s =0.349, p<0.01) although both remained statistically significant.

A binomial regression analysis was performed to identify factors associated with central obesity as determined by WtHpR. The logistic regression model was statistically significant (chi^2 (7)=96.23, p<0.01), correctly classifying 71.2% of cases. The area under the receiver operating characteristic (ROC) curve was 0.742 (95% CI: 0.699 - 0.785) consistent with an acceptable level of discrimination (Figure 6.2).

Figure 6.2: ROC curve for factors associated with central obesity



Of the seven predictor variables assessed, only two were statistically significant: age and sex (Table 6.4). This indicated that both increasing age (OR 1.03, 95% CI: 1.01 -1.05) and female sex (OR 6.76, 95% CI: 4.12 -11.1) are associated with an increased likelihood of an axSpA patient having central obesity.

Table 6.4: Determining likelihood of central obesity as per WtHpR

	Odds Ratio	95% CI	p value
Age	1.03	1.01, 1.05	**0.01**
Female sex	6.76	4.12, 11.1	**<0.01**
R-axSpA	0.75	0.46, 1.21	0.24
BASMI	1.06	0.93, 1.21	0.36
BASDAI	0.92	0.82, 1.04	0.18
BASFI	1.08	0.94, 1.24	0.30
ASQoL	1.04	0.98, 1.1	0.24

6.5 Discussion

The results of this study detail the high prevalence and the detrimental impact of central obesity in axSpA using data from a large, well characterised national axSpA registry. Obesity (as classified by BMI) has previously shown to be one of the most prevalent comorbidities in axSpA with numerous negative implications regarding disease activity and progression of disease. Although central obesity has known negative health consequences in the general population, there is scant literature on central obesity in the context of axSpA. This analysis is novel not only in capturing the prevalence of central obesity in axSpA, but also in demonstrating the significant negative impact of this modifiable risk factor on patient outcomes including disease activity, functional ability and quality of life.

Prevalence of obesity, as classified by BMI, in the ASRI was similar in both sexes (29.8% vs 29.8%, p=0.21). Obesity is one of the most prevalent comorbidities in axSpA, with a recent meta-analysis reporting a pooled prevalence of 14% in axSpA[271]. This is notably lower than the prevalence reported in the ASRI, which likely reflects the rising prevalence of obesity in the general population in Ireland[423,424]. Although it is difficult to capture the true national prevalence of obesity, most recent data reports an overall Irish obesity prevalence of 27%[425] compared to an overall prevalence of 25.2% in the European Union[426]. Additionally, longitudinal data has demonstrated that one of the European populations with the steepest recent rise in obesity is women in Ireland[424].

One of the most surprising findings from this analysis was the significantly higher prevalence of central obesity in females with axSpA compared to males (71.6% vs 29.9%, $p<0.01$). Previously, central obesity in the general population was perceived as more common in males[418]. However, a recent epidemiological study examining trends in central obesity in the United States noted that the prevalence was increasing steadily with an annual increase in rate of 0.56% in males and 0.75% in females, and that by 2030 would affect up to 55.6% of males and 80% of females[427]. This finding is a cause for alarm as central obesity is known to be associated with insulin resistance[428], renal impairment[429] and higher risk of mortality even in females with a normal BMI[414]. For females of childbearing age central obesity is associated with an increased risk of gestational diabetes, pre-eclampsia, polycystic ovary syndrome and need for caesarean sections[430,431]. Unfortunately, there is scant literature examining this issue specifically in axSpA. Research in obesity has demonstrated that presence of excess adipose tissue creates a persistent low-grade inflammatory state driven by pro-inflammatory adipocytokines[432]. This can trigger a number of downstream effects, including the development of obesity associated comorbidities[410]. This is especially concerning in patients with an inflammatory arthritis, such as axSpA, as persistent inflammation could contribute to worsening of disease activity. As the concentration of adipocytokines are directly related to body fat mass, reduction of excess adipose tissue has the potential to correct this systemic inflammatory reaction. Research on adipocytokines suggests common mechanisms in the inflammatory pathways involved in both obesity and rheumatic diseases including heightened T-helper (Th1) and Th17 responses with altered expression of adipokines[433]. Clinical data in axSpA, while limited, has demonstrated an inverse relationship between levels of leptin and risk of radiographic progression[434], while visfastin has been suggested to be associated with radiographic progression[435] and the role of resistin remains unclear[436]. Further data is needed to better understand the complex role of adipocytokines in axSpA and other RMDs.

Given the disproportionate percentage of females with central obesity and the trend for females with axSpA to average worse PROs compared to males this is a key modifiable lifestyle factor to target in this population. Thus, central obesity in women, especially those with axSpA, is a critical issue that requires greater public awareness and recognition.

Identification of central obesity is the first step in improving recognition in axSpA patients. This analysis highlights the disparity in detection of obesity as classified by two anthropometric tools (BMI and WtHpR) in females with axSpA. For males with axSpA the prevalence of obesity was similar regardless of the tool used for detection and classification (BMI vs WtHpR: 29.6% vs 29.9%). However, for females there was a stark change in prevalence when comparing results between BMI and WtHpR (29.8% vs 71.6%). This difference in classification between sexes was quantified in a correlation analysis which found the relationship between

BMI and WtHpR to be stronger in axSpA males (r_s =0.538, p<0.01) than females (r_s =0.349, p<0.01). This suggests that although BMI is a quick tool to screen for obesity, it underestimates obesity in females. This difference in the strength of association between sexes may be a reflection of the fact that the BMI was a tool developed and validated for use in males[437]. Since its development in the 1830s by a Belgian statistician to describe the average man, it has become one of the most commonly used tools to quantify physical size and general health[438]. However, studies in postmenopausal females indicate that BMI is not a reliable indirect indicator of obesity status in females[439]. Additionally, use of universal BMI cut-offs for obesity have been found to perform poorly in females of differing ethnic background[440]. This clearly demonstrates that it is time to reconsider use of BMI to screen for obesity in females, especially those with axSpA.

Prevalence of central obesity was similar between those with radiographic axSpA and non-radiographic axSpA (42.6% vs 37.4%, p=0.21). However, the prevalence of HLA-B27 was higher in patients with central obesity (90.4% vs 87.6%, p<0.01). There is limited knowledge of central obesity in axSpA, however a study in ankylosing spondylitis did note central obesity (classified by waist to height ratio) was associated with radiographic progression over time[441]. However, the ASAS Comorbidities in Spondyloarthritis (COMOSPA) study also demonstrated mean waist circumference to be significantly lower in HLA-B27 positive axSpA patients compared to HLA-B27 negative patients[442]. Further longitudinal data is required to investigate the relationship between radiographic disease, presence of HLA-B27 and central obesity in axSpA.

Assessment of baseline demographics between patients with central obesity and those without revealed those with central obesity to be older (48.6 vs 43.7, p<0.01) with a later age of onset (28.7 vs 25.7, p<0.01) but no significant difference in delay to diagnosis (7.9 vs 7.7, p=0.73). Risk of central obesity in the general population is recognised to increase with age[443], with both males and postmenopausal females found to have up to twice as much visceral adipose tissue compared to pre-menopausal females[444]. In females these changes are mediated by increased androgen secretion with a decline in oestrogen concentration associated with reduction in ovarian function occurring in menopause[419]. While females of the general population report an increase in myalgia and arthralgia during the onset of menopause[445], unfortunately there is limited and conflicting data on the effects of changes in oestrogen concentrations on disease activity in females with axSpA[20].

To examine this further, a model was constructed to determine factors associated with presence of central obesity in axSpA. Several factors were assessed including age, sex, axSpA subtype and patient outcome scores. Despite the numerous predictors assessed, only age and female sex were found to be significantly associated with central obesity in axSpA. The association was especially strong in females with axSpA who averaged 6.76 times higher odds of

central obesity compared to axSpA males, highlighting the dramatically higher prevalence of central obesity in axSpA females.

Women with axSpA have previously demonstrated worse patient reported outcomes compared to men, despite having a lower prevalence of radiographic disease and better spinal mobility[20]. This disconnect between radiographic burden and reporting of outcomes has perplexed researchers in axSpA for some time. Obesity in axSpA is known to contribute to worse patient outcomes regardless of sex[407,196]. Given the unexpectedly high prevalence of central obesity detected in females in this analysis, a follow up analysis examined the interaction between female sex and central obesity to determine if there was a synergistic effect on patient reported outcomes. This interaction did not reach statistical significance although the effects of both female sex and central obesity when considered individually remained significant. Central obesity was found to be significantly associated with all patient reported outcomes, with exception of the BASDAI which was associated with a non-significant trend toward worse scores in central obesity ($p=0.07$). Differences in BASDAI scores between the two cohorts were more subtle than other PROs, which is likely the reason the effect of central obesity did not reach statistical significance in this outcome. However, if tested on a larger scale it is suspected the effect of central obesity on BASDAI would be significant. These results suggests that central obesity could play a key role in explaining the sex differences observed in patient reported outcomes in axSpA. Further studies will be needed to corroborate these findings in other large axSpA cohorts, as well as development of longitudinal data to determine if there is a causal relationship between central obesity and patient reported outcomes.

The health risks associated with central obesity are attributed to the presence of visceral adipose tissue (VAT), which can be directly measured by various imaging modalities including dual energy x-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI)[446]. In daily clinical practice it is not practical or economical to repeatedly image patients to screen for central obesity. During a consultation for a patient with axSpA numerous physical measurements are routinely captured to allow calculation of the BASMI for monitoring of spinal mobility. In this setting, calculation of the WtHpR would be a simple yet effective modality to effectively assess a patient's body habitus. Improving recognition of central obesity is important as this is a potentially modifiable state especially given advancements in pharmacotherapy for managing obesity. Prompt identification would create a window of opportunity for multidisciplinary intervention including a clinician led discussion on lifestyle modification, improved dietary management with the help of dieticians and exercise therapy led by physiotherapists. Previous research in obesity has shown early intervention and comprehensive structured programs to be most effective at both weight reduction and maintenance of a healthy weight[447]. Thus, given the high prevalence and negative impact of central obesity in axSpA demonstrated in this

analysis, incorporation of the WtHpR is essential to improve identification of central obesity in axSpA and allow for early intervention.

Numerous future studies are needed on the topic of central obesity in axSpA to further explore this issue. Further sub-analysis comparing normal weight axSpA patients to those with central obesity in terms of patient outcomes, disease activity and response to pharmacotherapy would provide more nuanced insights into the impact of central obesity in axSpA. Additional comparative analyses on levels of adipocytokines on the basis of central obesity would also be informative.

6.5.1 Limitations

Due to the cross-sectional nature of the ASRI, relationships between variables could only be assessed for association and not causation. Plans are in place to collect longitudinal data within the ASRI which would allow further analysis of these relationships. Not all patients within the ASRI had all physical measurements recorded, as such they were excluded from the analysis where such measurements were not available. Lastly, data collection in terms of physical activity and sedentary behaviour is very limited. Currently an abbreviated version of the International Physical Activity Questionnaire collects this information via four questions regarding frequency of stretching as well as vigorous, moderate or light physical activity on a weekly basis. While informative, this information does not capture type of physical activity, duration or sedentary behaviour.

6.8 Conclusion

There is a high prevalence of central obesity as classified by the WtHpR in axSpA, most notably in females with axSpA. This modifiable comorbidity was significantly associated with worse functional ability, poorer quality of life and a trend towards worse disease activity. Presence of central obesity was also strongly associated with increasing age and female sex. These results are highly concerning and would support use of the WtHpR when screening for obesity in this population. Central obesity is a potentially modifiable state which if identified, may be a key target for intervention in axSpA patients. Further public health campaigns are needed to raise awareness and improve recognition of this issue in axSpA.

This chapter further demonstrates the importance of considering the impact of sex on patient outcomes in axSpA. However, a discussion of women with axSpA would be incomplete without considering pregnancy in this population, given the age of onset in the childbearing years. The following chapters will review current knowledge of this topic and areas requiring further exploration.

Chapter 7. Management of Pregnancy in Rheumatic Disease

Publication resulting from material contained within this chapter:

S Maguire, F O'Shea. Management of Pregnancy in Rheumatic Disease. *European Medical Journal (EMJ) of Rheumatology*. 2021 Jul; 8(1): 86-93

(Full manuscript available in Appendix A)

7.1 Abstract

Pregnancy is a common life event for many women with rheumatic disease. However, the management of patients with rheumatic diseases (RMD) during pregnancy and the postpartum period can be a challenge for both rheumatologist and obstetricians. While disease activity during the course of pregnancy varies by underlying condition, maintenance of remission from conception through to delivery increases the chances of an uncomplicated pregnancy. A period of remission of at least 6 months prior to conception increases the chance of successful conception while decreasing risk of flares during pregnancy. For this reason, discussion of pregnancy in women with RMDs should begin prior to conception with risk stratification and pregnancy planning. This allows for transfer to pregnancy compatible medications, disease stabilisation, determination of autoantibody status and evaluation of end organ damage. During pregnancy, where possible, disease activity should be monitored with scores modified to allow use in pregnancy. Prompt recognition and treatment of active disease is essential to minimise risk to pregnancy. Systemic lupus erythematosus (SLE) and axial spondyloarthropathy (axSpA) can present diagnostic dilemmas due to overlap of symptoms of disease activity and normal pregnancy. Patients with end organ involvement such as SLE or systemic sclerosis, face a higher risk of adverse pregnancy outcomes and disease progression. Close monitoring of RMD patients should be done by both obstetricians and rheumatologists with regular communication between specialties. Medications should be reviewed at each stage of pregnancy to ensure compliance with current ACR guidelines and adequate treatment of RMD.

7.2 Background

Many patients with rheumatic diseases (RMDs) are diagnosed during the course of their childbearing years[448]. This is especially true for women with axial spondyloarthritis (axSpA) where the age of symptom onset is typically the second to third decade of life[449]. The previous two chapters of this thesis highlight several significant sex differences in patient outcomes, burden of disease and recording of disease activity. However, a discussion of women with axSpA would be incomplete without mentioning pregnancy. This chapter will explore pregnancy in the context of rheumatic diseases, including axSpA.

For this reason, when discussing women with RMDs it is important that pregnancy is properly addressed. This major life event can be a source of considerable stress and concern for female patients but with careful planning and education, can be managed safely.

Historically women with RMDs were advised to avoid pregnancy due to potential risk to both mother and foetus driven by disease flares and adverse pregnancy outcomes[450]. Thanks to advances in detection of disease activity and therapeutics, this is no longer true and most women with RMDs can safely become pregnant[451,452]. However, they may face an increased risk of a number of pregnancy related complications, such as preterm birth and need for caesarean section, and thus require closer monitoring during the course of their pregnancy[453,454].

Pregnancy in women with RMDs should involve a period of planning between the patient and her rheumatologist prior to actively trying to conceive[455,456]. The primary objective in managing any woman during pregnancy is both a healthy mother and child. In order to ensure favourable outcomes a number of factors including medication usage, disease activity and antibody status must be evaluated and managed (table 7.1)[457]. Pregnancy planning to risk assess and address these issues allows the Rheumatologist to help their patients safely navigate both the pregnancy and postpartum period.

Table 7.1: Factors of RMDs contributing to Pregnancy Outcome

Positive Impact	Negative Impact
Pregnancy planning & counselling Disease remission[1] Known autoantibody status Medication adherence Use of Pregnancy safe medications[2] Close monitoring of disease activity[3] Optimisation of general health	Active Disease[4] End organ damage *-Lupus nephritis* *-Pulmonary hypertension* *-Restrictive lung disease* Unplanned pregnancy Unplanned cessation of treatment[5]
[1]Remission of disease for at least 6 months prior to conception and throughout pregnancy; [2]Adjusted for each stage of pregnancy; [3]With outcome measures adjusted for pregnancy where possible; [4]Both prior to conception and during pregnancy; [5]Without consultation with a Rheumatologist due to risk of disease activity	

During pregnancy the female body undergoes a series of significant physiological and hormonal changes, which can affect disease activity[458]. Managing these patients during pregnancy can pose a challenge to Rheumatologists, as symptoms of flares can be confused with complications or physiological changes of pregnancy. Advances in understanding of disease processes has helped differentiate between these processes. Level of inflammation at the time of conception has been shown to directly impact pregnancy outcome making control of disease activity essential[459,460]. A number of disease activity scores have been modified for use in pregnancy, however most are focused on rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) with a considerable paucity of tools for other rheumatic diseases[461]. For this reason, close monitoring by both Rheumatology and Obstetrics is necessary during the course of pregnancy.

7.3 Search Strategy

For the purposes of this review, we searched PubMed, Cochrane and EMBASE for articles related to pregnancy in rheumatic diseases, with more specific searches for each disease process. Preference was given to more recently published literature to reflect most recent research on the topic. Bibliographies of included articles were also searched for additional sources which may have been relevant to this review.

7.4 Prior to Conception

7.4.1 Pre-Pregnancy Counselling & Planning

For women with RMDs, pregnancy planning is an essential component of pregnancy in the months prior to conception. The importance of this period of planning and counselling in RMD patients cannot be understated. Lack of pregnancy planning in the general population has been shown to be associated with increased incidence of low birthweight and even neonatal mortality[462,463]. Unplanned pregnancies have also been shown to be associated with increased rates of smoking, stress and lack of prenatal care[464]. This is also seen in patients with RMDs but conception is further complicated by risk of active disease and use of medications not compatible with pregnancy. Recent studies in SLE demonstrated that lack of planning for pregnancy was a significant predictor of adverse pregnancy outcomes[465,466].

The silver lining of this dilemma is that it is correctable with improved patient education and increased physician- led discussion of family planning during rheumatology consultation[467]. Barriers to these conversations discussed in a SLE focus group include busy clinic schedules and difficulty initiating pregnancy conversations[468]. However, this group also highlighted the disconnect in patient and physician risk perception of pregnancy which could be remedied by open conversations about pregnancy as part of regular Rheumatology consultations.

7.4.2 Disease Control

Control of maternal disease activity during pregnancy is known to be associated with improved pregnancy outcomes and lower risk of fetal complications[455,459,469]. The importance of disease control begins in the preconception stage, as women with active disease are advised to wait until disease is controlled prior to actively trying to conceive[456,457]. Ideally, patients planning a pregnancy should be in a state of remission for at least 6 months prior to conception[460]. Patients with significant end organ damage, should be counselled on their risk stratification prior to conception[470]. In cases of severe disease including advanced pulmonary arterial hypertension (PAH), chronic renal impairment stage IV/V or cardiac failure there is considerable risk of maternal morbidity and mortality. In such cases women should be advised against pregnancy (table 7.2)[460,467,471].

Table 7.2: Relative and Absolute Contra-indications to Pregnancy in Patients with RMDs[460,467,471]

Relative Contraindications	Absolute Contraindications
Severe SLE flare within the past 6 months[1] Stroke in the past 6 months Pulmonary Hypertension Severe Restrictive Lung Disease Moderate to Severe Cardiac Failure Severe Valvular disease CKD stage 4-5 Uncontrolled Hypertension Previous early onset Preeclampsia or HELLP[2]	Advanced Pulmonary Hypertension End stage renal disease Severe Cardiac failure
[1]Including renal flare; [2]Despite therapy with aspirin & heparin ***Abbreviations**: CKD -chronic kidney disease; HELLP – haemolysis, elevated liver enzymes, low platelet count*	

7.4.3 Medication

One of the main causes of patient and physician concern during pregnancy is around medication usage[472] A number of medications used to treat RMDs are not safe in pregnancy[473], however this is not true for all medications as outlined by the recent ACR guidelines[457](table 7.3). Despite this, many women with RMD stop their RMD medication prior to conception or in the early stages of pregnancy[474]. Unfortunately, this increases their risk of flare which requires rescue treatment with steroids followed by a period of unstable disease while their disease modifying anti-rheumatic disease (DMARD) medication is re-started[475]. Open discussion with patients with RMD planning to conceive around pregnancy safe medication including the risks and benefits of stopping medication could aid in limiting such situations.

This also can be an opportunity to ensure that the patient has commenced a prenatal vitamin. Women on folic acid antagonists including sulfasalazine will require higher doses of folic acid of 5mg a day when trying to conceive through to the completion of the first trimester to decrease risk of neural tube defects[476].

A number of women with RMD are treated with medications that are not compatible with pregnancy or have limited data in pregnancy[473]. For these patients a period of transition to pregnancy safe medications should take place prior to conception. It is important to remind women taking medications such as methotrexate and mycophenolate mofetil, that these medications are not safe in pregnancy and the importance of using reliable contraception.

Table 7.3: Summary of the ACR guidelines on medication for rheumatic disease usage during conception and pregnancy[457]

Conception			
Safe to continue	***Conditionally recommend to continue***	***Stop prior to conception***	***Unknown***
Hydroxychloroquine Sulfasalazine Colchicine Azathioprine Certolizumab Cyclosporine Tacrolimus	Prednisolone[1] Cyclosporine NSAIDs Infliximab Etanercept Adalimumab Golimumab Rituximab[2] Anakinra[2] Belimumab[2] Abatacept[2] Tocilizumab[2] Secukinumab[2] Ustekinumab[2]	Methotrexate Leflunomide Mycophenolate mofetil Cyclophosphamide Thalidomide	Tofacitinib Apremilast Baricitinib
Pregnancy			
Safe to continue	***Conditionally recommend to continue***	***Not safe in Pregnancy***	***Unknown***
Hydroxychloroquine Sulfasalazine Colchicine Azathioprine Certolizumab Cyclosporine Tacrolimus	Prednisolone[1] Cyclosporine NSAIDs[3] Infliximab[4] Etanercept[4] Adalimumab[4] Golimumab[4] Cyclophosphamide[5] Rituximab[6]	Methotrexate Leflunomide Mycophenolate mofetil Thalidomide Anakinra[7] Belimumab[7] Abatacept[7] Tocilizumab[7] Secukinumab[7] Ustekinumab[7]	Tofacitinib Apremilast Baricitinib
[1]Minnimise dose to less than 20mg a day with use of alternative pregnancy compatible immunosuppressant; [2]Discontinue at conception; [3]Avoid after 32 weeks to prevent premature closure of PDA; [4]Discontinue in the 3rd trimester several half-lives prior to delivery; [5]Only to be used in life or organ threatening disease in the 2nd or 3rd trimester only; [6]Life or organ threatening disease only; [7]Conditionally recommend to discontinue in pregnancy;			

7.4.4 Autoantibody Status

Assessment for the presence of autoantibodies such as anti-Ro/SS-A, anti-La/SS-B & antiphospholipid status, can determine pregnancy risk and need for additional medication during conception and pregnancy. Presence of anti-Ro or anti-La antibodies is associated with risk of fetal congenital heart block and development of neonatal lupus. Treatment of antibody positive women during pregnancy with hydroxychloroquine significantly reduces this risk[477].

Patients with SLE, history of recurrent miscarriage or other severe pregnancy outcome, should be evaluated for presence of antiphospholipid antibodies(aPL)[471]. This includes screening for beta-2-glycoprotein 1(b2GP1), lupus anticoagulant (LAC) and anti-cardiolipin antibodies (aCL). Use of low dose aspirin is recommended for patients with aPL to decrease risk

of pre-eclampsia in pregnancy[478]. Once pregnant, patients with a previous history of obstetric or thrombotic antiphospholipid syndrome (APS) will require therapeutic or prophylactic low molecular weight or unfractionated heparin depending on their risk stratification[457,479].

7.5 Pregnancy

During the course of pregnancy, the female body undergoes a series of physiologic changes driven by dramatic alteration of hormone levels. These changes have varying effects on disease activity in rheumatic disease. Careful monitoring for signs of active disease is an essential component of care for the pregnant RMD patient. However, accuracy of conventional tools to detect active disease can be limited by physiologic changes of pregnancy. A recent article outlining these challenges highlighted that a number of instruments have been developed to more accurately assess disease activity in RMD pregnancies[461].

While there are no specific guidelines for how often these patients should be seen by a rheumatologist during their pregnancies, clinical assessment once a trimester would allow regular monitoring of disease activity. More frequent monitoring may be required in cases of active disease, pregnancy complications or underlying end organ damage. Joint care of pregnant RMD patients and regular communication between Obstetrics and Rheumatology can help to safely manage these challenging cases.

7.5.1 Systemic Lupus Erythematosus

Pregnancy in systemic lupus erythematosus (SLE) is commonly encountered as this disease has a strong female predominance with many patients diagnosed during their childbearing years. SLE can be a difficult disease to monitor and manage due to the multi-organ involvement of this autoimmune disease. This is further complicated by physiological changes of pregnancy which can mimic disease activity, such as observed increases in erythrocyte sedimentation rate (ESR)[480] or development of thrombocytopenia[481]. Other commonly encountered issues in pregnancy including fatigue and proteinuria, can also be signs of active disease and confuse commonly used measures of disease monitoring. However, pregnancy has not been shown to affect the presence of autoantibodies.

Disease activity is the most important predictor of pregnancy outcome in SLE, with a significant proportion of patients experiencing active disease during pregnancy[482,483]. Patterns of organ involvement in the months prior to conception accurately predicts organ involvement in pregnancy flares and can be helpful for targeted monitoring of disease

activity[484]. Fortunately, there are a number of SLE scores which have been adapted for use in pregnancy including: SLE Pregnancy Disease Activity Index (SLEPDAI)[485], modified Systematic Lupus Activity Measure (m-SLAM), Lupus Activity Index in Pregnancy (LAI-P)[486] and the British Isles Lupus Assessment Group 2004 for Pregnancy (BILAG2004-P)[487].

Patients with lupus nephritis or renal impairment have an increased risk or further renal deterioration and adverse pregnancy outcomes[488]. This risk remains even in patients with previous lupus nephritis which is in remission at the time of conception[453]. Patients should be assessed for presence of hypertension, proteinuria, raised serum creatinine >100umol/L routinely due to association with increased risk of adverse outcomes[489]. Risk for renal flare during pregnancy is associated with active renal disease at the time of conception, with a relative risk (RR) of 9.0 in cases of non-remission and RR of 3.0 in partial remission[490]. To reduce risk of flare, disease activity should be tightly controlled throughout pregnancy. This involves not only use of immunosuppressive medication but also adequate blood pressure control and use of low dose aspirin to decrease risk of pre-eclampsia[491]. Renin-angiotensin blockers should be stopped prior to pregnancy or during the first trimester and changed to alternative hypertensive therapy.

Onset of SLE can occur during the course of pregnancy in a patient with no previous history of connective tissue disease. These patients tend to have higher rates of thrombocytopenia, pregnancy loss and active disease in pregnancy as compared to those diagnosed with SLE prior to pregnancy[492]. Higher rates of adverse maternal complications have also been in this population[493], but more research is needed. Prompt recognition and treatment is critical to management but can be a challenge due to the overlap of symptoms with that of normal pregnancy. Monitoring levels of complement and anti-double stranded Deoxyribonucleic Acid antibodies (anti-dsDNA) can be helpful in identifying new onset SLE in a pregnant patient. Certain clinical features can also be helpful such as onset of renal impairment and hypertension prior to 20 weeks gestation, which would be suggestive of SLE rather than pre-eclampsia[467].

As mentioned in the discussion of pre-conception counselling, autoantibody status is crucial for management of SLE pregnancies. In SLE patients who have not had antibody status assessed prior to conception, this should be done as soon as possible in pregnancy along with an electrocardiogram. In cases of QTc prolongation or previous history of cardiac involvement, a baseline echocardiogram is useful to assess cardiac function. Women known to have anti-Ro or anti-La antibodies should be commenced on hydroxychloroquine to decrease risk of congenital heart block and neonatal lupus[494]. For those previously on hydroxychloroquine continuation throughout pregnancy is strongly advised due to association with improved renal outcomes, and

decreased risk of both flares and thrombotic events[495]. Presence of anti-Ro antibodies will also require serial fetal echocardiograms from week 16-26 as per ACR guidelines[457].

Pregnancy is a naturally pro-thrombotic event, requiring evaluation of need for additional anti-coagulation during this period. All SLE patients should be screened for antiphospholipid antibodies (aPL), and if positive, commenced on low dose aspirin in the first trimester. Previous history of obstetric APS requires commencement of prophylactic heparin, while history of previous thrombotic APS requires therapeutic heparin during pregnancy[496]. Positive aPL antibodies with no previous history can be managed with low dose aspirin alone and close monitoring due to increased risk of pre-eclampsia[457].

Active disease during pregnancy often requires a course of corticosteroids due to rapid onset of action. Frequency and duration of corticosteroid use should be limited due to potential increased risk of insulin resistance and infection[497]. Evaluation of previous treatment and adherence must be considered prior to changing therapy. Hydroxychloroquine could be commenced but will take time to take effect, azathioprine could also be considered. Current ACR guidelines recommend against the use of intravenous immunoglobulin (IVIG) due to limited evidence of benefit[457], however it has been previously deemed compatible with all stages of pregnancy including breastfeeding[473]. EULAR guidelines also recommend consideration of IVIG in cases of severe refractory maternal disease in pregnancy[498]. Belimumab is the first biologic agent approved for use in the treatment of SLE, unfortunately pregnancy data is not yet available to comment on its safety at this time.

7.5.2 Rheumatoid Arthritis

Retrospective research in rheumatoid arthritis (RA) has demonstrated that this inflammatory arthritis commonly goes into remission during the course of pregnancy[499]. These findings were validated in a number of prospective studies, which were included in a recent meta-analysis and reported improved disease activity in 60% during pregnancy with 46.7% developing a flare in the post-partum period[500]. This is driven by a series of modifications of the maternal immune system, including downregulation of effector T cell activity with increase in regulatory T cells, to allow placentation and fetal growth[501]. Following delivery, these immunomodulatory effects dissipate with decrease of pregnancy hormones resulting in postpartum flares[502].

Although many pregnant patients with RA will experience improvement of disease activity during pregnancy, disease activity must be monitored as part of routine care. Physiological changes of pregnancy resulting in increased erythrocyte sedimentation rate (ESR)[480], fatigue, weight gain and anaemia, all of which can affect commonly used indexes such as the Disease Activity Score in 28 joints (DAS28) and Health Assessment Questionnaire

(HAQ)[503]. However, the DAS28-CRP3 which excludes the global health score has been shown to be the best clinical metric to detect active disease in pregnant RA patients[504]. Ongoing research has shown additional indexes also perform well in this population including the Rheumatoid Arthritis Disease Activity Index(RADAI) and Clinical Disease Activity Index(CDAI)[505].

Risk of flare during pregnancy is commonly associated with medication cessation and active disease prior to conception[475]. There is no clear consensus on antibody presence and risk of flare in pregnancy. Data from the Dutch Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study demonstrated a decreased risk of flare in pregnant RA women who did not carry autoantibodies[506]. However, a smaller study showed RA women with active disease in pregnancy had higher levels of anti-citrullinated antibodies(ACPA) compared to those with lower disease activity[507]. Further studies are needed to characterise the relationship between RA antibodies and risk of flare in pregnancy.

Flare in an RA patient during pregnancy requires prompt management as early recognition can result in improved pain control and rapid inflammation reduction. Often rescue therapy in the form of corticosteroids is required for a limited period. Review of current therapy and compliance can be helpful to determine alternative treatment options. In a patient who had previously come off her treatment or not been on treatment, discussion of treatment initiation with a pregnancy safe medication (table 7.3) is required[457]. This should include discussion of duration of medication throughout pregnancy and the postpartum period.

7.5.3 Spondyloarthritis

Spondyloarthritis (SpA) includes both axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA). Unfortunately, research on pregnancy in SpA is not as abundant as other RMDs. Older research in axSpA failed to demonstrate a clear trend in disease activity during pregnancy, but more recent studies using standardised outcome measures suggests an increase in activity throughout pregnancy[508-510]. Studies in PsA report quiescent disease during pregnancy with increased disease 6 months postpartum[511]. Similar to other RMDs discussed in this article, stable disease at conception was associated with favourable pregnancy outcomes.

Pregnancy can mimic many symptoms of SpA including low back pain, night pain and fatigue, but currently there are no validated indices for monitoring SpA activity during pregnancy. In a disease where clinical assessment of the spine is a core component of monitoring disease, this is a significant limitation. This is further complicated by mechanical strain of the increasing mass of the gravid uterus on the spine during the course of the pregnancy and postpartum period[512]. Further development of tools for monitoring SpA disease activity in pregnancy will provide much needed insight into the effect of pregnancy on disease activity.

Ongoing development of national registers and collaboration between registers will allow for a rapid expansion of our understanding of pregnancy in SpA. The European Network of Pregnancy Registers in Rheumatology (EuNeP) is a collaboration of four European national registers of patients with RMDs, formed with a specific focus on improving data collection on pregnant women with RMDs[513]. This collaboration has identified challenges in collection and comparison of pregnancy data, in addition to recommendations for streamlining of pregnancy data going forward.

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat flares in SpA, however these should be avoided beyond 32 weeks due to risk of premature closure of the ductus arteriosus[514]. Biologics such as tumour necrosis factor (TNF) inhibitors are associated with stable disease in pregnancy and are recommended in pregnancy in the current ACR guidelines up to the third trimester, with the exception of certolizumab which can continue into the postpartum period[457].

7.5.4 Systemic Sclerosis

Pregnancy in systemic sclerosis (SSc) is uncommon as onset is typically after childbearing years. The primary concern in pregnancy is presence of pulmonary arterial hypertension (PAH), which is the leading cause of maternal mortality[515]. Women considering pregnancy should be evaluated for PAH as part of routine monitoring and counselled when considering pregnancy. In cases of established PAH, patients should be strongly advised against pregnancy[516]. For SSc patients who achieve pregnancy, there is a high prevalence of adverse pregnancy outcomes however optimisation of disease control prior to conception decreases this risk[517]. Close monitoring in specialist centres with adequate support from Obstetrics, Rheumatology and Respiratory can aid in optimising outcomes.

Although now uncommon due to the advent of angiotensin converting enzyme (ACE) inhibitors, there is a risk of scleroderma renal crisis in pregnancy[518]. To avoid this, ACE inhibitors should be continued during pregnancy[519]. Prior to conception, a trial period on an alternative anti-hypertensive agent could be considered to optimise blood pressure control. In cases of hypertension despite alternative medication, ACE inhibitors should be restarted promptly. Use of low molecular weight heparin can reduce thrombotic risk while sildenafil and epoprostenol are additional therapeutic options in pregnancy[520]. In cases of disease acceleration or rapid progression during pregnancy, additional life-saving therapies may need to be considered including preterm labour induction to allow use of additional medications not compatible with pregnancy.

7.5.5 Vasculitis

There is limited data on pregnancy in vasculitis as age of onset is typically beyond childbearing years, with a male predominance in most types of vasculitis. Disease activity varies by disease, but all women with vasculitis should be considered for thromboprophylaxis during pregnancy. Pregnancy in these patients is associated with increased prevalence of pregnancy complications especially pregnancy loss and pre-eclampsia[521-523], however improved disease control prior to conception can improve outcomes[524].

Patients with a new diagnosis or recently active disease prior to pregnancy, are at higher risk of flares during pregnancy. Transitioning to pregnancy safe treatment prior to pregnancy is essential to ensure stable disease during pregnancy. This is especially important as flares in eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA) can have high fatality rates[525,526]. A number of medications used to treat vasculitis are not compatible with pregnancy, leading to greater reliance on corticosteroids during this time. This should be limited when possible due to associations with adverse pregnancy outcomes[527], with increased reliance on low risk medications including azathioprine and TNF inhibitors[524].

7.5.6 Inflammatory Myopathies

The most common types of inflammatory myopathies are polymyositis (PM) and dermatomyositis (DM). A Japanese study reported that 4-11% of women with these diseases had an age of onset between 25 to 34 years[528], highlighting the importance of addressing pregnancy in this cohort. Pregnancy complications, such as preterm birth and spontaneous abortion, in this population were associated with active disease during pregnancy (OR 435.4, 95% CI 5.32-35628.2) and onset of disease prior to pregnancy (OR 9.36, 95% CI 1.1-79.9)[529]. Hypertensive disorders in pregnancy have also been found to occur more commonly (OR 2.90, 95% CI 2.0-4.22)[530]. Although there is limited data on disease activity during pregnancy a retrospective analysis reported remission of disease during pregnancy with 10% reporting postpartum flares[531]. Treatment in pregnancy is mainly intravenous immunoglobulin (IVIG) and azathioprine, both proven to be safe in patients with other RMDs, with limited use of glucocorticoids[532].

7.6 Postpartum

The months following pregnancy can be a time of considerable stress and strain for many women, especially those with RMDs. During this time the mother's body again undergoes significant hormonal and physiological transitions, as it recovers from the birth while adapting to breastfeeding. These changes are compounded by the physical strain and sleep deprivation which comes with caring for a new infant. All of these factors can contribute to risk of postpartum flare. In order to minimise this risk, prompt re-evaluation of therapy is required following delivery.

A EULAR consensus statement in 2016 encouraged decisions on medication use during the postpartum period to provide as much benefit as possible to the mother while offering minimal risk to the infant[498]. The 2020 American College of Rheumatology guidelines on medication use in pregnancy includes a detailed section on postpartum use and lactation[457]. These guidelines highlight the range of therapeutic options which can be safely offered to breastfeeding women to optimise disease control during this time (table 7.4).

Table 7.4: Summary of the ACR Guidelines on medication usage in lactation[457]

Safe to Continue	***Conditionally recommend to continue***	***Not Recommended***	***Unknown***
Hydroxychloroquine Sulfasalazine Colchicine Certolizumab Infliximab Etanercept Adalimumab Golimumab Rituximab	Azathioprine[1] Prednisolone[2] Cyclosporine[1] Tacrolimus[1] NSAIDs[3] Anakinra[4] Belimumab[4] Abatacept[4] Tocilizumab[4] Secukinumab[4] Ustekinumab[4]	Methotrexate[5] Leflunomide Mycophenolate mofetil Cyclophosphamide Thalidomide	Tofacitinib[6] Apremilast[6] Baricitinib[6]

[1]Low transfer in breastmilk; [2]In doses over 20mg breastfeeding should be delayed by 4 hours following consumption; [3]Preferrably use ibuprofen when needed; [4]No data currently available but due to large size of molecule minimal transfer in breastmilk anticipated; [5]Limited data available which suggests low transfer in breast milk; [6]No data available but small size of molecule suggests transfer into breast milk likely

7.7 Conclusion

Risk stratification and pregnancy planning are key to ensuring women with rheumatic diseases have safe pregnancies with minimal risk of complications. This involves disease stabilisation, transition to pregnancy compatible medications, assessment of autoantibody status and evaluation of end organ damage. Disease activity during the course of pregnancy varies by disease, with active disease in pregnancy associated with increased risk of pregnancy complications. The recent ACR guidelines detail the medications which are safe to use in pregnancy to control disease activity. Regular monitoring and communication between Obstetrics and Rheumatology is essential for maintaining stable disease in pregnancy and monitoring for complications.

This chapter highlights the significant paucity of data available on pregnancy specifically in axSpA compared to other rheumatic diseases. As the age of onset is in the childbearing years, pregnancy is a common occurrence in women with axSpA. For this reason, it is crucial to carry out further research to determine the risk of pregnancy and fetal complications in these women, in addition to understanding trends in variation in disease activity over the course of pregnancy. This information has the potential to improve quality of care, management of disease activity in pregnancy, and optimise pregnancy outcomes in women with axSpA.

Chapter 8. Pregnancy in Axial Spondyloarthritis: A Systematic Review & Meta-Analysis

Publication resulting from material contained within this chapter:

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(Full manuscript available in Appendix A)

8.1 Abstract

Background

Females with axial spondyloarthritis (axSpA) are typically of childbearing age at the time of diagnosis. At present it is unclear how axSpA affects pregnancy, in terms of incidence of pregnancy related complications, and fetal outcomes. Similarly, studies exploring the effects of pregnancy on axSpA disease activity and medication use have been limited, with divergent conclusions drawn. Studies of women with other forms of inflammatory arthritis have suggested improved disease control during pregnancy with increased risk of postpartum flares. It is unknown if axSpA follows this pattern.

Objective

To review current literature on axSpA in pregnancy to determine the effect of disease on pregnancy outcomes.

Methods

A systematic review of case-controlled trials, observational studies, cross sectional studies and case series (n>5) focusing on axSpA in pregnancy. Studies were compiled by searching EMBASE, Medline (OVID), CINAHL, Maternity and Infant Care (MIDIRS online), and Web of Science from time of inception to October 2019 for key words related to axSpA, pregnancy, and pregnancy complications. Two reviewers independently reviewed articles to determine suitability for inclusion. The Newcastle & Ottawa Scale was used to assess risk of bias. Data extraction was performed using a standardised template to streamline data to allow comparison and meta-analysis. Where suitable data was assessed for suitability for pooling with a random effects model. Statistical heterogeneity was assessed by confidence interval overlap of the odds ratio, chi^2 test output and output of the I^2 statistic. Studies with high heterogeneity were assessed with sensitivity analysis and calculation of a weighted pooled means. The protocol for this review was prospectively registered with an international registry for systematic reviews (PROSPERO, Ref CRD42020147814).

Results

The search strategy returned 884 records. Of these, 130 full text articles were assessed for eligibility. Following assessment by two reviewers, 18 studies with a total of 3,166 axSpA women were eligible for inclusion in this review. There was a trend towards an increased prevalence of pre-eclampsia (OR 1.35, 95% CI 0.99-1.82) and a statistically significant increase in prevalence of caesarean section (OR 1.65, 95% CI: 1.52-1.80) and preterm birth (OR 1.33, 95% CI: 1.05-1.70) in axSpA females. Prevalence of all analysed fetal complications was higher in axSpA pregnancies (LBW OR

1.47, 95% CI: 0.98-2.21; SGA OR 1.66, 95% CI: 0.93-2.95; congenital abnormalities OR 1.40, 95% CI: 0.65-2.99; NICU admissions OR 1.55, 95% CI: 0.96-2.51), this did not reach significance. Disease activity during pregnancy varied significantly, but overall 47.8% of patients assessed by standardised outcomes reported increased disease activity in pregnancy. Few studies examined medication usage in pregnancy.

Conclusion

Females with axSpA overall have significantly higher prevalence of caesarean section, especially elective, and preterm birth then the general population. This analysis suggests a trend towards increased prevalence of pre-eclampsia, IUGR and a number of fetal complications, although further research is needed to explore this. There is a risk of active disease in pregnancy for a high proportion of axSpA females. Medication usage and prevalence of breastfeeding vary with time and country. Ongoing development of national registries could help to better understand axSpA in pregnancy.

8.2 Background

The previous chapter outlined how the management of women with axial spondyloarthritis (axSpA) in pregnancy presents a number of challenges for both the patient and the clinician. The priority when managing a pregnant patient with inflammatory arthritis is to ensure a healthy, uncomplicated pregnancy[533]. This includes close monitoring of disease activity, a healthy lifestyle, monitoring medication usage and regular reviews with both Rheumatology and Obstetrics[534].

One narrative[535] discussed this topic as part of a broader scoping article which included pathogenesis of ankylosing spondylitis (AS), physiological changes in pregnancy and fertility. One of the main issues highlighted by the authors was the lack of data specific to individuals with axSpA, as many studies included low numbers of patients with axSpA within a broader inflammatory arthritis cohort. There is currently no published evidence synthesis and meta-analysis of data in this area to guide practice. This chapter will aim to correct this issue by evaluating and summarising the current published literature available on axSpA in pregnancy.

In recent years, further development of national registries has led to an increase in pregnancy data published for women with axSpA[536-539]. Increased use of standardised outcome measures within registries has increased the comparability of data. Pooling of newly published registry data could provide the power needed to detect significant differences in pregnancy outcomes of axSpA patients.

Pregnancy related complications include any adverse health outcome encountered by the mother during the course of the pregnancy. Commonly discussed complications include stillbirth[540], miscarriage[541], caesarean sections[542] and pre-eclampsia[543]. These complications are known to occur less frequently in women with no past medical comorbidities[544]. There are a number of additional outcomes which must also be considered when discussing pregnancy. Fetal outcomes including low birt weight (LBW)[545], small for gestational age (SGA)[546] and congenital abnormalities[547] are important outcomes that have been studied in axSpA patients. Disease activity in axSpA during the course of pregnancy is an area of recent research interest, Lui et al[548] found high rates of disease improvement in pregnancy while van den Brandt et al[549] reported high rates of flare in disease during pregnancy especially in females taken off anti-TNF (tumour necrosis factor) treatment. A consistent pattern of axSpA disease activity during the course of pregnancy has not yet been established. Studies in rheumatoid arthritis (RA) have shown decreased disease activity during pregnancy with a high risk of flares in the postpartum period[550]. Pooling of data for axSpA could clarify if this holds true for axSpA. Medication usage during pregnancy has changed with the evolution of guidelines and increased drug development. With publications from national registry data, evaluation of medication usage can be robustly assessed.

The main aim of this review was to determine if women with axSpA have similar prevalence of pregnancy related complications as healthy controls, or if they are at an increased risk of complications. Secondary objectives were to explore fetal outcomes, disease activity, medication and breastfeeding among women with axSpA during pregnancy. This will inform guidance for the monitoring and management of women with axSpA during pregnancy.

8.3 Methods

The protocol for this review was prospectively registered with an international registry for systematic reviews (PROSPERO, Ref number CRD42020147814). The 'Preferred Reporting Items for Systematic Reviews and Meta-analysis' (PRISMA) guidelines[551] were followed in completing this review.

8.3.1 Patient & Public Involvement

There was no direct patient or public involvement in the design of this systematic review. However, this review was designed to address concerns previously expressed by axSpA patients. The results of this analysis will be disseminated and discussed with patients to guide further research.

8.3.2 Eligibility Criteria

Case control trials, observational studies, cross sectional studies and case series (with n >5) were considered for inclusion. Case reports, commentaries, expert opinions, review articles and case series with <5 axSpA patients were excluded.

In the initial registered protocol, at least one of the groups studied had to include adult women, aged 18 years or older, with a diagnosis of axSpA as per the modified New York Criteria. Upon initial evaluation of full texts for inclusion this was amended to also include the Assessment of Spondyloarthritis International Society (ASAS) criteria for axSpA following discussion among reviewers to reflect changing terminology in the field of axSpA. Studies with participants less than 18 years old were excluded.

Studies documenting the frequency of pregnancy related complications in females with axSpA were included in analysis. Comparison groups included pregnant females with other forms of inflammatory arthritis, or healthy pregnant females. Studies not focused on pregnant females were excluded. The primary outcome of this review was prevalence of pregnancy related complications including: miscarriage, pre-eclampsia, caesarean section (CS), intrauterine growth restriction (IUGR), gestational diabetes, premature rupture of membranes (PPROM), pre-term

delivery and stillbirth. The prevalence of these complications was compared between groups and pooled for the purpose of analysis. Primary outcome was required to be present prior to considering secondary outcomes such as fetal outcomes, disease activity (using BASDAI, BASFI, HAQ, ASQoL and BASMI), medication usage (NSAIDs, sDMARD or biologic agents) and breastfeeding.

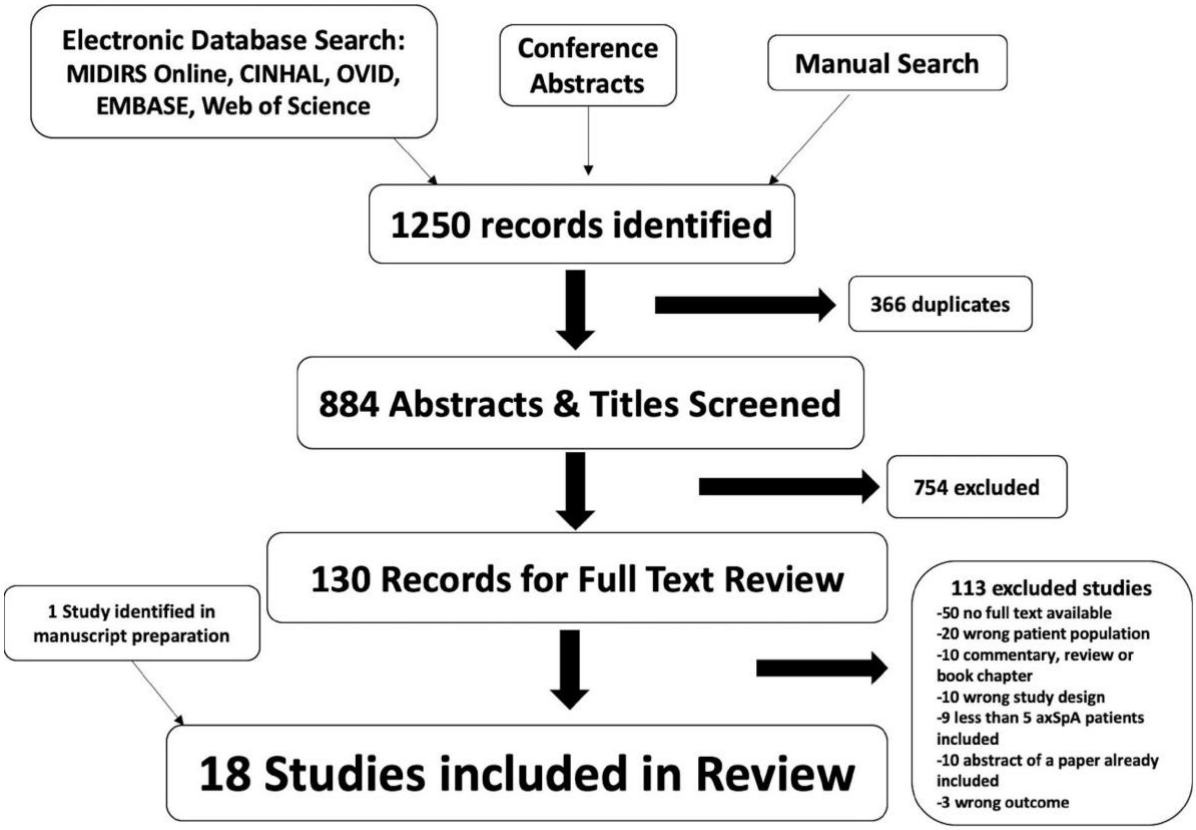
8.3.3 Sources and Study Selection

Studies were identified by searching the following electronic bibliographic databases: EMBASE, Medline (OVID), CINAHL, Cochrane library (central), Web of Science, and Maternity and Infant Care (MIDIRS online) from time of inception to September 2019. Electronic database search was supplemented by searching the European League against Rheumatism (EULAR) Congress (2002-2019) and the American College of Rheumatology (ACR) annual meeting (2006-2019) for relevant abstracts. A manual search of references for all eligible studies was also carried out. Search terms were adapted for use within each database and consisted of common key works and medical headings related to pregnancy, pregnancy outcomes, pregnancy complications, ankylosing spondylitis, and axial spondyloarthritis. No language or date restriction was placed on the searches. The search was repeated immediately prior to final analysis to ensure inclusion of all suitable studies. An experienced librarian (DM) conducted the search strategy which is presented in Appendix F.

In cases where only abstracts were available for relevant records, authors were contacted requesting full text manuscripts. If no response was received, a second attempt to contact authors was made, after which the abstract was excluded if no response was received. Lastly, a manual search of the reference lists of included studies was carried out.

Two reviewers (SM and TOD) independently screened titles, abstracts and keywords to select studies which met the eligibility criteria. Once selected full texts of the studies were retrieved and assessed in detail for eligibility (SM and TOD). Disagreements between reviewers were resolved by discussion to achieve a consensus. All conflicts were resolved on further discussion and a third reviewer did not need to be consulted. The Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) was used to facilitate the study selection process. Due to the high-quality study design and outcome measures assessed, reviewers selected to include this as grey literature.

Figure 8.1: PRISMA Study Selection



8.3.4 Data Extraction and Analysis

A data extraction template was developed based on Cochrane recommendations[552]. This was piloted on the oldest and most recent included studies and subsequently refined prior to data extraction of the remaining studies.

For each study the reviewers recorded data on pregnancy related complications. For pregnancy outcomes and complications, prevalence within both axSpA and control groups were recorded. Odds ratios were also extracted from the three studies[536,553,554] in which they were reported. In studies with no control group prevalence of complications was recorded for the axSpA group only.

Where available, fetal outcomes, disease activity changes related to pregnancy, medication usage during pregnancy and rates of breastfeeding were recorded. Data on medication use during pregnancy was recorded as a percentage within each exposure group where this information was available.

8.3.5 Data Synthesis

For all outcomes included in analysis, data was assessed for suitability of pooling data for comparable groups. In cases where this was deemed suitable a random effects model was used. Pooling of data and selection of effects model was based on heterogeneity across the pooled studies. Clinical heterogeneity was assessed based on study design, study population, outcomes and outcome measures documented within each study. Statistical heterogeneity was assessed with confidence interval overlap, statistical output of the Chi^2 test ($p<0.1$ indicating significant heterogeneity), and output of the I^2 statistic (>75% indicating significant heterogeneity). A weighted pooled means was calculated for primary outcomes.

8.3.6 Risk of Bias Assessment

Two independent reviewers (SM and FW) performed independent assessment of risk of bias for each of the included studies. The ROBINS-I tool was selected for risk of bias assessment in the original protocol but was later changed to the Newcastle Ottawa Score (NOS). This grades bias across three domains: selection, comparability, outcome[555]. The NOS consists of nine items grouped into three sections that are relevant to the quality of an observational study. The sections assess for selection bias, comparability of the exposed and unexposed cohorts, outcome assessment, and attrition bias. Quality was judged as follows:

- *Good quality*: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in the outcome/exposure domain.
- *Fair quality*: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in the outcome/exposure domain.
- *Poor quality*: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

8.4 Results

8.4.1 Study Selection

In total eighteen articles were selected for inclusion in analysis, representing the results of 18 studies published from 1980 to 2019 (figure 8.1: Study Selection). These 18 studies present data from thirteen countries; seventeen of the studies were based within a single country, with one study[556] collecting data from 13 countries. Three articles were not published in English and were translated from Icelandic[537], Hungarian[557] and Croatian[558].

8.4.2 Study Design & Characteristics

Thirteen retrospective studies and five prospective studies were selected for inclusion and analysis. Of the retrospective studies, eight[536,537,539,548,553,554,557,559] included matched controls. In one study[556] a retrospective cross-sectional analysis included a sub-analysis on recent pregnancies, which was not controlled. Of the five prospective studies[538,560-563] included, three studies[560,562,563] included matched controls (Table 8.1).

There were differences in control populations, with ten studies including healthy controls[536,537,539,553,554,559,560,562,563] and other studies including control groups with psoriasis[548] and other musculoskeletal diagnosis[557]. In five studies[539,553,560,562,563] more than one control was used for comparison, typically one group with another form of inflammatory arthritis and one group of healthy controls.

Table 8.1: Description of included studies

Authors	Publication	Data Source Period	Country	Study Type	Data Source	Control Population
Retrospective Studies						
Gomor et al[557]	1980	not stated	Hungary	Cross-sectional	Not stated	Other MSK disorders
Ostensen et al [564]	1982	1974-1980	Norway	Cross-sectional	Single centre	None
Jajic et al [558]	1995	not stated	Croatia	Cross-sectional	Not stated	None
Ostensen et al [556]	1998	prior to 1994	Norway & 12 other countries	Cross-sectional	Multi-centre	None
Sampaio-Barros et al [565]	2005	1990-2004	Brazil	Cross-sectional	Single centre	None
Lui et al [548]	2011	prior to 2010	Canada	Cross-sectional	Single centre	Females with Psoriasis
Zhou et al [566]	2012	2004-2011	China	Cross-sectional	Single centre	None
Jakobsson et al [536]	2016	2001-2009	Sweden	Cross-sectional	National Register	Healthy controls
Timur et al [559]	2016	2007-2015	Turkey	Case control	Single centre	Healthy controls
Kristjandottir et al [537]	2019	1981-2017	Iceland	Cross-sectional	National Register	Healthy controls
Park et al [554]	2019	1994-2017	Korea	Cross-sectional	Multi-centre	Healthy controls
Strouse et al [553]	2019	2007-2012	USA	Case control	Multi-centre	Healthy controls
Mork et al [539]	2019	1997-2016	Denmark	Cross-sectional	National Register	Healthy controls
Prospective Studies						
Ostensen et al [560]	1983	1979-1982	Norway	Case control	Single centre	Healthy controls
Ostensen et al [561]	2004	not stated	Switzerland	Cohort	Single centre	None
Ursin et al [538]	2018	2006-2016	Norway	Cohort	National Register	None
Zbinden et al [563]	2018	2000-2016	Switzerland	Case control	Single centre	Healthy controls
Smith et al [562]	2019	2004-2018	USA	Case control	Multi-centre	Healthy controls

8.4.3 Study Participants

The number of participants with axSpA in each study varied from 9[561] to 996[554](table 8.2). Median number of participants was 63 [IQR 20 - 129]. In total 4,881 pregnancies in 3,166 patients with axSpA were included in the pooled data of this review.

Diagnosis of axSpA varied between studies with three of the most recently published studies[538,539,563] using the 2009 Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial spondyloarthritis and older studies including patients who meet the 1984 modified New York criteria. One study[558] from 1995 included patients who met the Amor criteria and one study[561] used the European Spondyloarthropathy Study Group (ESSG) for AS criteria. Four studies did not specify the criteria used to classify patients as axSpA[537,553,556,562]. All included participants were diagnosed with axSpA by a physician as eligibility was determined on the basis of the diagnosis recorded in their medical records.

Table 8.2: Study Participants

Study	Group; axSpA Classification	N	Conception Age[1]	Disease Duration[1]	Primiparous	Pregnancies (n)
Retrospective Studies						
Gomor et al 1980 [557]	axSpA; mNY	65	Not reported	Not reported	Not reported	65
	Control	65	Not reported	N/A	Not reported	65
Ostensen et al 1982 [564]	axSpA; mNY	50	26.3	7.5	56% (28)	120
Jajic et al 1995[558]	axSpA; Amor	20	20	6	Not reported	20
Ostensen et al 1998 [556]	axSpA; not specified	939	Not reported	Not reported	Not reported	1,586
Sampaio-Barros et al 2005 [565]	axSpA; mNY	40	Not reported	15.5	Not reported	83
Lui et al 2011 [548]	axSpA; mNY	19	27.5	Not reported	Not reported	35
	Control	33	28.4	N/A	Not reported	77
Zhou et al 2012 [566]	axSpA; mNY	12	32.6	7.7	91.7% (11)	12
Jakobsson et al 2016 [536]	axSpA; mNY	301	30-34[2]	Not reported	Not reported	388
	Control	698	30-34[2]	N/A	43% (465)	1082
Timur et al 2016 [559]	axSpA; mNY	20	30.2	6.6	Not reported	20
	Control	40	27	N/A	Not reported	40
Kristjansdottir et al 2019 [537]	axSpA; not specified	60	26-30[2]	Not reported	Not reported	132
	Control	Not reported	26-30[2]	N/A	Not reported	3,214
Park et al 2019 [554]	axSpA; mNY	996	32	4.2	57.9% (749)	1,293
	Control	Not reported	32	N/A	49.5% (6903)	12,926
Strouse et al 2019 [553]	axSpA; not specified	128	Not reported	Not reported	Not reported	128
	Control	Not reported	> 34[2]	N/A	Not reported	10,244
Mork et al 2019 [539]	axSpA; ASAS	129	30.5	Not reported	Not reported	590
	Control	Not reported	31	N/A	44.6% (526,519)	1,195,882
Prospective Studies						
Ostensen et al 1983 [560]	axSpA; mNY	13	28	7.2	38% (5)	13
	Control	31	26.3	N/A	42% (13)	31
Ostensen et al 2004 [561]	axSpA; ESSG	9	31	9	60% (6)	10
Ursin et al 2018 [538]	axSpA; ASAS	166	30.6	5.9	92.7% (154)	179
Zbinden et al 2018 [563]	axSpA; ASAS	70	32[3]	Not reported	64.3% (45)	78
	Control	70	323	N/A	61.4% (43)	70
Smith et al 2019 [562]	axSpA; not specified	129	32.63	6.1	51.2% (66)	129
	Control	Not reported	32.2[2]	N/A	34.4% (247)	717

[1]Years, [2]Most common reported age range; [3]Age at delivery
Abbreviations: axSpA -axial spondyloarthritis; mNY -modified New York Criteria; N/A -not applicable, ESSG -European Spondyloarthropathy Study Group; ASAS -Assessment of Spondyloarthritis International Society

8.4.4 Risk of Bias within Studies

The risk of bias assessment for all studies is detailed in table 8.3. First round assessment by two reviewers lead to a strong level of agreement by calculation of Cohen's kappa (kappa = 92.7%, $p<0.01$). Following discussion between the reviewers, a 100% level of agreement was reached ($p<0.01$).

Ten studies were rated as 'good quality' overall[536-539,553,554,559,560,562,563]. All ten studies were rated as good across all three domains assessed. Participants were selected on the basis of a confirmed diagnosis most commonly following review of medical records. All participants were females with axSpA who were also pregnant making satisfying comparability requirements for control of potential confounding variables. Outcomes were well controlled as they were most commonly obtained via medical records and there were no participants lost to follow up.

Four studies[561,564-566]were judged to be 'fair quality'. All these studies rated similarly across all domains. Selection was fair as there was no control group and so selection of the non-exposed cohort could not be assessed. Comparability was rated as good, as all participants were female axSpA females who were also pregnant. Outcome assessment was rated as fair in three studies as no statement was made regarding rate of patients lost to follow up, however this was rated as good in one study[561] which accounted for all patients in follow up.

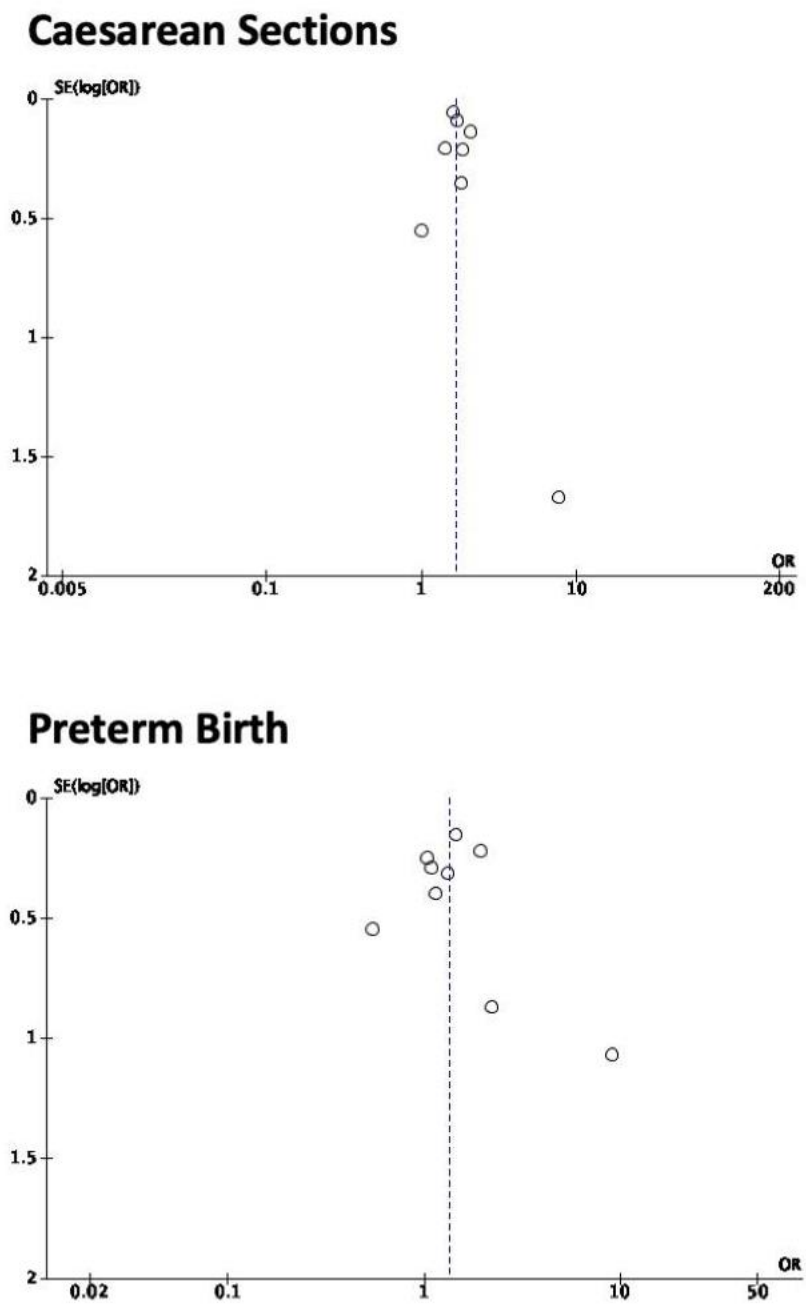
Four studies were judged as 'poor quality'. Of these studies only one[558] was rated as poor across all three domains. This brief publication did not include details on exposure, outcome assessment or details on control selection. Authors were contacted to clarify these details, but no response was received. The other three studies[548,556,557] rated similarly in their assessments. These studies were judged as fair regarding selection bias for most commonly due to lack of control group. All three were noted to have comparable study populations in that they included females with axSpA who were pregnant. These studies were deemed to have poor outcome assessment as the outcomes included were self-assessments.

Table 8.3: Risk of Bias Assessment

	Selection	Comparability	Outcome	Overall
Retrospective Studies				
Gomor et al 1980 [557]	Fair	Good	Poor	Poor
Ostensen et al 1982 [564]	Fair	Good	Fair	Fair
Jajic et al 1995 [558]	Poor	Poor	Poor	Poor
Ostensen et al 1998 [556]	Fair	Good	Poor	Poor
Sampaio-Barros et al 2005 [565]	Fair	Good	Fair	Fair
Lui et al 2011 [548]	Fair	Good	Poor	Poor
Zhou et al 2012 [566]	Fair	Good	Fair	Fair
Jakobsson et al 2016 [566]	Good	Good	Good	Good
Timur et al 2016 [559]	Good	Good	Good	Good
Kristjansdottir et al 2019 [537]	Good	Good	Good	Good
Park et al 2019 [554]	Good	Good	Good	Good
Strouse et al 2019 [553]	Good	Good	Good	Good
Mork et al 2019 [539]	Good	Good	Good	Good
Prospective Studies				
Ostensen et al 1983 [560]	Good	Good	Good	Good
Ostensen et al 2004 [561]	Fair	Good	Good	Fair
Ursin et al 2018 [538]	Good	Good	Good	Good
Zbinden et al 2018 [563]	Good	Good	Good	Good
Smith et al 2019 [562]	Good	Good	Good	Good

Funnel plots were constructed for caesarean sections and preterm birth (figure 8.2). Visual inspection revealed no obvious publication bias in included studies for either caesarean sections or preterm birth rate.

Figure 8.2: Funnel plot of Caesarean Sections & Preterm Births



8.4.5 Primary Outcome: Pregnancy Outcomes in axSpA

Caesarean sections were recorded in 12 studies[536,537,539,554,556,559-563,566] with 1,163 recorded in axSpA pregnancies and 225,359 in controls (table 8.4). Low heterogeneity was noted between studies (I^2 =0%, p =0.56). A random effects model was used to calculate a significant overall odds ratio (OR) of 1.65 (95% CI 1.52-1.80) indicating increased prevalence in axSpA pregnancies (figure 8.3). Weighted pooled means calculation resulted in a weighted mean prevalence of 37.3% in axSpA pregnancies and 18.6% in control pregnancies.

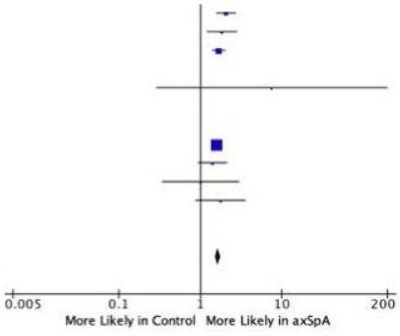
Further analysis was then performed on 5 studies[536,537,539,554,563] with data on elective and emergency caesarean sections. Emergency caesarean sections were recorded in 145 axSpA pregnancies. Low heterogeneity was noted between studies (I^2=0%, p =0.58). A random effects model calculated an overall OR of 1.29 (95% CI 1.06-1.56) indicating a significant increased prevalence in axSpA pregnancies. Weighted pooled means calculation resulted in a weighted means prevalence of 11.9% in axSpA pregnancies and 10.8% in controls. Elective caesarean sections were recorded in 193 axSpA pregnancies. Low heterogeneity was noted between studies (I^2 =0%, p =0.55), a random effects model calculated an overall OR of 2.31 (95% CI 1.94-2.75) indicating significant increased prevalence in axSpA pregnancies. Weighted pooled means revealed a prevalence of 15.9% in axSpA pregnancies versus 7.5% in control pregnancies.

Figure 8.3: Caesarean Section Prevalence

Total Caesarean Sections

Study or Subgroup	axSpA Events	axSpA Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Jakobsson et al 2016	112	388	177	1082	10.0%	2.07 [1.58, 2.72]
Kristiandottir et al 2019	31	132	460	3214	4.3%	1.84 [1.21, 2.78]
Mork et al 2019	162	590	219395	1195882	22.6%	1.68 [1.41, 2.02]
Ostensen et al 1982	4	87	0	0		Not estimable
Ostensen et al 1983	1	13	0	31	0.1%	7.56 [0.29, 198.31]
Ostensen et al 1998	103	366	0	0		Not estimable
Ostensen et al 2004	1	9	0	0		Not estimable
Park et al 2019	657	1293	5098	12926	56.3%	1.59 [1.41, 1.78]
Smith et al 2019	43	129	188	717	4.6%	1.41 [0.94, 2.10]
Timur et al 2016	11	20	22	40	0.6%	1.00 [0.34, 2.94]
Zbinden et al 2018	31	78	19	70	1.5%	1.77 [0.88, 3.55]
Zhou et al 2012	7	12	0	0		Not estimable
Total (95% CI)		3117		1213962	100.0%	1.65 [1.52, 1.80]
Total events	1163		225359			

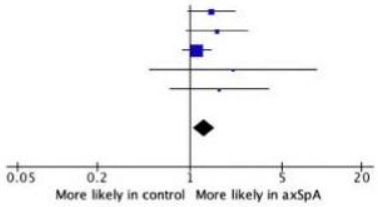
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.79$, $df = 7$ ($P = 0.56$); $I^2 = 0\%$



Emergency Caesarean Sections

Study or Subgroup	axSpA Events	axSpA Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Jakobsson et al 2016	38	388	75	1082	21.7%	1.46 [0.97, 2.19]
Kristiandottir et al 2019	16	132	255	3214	12.6%	1.60 [0.93, 2.74]
Mork et al 2019	71	590	129061	1195882	59.1%	1.13 [0.88, 1.45]
Park et al 2019	3	27	6	108	1.7%	2.13 [0.50, 9.11]
Zbinden et al 2018	17	78	10	70	4.9%	1.67 [0.71, 3.95]
Total (95% CI)		1215		1200356	100.0%	1.29 [1.06, 1.56]
Total events	145		129407			

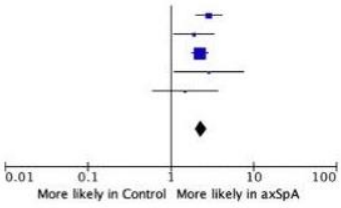
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.85$, $df = 4$ ($P = 0.58$); $I^2 = 0\%$



Elective Caesarean Sections

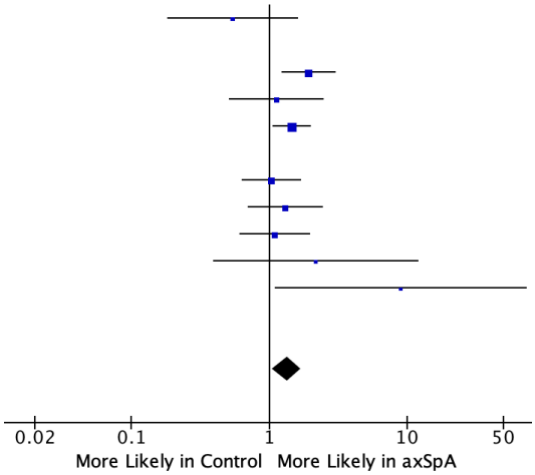
Study or Subgroup	axSpA Events	axSpA Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Jakobsson et al 2016	64	388	70	1082	23.1%	2.86 [1.99, 4.10]
Kristiandottir et al 2019	15	132	204	3214	9.7%	1.89 [1.08, 3.30]
Mork et al 2019	91	590	90282	1195882	60.3%	2.23 [1.79, 2.79]
Park et al 2019	9	27	16	108	3.3%	2.88 [1.10, 7.51]
Zbinden et al 2018	14	78	9	70	3.7%	1.48 [0.60, 3.68]
Total (95% CI)		1215		1200356	100.0%	2.31 [1.94, 2.75]
Total events	193		90581			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.02$, $df = 4$ ($P = 0.55$); $I^2 = 0\%$



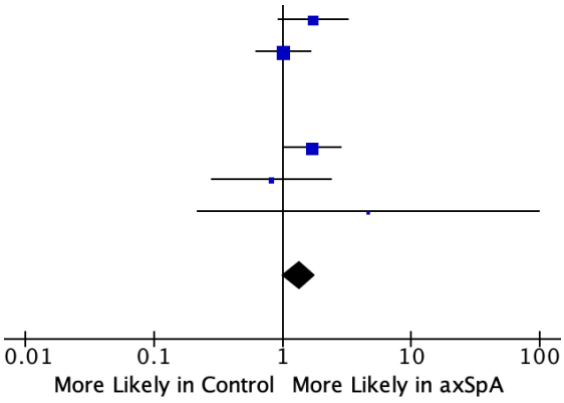
Preterm birth prevalence was documented in 11 studies[536,537,539,553,554,556,557,559,562,563,566], with 173 documented cases in axSpA pregnancies and 64,226 in controls. Low heterogeneity was noted between studies (I^2 =26%) (figure 8.4). A random effects model calculated an overall OR of 1.33 (95% CI 1.05-1.70) indicating a significant trend towards increased prevalence of preterm birth in axSpA. Weighted pooled means calculation resulted in a weighted mean of 5.4% in axSpA pregnancies and 5.2% in control pregnancies. In all 9 controlled studies pre-term delivery was more common in patients with axSpA.

Figure 8.4: Preterm Birth Prevalence



Pre-eclampsia was documented in 7 studies[536,539,554,556,562-564] with 5 of the studies controlled. In total 70 pregnancies of axSpA patients were affected with 34,217 affected controls. Low heterogeneity was noted between studies (I^2 =5%) (figure 8.5). A random effects model calculated an overall OR of 1.34 (95% CI 0.99-1.82) indicative of a significantly increased prevalence in axSpA pregnancies. Weighted pooled means calculation resulted in a weighted mean of 2.4% in axSpA pregnancies versus 2.8% in control studies.

Figure 8.5: Pre-eclampsia Prevalence

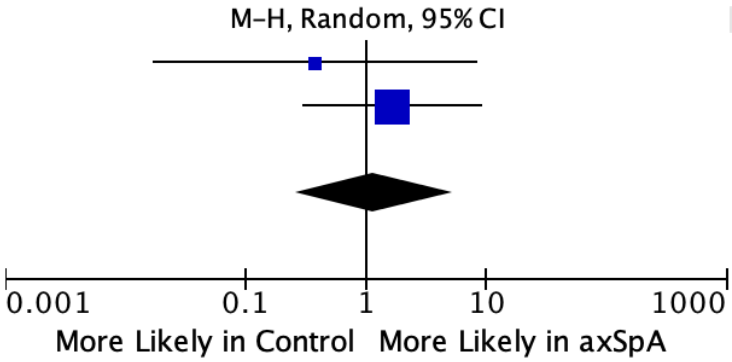


PPROM was recorded in only two studies[563,566] with 6 affected pregnancies in axSpA females, no control results were available for comparison. A weighted pooled means calculation resulted in a weighted mean of 6.7% for axSpA pregnancies.

M**iscarriage** was recorded in 5 studies[538,556,560,564,565] with 56 total events in axSpA patients. Only one study[560] was controlled, which reported higher prevalence of miscarriage(3.2%) in control pregnancies . A weighted pooled means calculation showed a weighted mean of 3% in axSpA pregnancies.

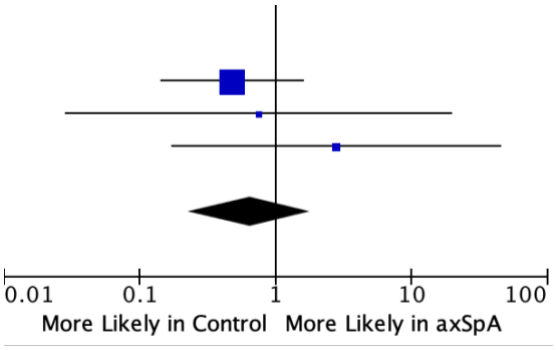
IUGR incidence was noted to be low in the two studies[554,559] it was recorded in, with only 2 axSpA patients affected in total and seven cases in controls. Heterogeneity was not noted between studies (I^2 =0%, p value =0.4) (figure 8.6). A random effects model was used to calculate an overall OR of 1.17 (95% CI 0.26-5.17), indicating a non-significant increased prevalence in axSpA pregnancies. A weighted pooled means calculation showed a weight means of 4.3% in axSpA pregnancies compared to 4.7% in control pregnancies.

Figure 8.6: IUGR Prevalence



Stillbirth was documented in 5 studies[536,556,560,561,563]of which 3 were controlled, with 6 affected axSpA pregnancies and 29 affected control pregnancies. Heterogeneity was low between studies (I^2 =0%, p =0.51) (figure 8.7). A random effects model was used to calculate an overall OR of 0.64 (95% CI of 0.23-1.82) indicating no significant difference in prevalence in axSpA pregnancies compared to controls. A weighted pooled means calculation showed a weight means of 0.7% in axSpA pregnancies compared to 1.1% in control pregnancies.

Figure 8.7: Stillbirth Prevalence



Gestational diabetes was recorded in 3 studies[554,562,563] and affected 10 axSpA pregnancies and 52 controls. Heterogeneity was not noted between the studies (I^2 =43%, p =0.17) (figure 8.8). A random effects model was used to calculate an overall OR of 0.86 (95% CI 0.24-3.15), indicating a non-significant trend to lower prevalence in axSpA pregnancies. A weighted pooled means showed a weighted mean of 4.3% in axSpA pregnancies and 5.8% in control pregnancies (table 8.4).

Figure 8.8: Gestational Diabetes Prevalence

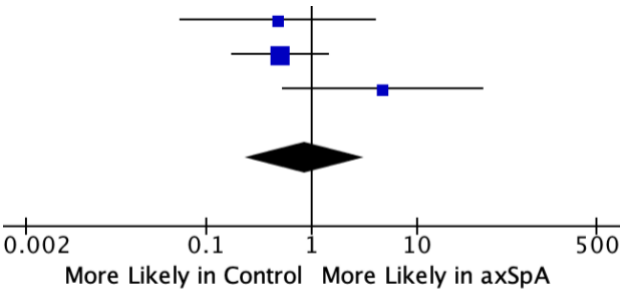


Table 8.4: Summary of Pregnancy Related Complications

	n in axSpA group	n in control group	OR (95% CI)	I^2 (p-value)	axSpA Weighted Pooled Mean (%)	Control Weighted Pooled Means (%)	References
Caesarean Sections Total	1,163	225,359	1.65 (1.52-1.80)	0% (0.56)	37.3	18.6	*[536,537,539,554,556,559-563,566]*
Emergency CS[1, 2]	*145*	*129,407*	*1.29 (1.06-1.56)*	*0% (0.58)*	*11.9*	*10.8*	*[536,537,539,554,563]*
Elective CS[1, 2]	*193*	*90,581*	*2.31 (1.94-2.75)*	*0% (0.55)*	*15.9*	*7.5*	*[536,537,539,554,563]*
Preterm birth	173	64,226	1.33 (1.05-1.70)	26% (0.21)	5.4	5.2	*[536,537,539,553,554,556,557,559,562,563,566]*
Miscarriage	56	1	0.75 (0.03-19.7)	N/A	3	3.2	*[538,556,560,564,565]*
Pre-eclampsia	70	34,217	1.35 (0.99-1.82)	5% (0.38)	2.4	2.8	*[536,539,554,556,562-564]*
Gestational Diabetes	10	52	0.86 (0.23-3.15)	43% (0.17)	4.3	5.8	*[554,562,563]*
IUGR	2	7	1.17 (0.26-5.17)	0% (0.4)	4.3	4.7	*[554,559]*
PPROM	6	N/A	N/A	N/A	6.7	N/A	*[563,566]*
Stillbirth	6	29	0.64 (0.23-1.82)	0% (0.51)	0.7	1.1	*[536,556,560,561,563]*

[1]CS: caesarean section

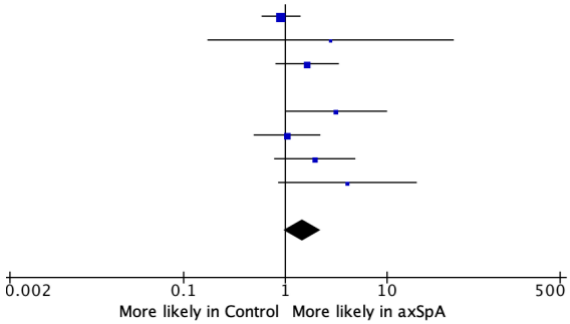
[2]Data on emergency and elective caesarean sections only available in the hospital cohort of the Park et al 2019 study, which accounts for the differences in group size between total, emergency and elective caesarean sections.

8.4.6 Secondary Outcomes:

8.4.6.1 Fetal Complications

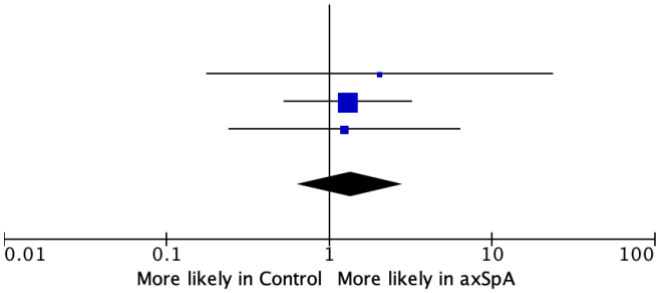
Low birthweight (LBW) was documented in 8 studies[536,537,553,554,556,557,559,562] of which 7 were controlled. Overall LBW occurred in 94 neonates delivered to axSpA females and in 467 control pregnancies. Heterogeneity was low between the studies (I^2 =34%, p value =0.17) (figure 8.9). A random effects model was used to calculate an overall OR of 1.47 (95% CI 0.98-2.21) which is not significant but indicates a trend towards increased prevalence in axSpA pregnancies. Seven of the studies were controlled, in all of these studies rates of LBW were higher in pregnancies of axSpA patients. Calculation of weighted pooled means equalled 6.3% in axSpA pregnancies and 2.9% in controls (table 8.5).

Figure 8.9: Low Birthweight Prevalence



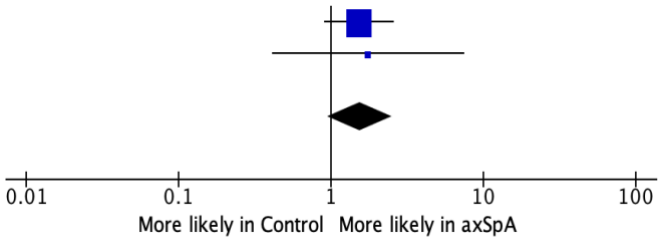
Congenital abnormalities were documented in five studies[553,554,556,563,564], three of which were controlled. In total this occurred in 23 neonates of axSpA females and 315 neonates from control pregnancies. Heterogeneity was not noted between the studies (I^2 =0%, p value =0.73) (figure 8.10). A random effects model was used to calculate an overall OR of 1.40 (95% CI 0.65-2.99), indicating a non-significant trend towards increased congenital abnormalities in neonates from axSpA pregnancies. A weighted pooled means calculation showed a weighted means of 3.4% in axSpA pregnancies and 3% in control births.

Figure 8.10: Congenital abnormalities



NICU admission prevalence was discussed in only two studies[559,562], with 26 neonates requiring NICU admission post-delivery in axSpA pregnancies and 90 neonates in control pregnancies. Heterogeneity was not found between the studies (I^2 =0%, p value =0.86) (figure 8.11). A random effects model was used to calculate an overall OR of 1.55 (95% CI of 0.96-2.51), which is not significant yet indicates a trend towards increased prevalence in axSpA pregnancies. A weighted pooled means calculation showed a weighted means of 17.4% in axSpA pregnancies and 11.9% in controls.

Figure 8.11: NICU Admission prevalence



Small for gestational age (SGA) was recorded in 5 controlled studies[536,539,553,554,563] with 106 affected neonates of axSpA females and 132,515 affected neonates of controls. Moderate heterogeneity was noted between the studies (I^2=72%) (figure 8.12). A random effects model was used to calculate an overall OR of 1.66 (95% CI 0.93-2.95), which is a significantly increased prevalence in axSpA pregnancies. A weighted pooled means calculation showed a weighted means of 8.8% in axSpA pregnancies and 11% in control pregnancies.

Figure 8.12: SGA Prevalence

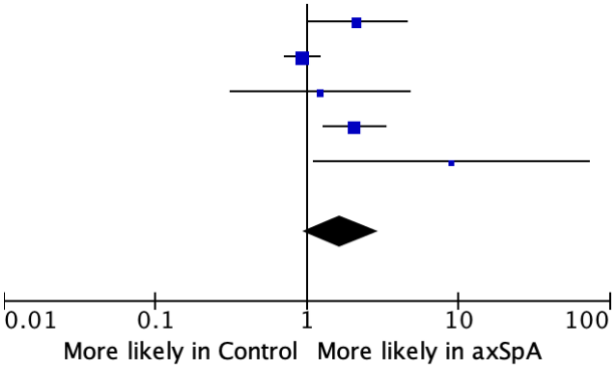


Table 8.5: Summary of Fetal Complications

	n in axSpA group	n in Control group	OR (95% CI)	I^2 (p-value)	axSpA Weighted Pooled Mean (%)	Control Weighted Pooled Mean (%)	References
LBW	94	467	1.47 (0.98-2.21)	34% (0.17)	6.2	2.9	[536,537,553,554,556,557,559,562]
SGA	106	132,515	1.66 (0.93-2.95)	72% (0.007)	8.8	11	[536,539,553,554,563]
Congenital abnormalities	23	315	1.40 (0.65-2.99)	0% (0.73)	3.4	3	[553,554,556,563,564]
NICU admissions	26	90	1.55 (0.96-2.51)	0% (0.86)	17.4	11.9	[559,562]
Abbreviations: LBW -low birthweight, SGA -small for gestational age, NICU -neonatal intensive care							

8.4.6.2 AxSpA Disease Activity

Review of the initial two studies for the data extraction template revealed that reporting of disease activity was often limited to being categorised as worsened, improved or no change over the course of the pregnancy. In eight studies[538,548,559-564], pre-defined criteria were used to assess changes in disease activity. In three studies[556,558,566], no criteria were described on how the clinician reached their decision regarding change in level of disease activity. In these studies, the level of disease activity was recorded at the observing clinicians' discretion. This was likely due to many of the studies being retrospective, so application of set criteria to determine level of disease activity may not have been possible due to variation in information available for each patient.

Standardised Outcomes

Six of the eleven studies discussing disease activity in pregnancy used standardised outcome measures (table 8.6). Outcome measures used (BASDAI[538,561], HAQ[562], ASDAS-CRP[559,563], Roland Morris Questionnaire[548]) are all validated and accepted measures for the assessment of patients with axSpA. The use of these tools allows for reliable comparisons to be made between studies.

Ursin et al[538] measured BASDAI throughout the pregnancy and showed disease activity peaked in the second trimester with 45% of patients noted to have active disease. Analysis of postpartum scores showed disease activity was lowest at 1 year postpartum. This was also the case in Ostensen et al[561] which reported BASDAI pain and stiffness scores highest in the second trimester, but lowest in the 3rd trimester.

Smith et al[562] assessed disease activity using the HAQ at study initiation and at 32 weeks of pregnancy. This prospective cohort study showed active disease in 34.5% as indicated by HAQ score greater than 0.5 during the course of pregnancy.

ASDAS-CRP was used by Timur et al[559] and Zbinden et al[563]. Timur et al recorded changes in scores throughout the time point in pregnancy and the post-partum period. From conception to pregnancy the most common change was decrease in the ASDAS-CRP as seen in 70% of individuals. From pregnancy to the postpartum period an increase in ASDAS-CRP was the most common finding as noted in 75% of pregnancies. Zbinden et al reported exact ASDAS-CRP scores and found axSpA patients had persistent disease activity throughout pregnancy with mean scores by trimester of 2.5, 2.4 and 2.2. In total 78% of patients experienced active disease during their pregnancy.

Lui et al[548] used the Roland Morris questionnaire and numerical rating scales to monitor disease activity in pregnancy. Results were reported as overall changes in pregnancy and

showed decrease in disease activity in pregnancy was the most commonly encountered change in 51% of pregnancies, while 26% experienced an increase and 23% experienced no change in disease activity during pregnancy.

Data on patients with active disease or increased disease activity via assessment with standardised outcomes during pregnancy was pooled. This found that overall, 47.8% of patients (211 of 451) were found to have increased disease activity during pregnancy, with three studies[538,561,563] identifying the second trimester as the peak of disease activity. Additional data was not available to calculate the percentage of patients with no change or decreased disease activity in pregnancy.

Table 8.6: Summary of disease activity in pregnancy in studies using **standardised outcome measures**

Study	Outcome Measure	Findings
Ostensen et al 2004	BASDAI	Pain and stiffness scores peaked in the 2nd trimester Pain and stiffness scores lowest in the 3rd trimester
Lui et al 2011	Roland Morris Questionnaire	51% decreased disease activity in pregnancy 26% increased disease activity 23% no change
Timur et al 2016	ASDAS-CRP	Conception - Pregnancy: 70% of females had a decrease in score Pregnancy - Postpartum: 75% of females had an increase in score
Ursin et al 2018	BASDAI	Highest disease activity in 2nd trimester (active disease in 45% with mean BASDAI 3.97) Lowest disease activity one year postpartum (mean BASDAI 3.35)
Zbinden et al 2018	ASDAS-CRP	78.3% of females had active disease during pregnancy Active disease most common in 2nd trimester Mean scores by trimester: 1st = 2.5, 2nd = 2.4, 3rd = 2.2
Smith et al 2019	HAQ	34.5% had active disease at study initiation Mean HAQ increased over the course of the pregnancy

Non-Standardised Outcomes

Five[556,558,560,564,566] of the eleven studies used non-standardised outcomes to explore disease activity in pregnancy (table 8.7). Most studies were retrospective, except one[560], and four studies[556,558,560,564] used data on patients recorded prior to the early 1990s, during which time a number of standardised outcome measures were developed for axSpA[115,128]. Jajic et al[558] found 65% of the patients to have increased disease activity during pregnancy while 35% of patients had no change in pregnancy. Ostensen et al 1998[556] also showed increased disease activity as the most common finding in pregnancy in 39.9%, however, an analysis on 366 recent pregnancies reported decreased disease activity as the most common finding in 37%. Of note that 57.3% of patients experienced a postpartum flare. Ostensen et al 1982[564] recorded active disease in 87.4% prior to conception, while during pregnancy 55% experienced no change, 24% increased disease activity and 21% decreased disease activity. In the postpartum period 45% noted increased disease activity. Ostensen et al 1983[560] recorded active disease in 61.5% throughout pregnancy and all flared 4-8 weeks postpartum. Zhou et al[566] reported no change in disease in 66.7%, with 25% reporting aggravation of symptoms throughout pregnancy.

Table 8.7: Summary of disease activity in pregnancy in studies using **non-standardised outcome measures**

Study	Outcome Measure	Findings
Ostensen et al 1982	Not reported	87.4% had active disease prior to conception During pregnancy: 55% no change in disease activity (24% increased disease activity, 21% decreased disease activity)
Ostensen et al 1983	Not reported	Active disease in 61.5% throughout pregnancy 100% of patients flared 4-8 weeks postpartum
Jajic et al 1995	Not reported	65% of patients have increased disease activity in pregnancy 35% noted no change in activity during pregnancy
Ostensen et al 1998	Not reported	39.9% of patients overall had increased disease activity in pregnancy Subgroup analysis of recent pregnancies: decreased disease activity most common in 37% 57.3% overall experienced a postpartum flare
Zhou et al 2012	Not reported	No change in disease activity in 66.7% Aggravation of symptoms throughout pregnancy in 25%

8.4.6.3 Medication Usage in Pregnancy

Medication usage was recorded during pregnancy in four studies[538,559,560,562]. Description of exposure to medication was most commonly classified as no treatment, NSAIDs, corticosteroids, sDMARDs and anti-TNF or other biologic therapy. Medication use during pregnancy had significant variation, which could reflect changing practices with time and prescribing patterns of a number of geographical locations.

Smith et al 2019 reported the majority of pregnancies in axSpA (81.4%) occurred while on anti-TNF treatment. This is in contrast to Ursin et al who report significantly lower rates of usage in pregnancy of 1 to 6% (see table 8.8). No treatment rates were high with Ursin et al reporting up to 55-69% of patients on no treatment at varying stages of their pregnancy. Zhou et al reported up to 50% of their patients were on no treatment prior to pregnancy but does not have data for medication exposure during pregnancy.

Table 8.8: Medication Usage in Pregnancy

	NSAIDs	**sDMARDs**	**Corticosteroids**	**anti-TNF**	**Other**
Ostensen et al 1983[560]	93%	Not reported	Not reported	Not reported	no tx 7%
Timur et al 2016 [559]	20%	Not reported	35%	Not reported	Not reported
Ursin et al 2018 [538]	18/23/8%*	16/13/10%*	6/5/8%*	6/4/1%*	no tx 58/55/69%*
Smith et al 2019 [562]	24%	7.8%	38%	81.4%	Not reported

Abbreviations: Anti-TNF: anti-tumour necrosis factor; NSAIDs: Non-steroidal anti-inflammatory drug; sDMARDs: synthetic Disease modifying anti-rheumatic drug; Tx: treatment
* Medication use reported for each trimester, recorded here as trimester 1/2/3 in percentages (%)

8.4.6.4 Breastfeeding:

Breastfeeding was reported in four studies. Rates of breastfeeding showed considerable variation from 0.8% to 50% to 81.3% to 90%[554,558,561,563]. It is important to consider significant variation in cultural and societal practices related to this topic. Of the four papers, none remarked or discussed the prevalence of breastfeeding within the study population.

8.5 Discussion:

This review identified published research on pregnancy outcomes in females with axSpA and is a thorough systematic review on this topic which synthesises data through meta-analysis. Many women with axSpA will seek advice from health practitioners prior to conception. It is essential to be able to inform women with axSpA of the anticipated course of their pregnancy and the effect it could have on their disease so that management during this time can be as effective as possible.

Increased caesarean section rate was the most significant finding within this analysis (OR 1.65, 95% CI 1.52-1.80), with studies of women with axSpA consistently reporting a higher prevalence of caesarean section than control groups, with weighted pooled means of 37.3% and 18.6% respectively. This higher prevalence remained significant even when data was split to examine elective (OR 2.31, 95% CI 1.94-2.75) and emergency procedures (OR 1.29, 95% CI 1.06-1.56), both of which were occurred at a higher prevalence in axSpA pregnancies compared to control pregnancies. Variation in clinical guidelines and obstetric practices over time and between countries should be considered when interpreting this information[567,568]. Rates of caesarean section deliveries have increased[569] and current research suggests reasons for this are multifold[570]. The increased rate of elective caesarean section could represent physician concerns regarding vaginal delivery in axSpA women, or increased preference of axSpA women for this mode of delivery. However, this review did not uncover any evidence of increased risk of vaginal delivery versus caesarean section in axSpA pregnancies. So why is the prevalence of elective caesarean sections so high in axSpA pregnancies? Further research focusing on indications for caesarean sections in axSpA pregnancies would provide significant insight into this complex issue.

Preterm birth in axSpA pregnancies was also found to occur significantly more frequently compared to control pregnancies (OR 1.33, 95% CI 1.05-1.70). This result is especially concerning as preterm birth is known to be associated with increased risk of numerous fetal complications, thus identification of modifiable risk factors to minimise the risk of this complication is critical to both mother and child[571]. Up to one third of preterm births are due to maternal or fetal complications[572], which could be a contributor to the higher prevalence of emergency caesarean sections detected in this analysis. Research into risk factors for preterm birth in axSpA pregnancies would provide much needed insight into this critical area of fetal and maternal health.

Pregnancy related complications were the primary outcome assessed in this analysis. Of the complications assessed, some were found to occur more frequently in patients with axSpA than controls. There was a strong trend towards increased prevalence of pre-eclampsia in axSpA

pregnancies (OR 1.35, 95% CI 0.99-1.82), with a subtler trend of higher prevalence of IUGR detected in axSpA compared to control pregnancies (OR 1.17, 95% CI 0.26-5.17). Understanding why these complications are occurring with greater frequency in axSpA pregnancies will be the next challenge. Variations in frequency of pregnancy checks and criteria for both complications between centres and countries must be controlled for before conclusions can be drawn on the effects of axSpA on these outcomes.

Three pregnancy related complications had a non-significant trend to occur less frequently in pregnancies of axSpA women. Stillbirth, gestational diabetes and miscarriage all demonstrated non-significant trends to occur less frequently in axSpA pregnancies.

Review of fetal outcomes showed low birthweight, congenital abnormalities, NICU admission rate and small gestational weight tended to occur more frequently in neonates of axSpA mothers, though not at statistically different rates. Assessment of pooled results from included studies shows a trend towards increased fetal complications from axSpA pregnancies. This could reflect the high rate of active disease in pregnancy or the high prevalence of certain pregnancy related complications. Higher incidence of hypertension and diabetes in women with axSpA was noted in two studies[536,562] which could be a contributing factor in the increased prevalence of fetal complications.

This information leads to many new questions. Could the increased rate of fetal complications explain why women with axSpA are more likely to require delivery by caesarean section? Or are pregnancy complications such as preterm birth and pre-eclampsia the driving factor in the rate of caesarean section which could be associated with low birthweight and need for a NICU admission? Further prospective or registry studies are needed to understand these issues better. Focused research on fetal outcomes would aid clinicians in informing women with axSpA who are planning a pregnancy.

Other forms of inflammatory arthritis have been shown to have low levels of disease activity in pregnancy with high frequencies of flares in the postpartum period[550,573]. Studies in axSpA have not shown consistent patterns of disease in pregnancy[535]. Individual study results range from improved disease control in pregnancy[561] especially noted in the first trimester[548], to high risk of flares late in pregnancy[549]. Pooled data of publications using standardised outcomes from this analysis show a high rate (47.8%) of increased disease activity in axSpA, which tends to peak in the second trimester.

Medication usage in pregnancy is a common cause for concern in patients with a rheumatic disease planning a pregnancy. Many patients with axSpA will require ongoing medication during the course of their pregnancy. Recent guidelines from the British Society of Rheumatology (BSR) have provided clear guidelines and safety data for a number of commonly used medications in axSpA and other rheumatic diseases[533]. Pooled data from this analysis

shows significant variation in medication usage in pregnancy, however this was only documented in four[538,559,560,562] of the 18 studies included in analysis, representing a 36-year timespan in treatment. During this time advances in treatments beyond NSAIDs, changes in prescribing guidelines, increased use of medication in pregnancy following development of dedicated pregnancy guidelines are significant contributing factors accounting for these observed variations.

Many obstetric and neonatal guidelines recommend breastfeeding as an essential source of nutrition for newborns. The WHO states that it "is the most effective way to ensure child health and survival[574]." However, breastfeeding was documented in only four studies[554,558,561,563] with significant variation in incidence and no discussion. Reasons for this could be multifold, but further research is needed to understand true incidence, patient understanding and clinical practices around breastfeeding for axSpA mothers.

This analysis included a large number of females with axSpA and represented populations from thirteen countries around the world. Some of the populations were drawn from national registries while others were from single centre cohorts. Diagnosis of pregnancy outcomes were well documented and confirmed via review of medical records. In most studies, diagnosis of axSpA was also obtained from medical records, which included patients diagnosed according to internationally accepted diagnostic criteria for axSpA. This resulted in a large, multi-national cohort of females with axSpA and their pregnancy experiences. This patient population is one of the main strengths of this analysis and lends greater significance to its results.

Going forward, the results of this analysis could aid in educating and managing axSpA females planning to conceive. Given the trend towards increased prevalence of pre-eclampsia, IUGR and certain fetal complications, regular communication between Rheumatology and Obstetrics is essential from conception through to the postpartum period. This would ensure close monitoring of patients, rapid recognition of disease activity and increased awareness of concerns from either specialty. In addition to larger and more numerous studies focusing on axSpA in pregnancy, one of the issues highlighted in this review is the significantly increased rate of caesarean sections in axSpA females. Further research on indications of these deliveries would better characterise these deliveries and understand why axSpA patients require caesarean section deliveries more frequently. A collaborative effort with Obstetrics would provide valuable insight into this topic.

8.5.1 Limitations

Most studies were retrospective and few studies were controlled. Changes in terminology and classification criteria of AS and axSpA presented a challenge in comparing literature. The modified New York Criteria and the ASAS Criteria for axial SpA were the most

commonly used criteria for confirming diagnosis used in 9 and 3 studies respectively (table 2). One study used the Amor criteria, one used the ESSG criteria, and four studies did not document classification criteria. Disease activity in pregnancy was documented in eleven studies and variation in assessment of disease activity was a significant limitation. There was variation in standardised outcomes used, with a number of studies not describing how disease activity was assessed. This analysis included publications from a 40-year timespan, during which time considerable advancements occurred in both Rheumatology and Obstetrics. Attitudes and expectations towards reproductive issues have also changed dramatically during this period. Lastly, the relatively rarity of certain outcomes including IUGR and stillbirth require additional larger studies to power detection of trends in incidence in axSpA.

8.5.2 Differences Between Protocol & Systematic Review

The original protocol specified the ROBINS-I tool would be used for risk of bias assessment. This was later deemed unsuitable as the included studies were observational and did not involve an intervention. For this reason, the Newcastle Ottawa Score (NOS) was used instead.

8.6 Conclusion

Women with axSpA have significantly higher prevalence of caesarean sections and preterm birth than the general population. This analysis suggests a trend towards increased prevalence of pre-eclampsia, IUGR and a number of fetal complications in axSpA females. Large, dedicated pregnancy studies are needed to capture these relatively infrequent complications in greater volume to determine the significance of these trends. There is a risk of active disease in pregnancy for a high proportion of axSpA females, there are conflicting reports of disease activity throughout the course of pregnancy. As national registries and pregnancy registries continue to develop, the larger patient populations they represent could help to better understand the true impact of axSpA on pregnancy outcomes.

The following chapter will build upon this information to inform the collection of pregnancy data for axSpA women in Ireland as part of a large national registry. It will also offer an opportunity to compare pregnancy outcomes in axSpA women to national averages as well as global reference norms.

Chapter 9.

What to Expect when Women with Axial Spondyloarthritis are Expecting: Prevalence of Complications of Pregnancies in Women with Axial Spondyloarthritis

Publication resulting from material contained within this chapter:

Maguire S, Wilson F, Gallagher P, Mohamed MM, Maher S, O'Shea F. What to expect when women with axial spondyloarthritis are expecting: Prevalence of complications of pregnancies in women with axial spondyloarthritis. Semin Arthritis Rheum. 2022 Mar 10; 54:151993. doi: 10.1016/j.semarthrit.2022.151993. Epub ahead of print.

(Full manuscript available in Appendix A)

9.1 Abstract

Background

The understanding of axSpA is evolving rapidly. Unfortunately, for women with axSpA there is limited data available on pregnancy complications. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data on axSpA in Ireland. The aim of this study was to examine the prevalence of pregnancy and fetal complications in axSpA women.

Methods

The ASRI records information on demographics, imaging, treatment, and patient outcomes. A dedicated section collects data on pregnancy, fertility and breastfeeding. Results were compared to global reference norms (GRN). All patients were diagnosed with axSpA by a Rheumatologist and met the ASAS classification criteria. Informed consent was obtained from all patients, with ethical approval obtained from local hospital ethics committees.

Results

Data was available on 98 women with axSpA. There were 335 pregnancies resulting in 279 live births. Of these pregnancies 51.6% (173) were uncomplicated and 48.5% (162) were complicated, with 13.1% (44) encountering multiple complications.

Preterm birth (12.5% vs 5.2%, $p<0.01$) and pre-eclampsia (6.8% vs 2.8%, $p<0.01$) were more prevalent in axSpA pregnancies than GRN. Low birthweight was also more prevalent in axSpA pregnancies (8.2% vs 2.9%, $p<0.01$).

Conclusion

Preterm birth, pre-eclampsia and low birthweight are significantly more prevalent in pregnancies of axSpA women. Furthermore, there is a high prevalence of complications in axSpA pregnancies overall. These results provide essential insight into the impact of axSpA in pregnancy and call for further research to understand the pathogenesis of these complications.

9.2 Background

As discussed in the previous chapters, understanding the impact of axSpA on pregnancy outcomes is a vital component of improving management of women with axSpA at every stage of their lives. This was highlighted by the European League Against Rheumatism (EULAR) who recently proposed a core data set for collection of pregnancy data in registries for rheumatic disease[575]. Improved data collection via national registries have been key to recent advances in the understanding of the impact of rheumatic disease on pregnancy[576,577,513]. Research focus on pregnancy in rheumatic diseases has been biased towards systemic lupus erythematosus (SLE)[488,455] and rheumatoid arthritis (RA)[578,500] with a paucity of publications in other rheumatic diseases such as axSpA. For this reason, further studies are needed to ensure equality of care for all women with rheumatic diseases during the course of their pregnancy.

Research on pregnancy in axSpA has previously been limited with conflicting results[579-581]. Recent studies have demonstrated that axSpA pregnancies have higher rates of certain pregnancy and fetal complications compared to pregnancies in the general population[562,582]. This was supported by findings from our 2020 systematic review and meta-analysis in the previous chapter[400]. Of the studies included in this analysis, the lack of data on Irish women with axSpA was notable. This is important as certain pregnancy outcomes including breastfeeding and caesarean sections vary globally due to differences in practice, social preferences and cultural influences[583-585]. Thus, it is important to understand pregnancy outcomes within each country to improve local practice as well as to deliver appropriate patient education from both an Obstetric and Rheumatology perspective. Collection of pregnancy data within a national registry also allows for ongoing contribution to the current knowledge of the topic worldwide.

The aim of this study was to capture the prevalence of pregnancy and fetal complications in women with axSpA in Ireland. This data was compared to global reference norms (GRN) as well as latest Irish data for normative context. Secondary outcomes included capturing the prevalence of breastfeeding, infertility and disease activity during the course of pregnancy.

9.3 Methods

9.3.1 Patient Population

Data for this analysis was captured via the Ankylosing Spondylitis Registry of Ireland (ASRI). This large national registry recruits patients with axSpA from Rheumatology centres across the country. Full details on patient population including eligibility criteria and data captured as part of this registry are discussed at length in Chapter 3: Methods under "Patient Population". For the purposes of this study, all female participants with a history of pregnancy were included.

9.3.2 Patient & Public Involvement

Pregnancy in axSpA was discussed with several women attending the axSpA clinic in St James' Hospital. Strong interest was expressed in the topic and related issues (including fertility and breastfeeding) were raised. This contributed to the pregnancy outcomes captured within the ASRI.

9.3.3 Pregnancy Outcomes

Information on pregnancy was recorded via a dedicated section within the ASRI to capture data on pregnancy outcomes, fetal outcomes, breastfeeding and fertility. Pregnancy complications captured included miscarriage, pre-eclampsia, gestational diabetes, pre-term delivery and caesarean section. More specific information such as indication for caesarean section and type of caesarean section (emergency versus elective) were not gathered to limit the risk of recall bias and misrepresentation of our results. Fetal complications captured were low birthweight (less than 2.5kgs), small for gestational age (SGA) and neonatal intensive care unit (NICU) admission following birth. Information regarding pregnancy was obtained via focused interview of female participants and verified via medical records where possible. Additionally, data on breastfeeding was recorded for each pregnancy (table 9.1).

Table 9.1: Pregnancy questionnaire for female patients enrolled in the ASRI

Pregnancy Questionnaire:

(For each pregnancy answer: yes/no/don't know)

- Have you ever been pregnant?
    - How many children do you have?
- Have you ever had a miscarriage?
    - Number of miscarriages:
- During each pregnancy did you have any of the following:

Pregnancy	1	2	3	4
Pre-eclampsia				
Gestational diabetes				
Serious Infection *(requiring hospitalisation)*				
Small for Gestational Age				
Caesarean section (c-section)				
Preterm delivery (< 37 weeks gestation)				
Intensive care after delivery for the baby (NICU)				
Low Birthweight (<2.5 kg)				
Did you breastfeed?				

How would you rate your disease activity:

	Increased Activity	No change	Decreased Activity	Cannot Recall
Preconception				
During Pregnancy				
After Delivery				

Did you have difficulty conceiving? (Regular unprotected intercourse for >1 year without resulting in pregnancy) Yes No

Did you ever need to consult a fertility specialist? Yes No

Have you ever undergone IVF (in vitro fertilisation)? Yes No

Data on these outcomes was recorded retrospectively for women with axSpA enrolled in the ASRI with a history of at least one pregnancy. Given the prolonged delay from time of symptom onset to diagnosis as discussed in previous chapters, data on all pregnancies was included both before and after diagnosis of axSpA.

The prevalence of each recorded pregnancy outcome was compared to weighted pooled prevalence from a recent meta-analysis on this topic [400]. Data was also captured on difficulty conceiving (defined as regular unprotected sex for over one year not resulting in pregnancy), need for consultation with a fertility specialist and prevalence of in vitro fertilisation (IVF).

Participants with a history of pregnancy were directly questioned about severity of axSpA symptoms or disease activity overall during the following timepoints: time of conception, during pregnancy and postpartum. Responses were recorded as increased, decreased, no change and cannot recall. If patients were unsure of their disease activity during this time their response was recorded as cannot recall. To limit the risk of recall bias, no differentiation was made between axial or peripheral flares.

For this same reason, data on medication usage during pregnancy was also not recorded. This was in terms of both axSpA specific medications such as biologics agents and pregnancy specific medications such as Aspirin.

9.3.4. Comparison Population

Prevalence of pregnancy and fetal complications within the ASRI were compared to data of a control population from a systematic review and meta-analysis on this topic published in 2020 [400] which generated a global reference norm (GRN) for comparison analyses. This included data on eleven studies from ten countries around the world with data on 1,224,348 pregnancies (Table 9.2). Results were also discussed in the context of the latest Irish national data to provide normative context.

Table 9.2: Details of studies contributing to the global reference norm (GRN)

Authors	Publication	Data Source Period	Country	Study Type	Data Source	Number of Pregnancies
Retrospective Studies						
Gomor et al	1980	not stated	Hungary	Cross-sectional	Not stated	65
Lui et al	2011	prior to 2010	Canada	Cross-sectional	Single centre	77
Jakobsson et al	2016	2001-2009	Sweden	Cross-sectional	National Register	1,082
Timur et al	2016	2007-2015	Turkey	Case control	Single centre	40
Kristjansdottir et al	2019	1981-2017	Iceland	Cross-sectional	National Register	3,214
Park et al	2019	1994-2017	Korea	Cross-sectional	Multi-centre	12,926
Strouse et al	2019	2007-2012	USA	Case control	Multi-centre	10,244
Mork et al	2019	1997-2016	Denmark	Cross-sectional	National Register	1,195,882
Prospective Studies						
Ostensen et al	1983	1979-1982	Norway	Case control	Single centre	31
Zbinden et al	2018	2000-2016	Switzerland	Case control	Single centre	70
Smith et al	2019	2004-2018	USA	Case control	Multi-centre	717

9.3.5 Statistical Analysis

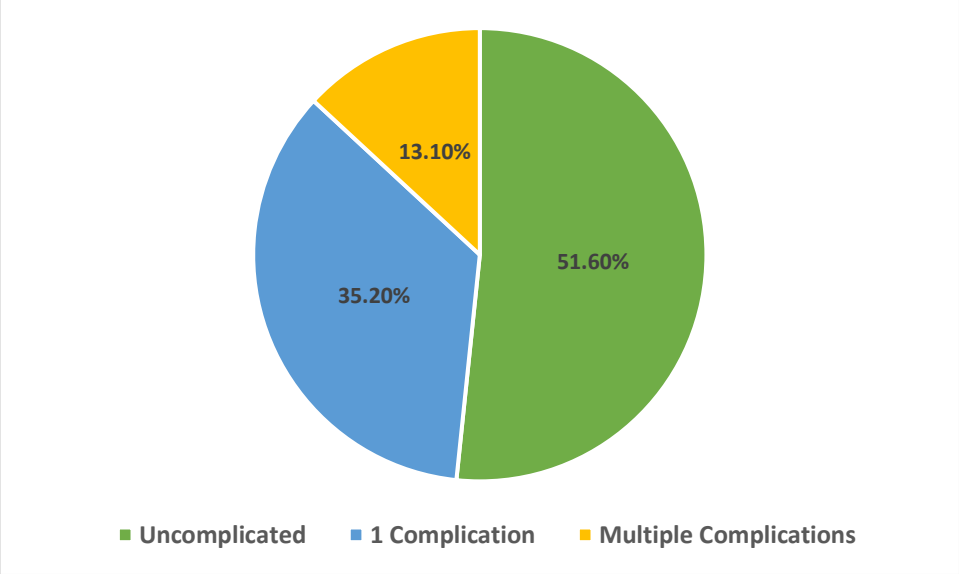
Prevalence of both pregnancy and fetal complications was expressed as frequency counts with percentages (%). Differences in prevalence between the axSpA women and the GRN was tested for statistical significance via a chi^2 test of independence or Fisher's exact test as appropriate. Significance was determined by an alpha level of $p < 0.05$. Odds ratios with 95% confidence intervals (95% CI) were then calculated to express the risk of each given complication in pregnancies of axSpA women compared to GRN. IBM Statistical Package for Social Sciences (SPSS) version 26 was used to facilitate all data analysis performed within this study.

9.4 Results

At the time of analysis 232 females were enrolled in the ASRI, representing 26.2% of the total population of the registry. Mean age of females was 43.8 years (SD 11.7), with a median disease duration of 15.8 years and median delay to diagnosis of 5 years. 70.7% (164) had radiographic axSpA, while 29.3% (68) had non-radiographic disease. Mean scores for females in the ASRI were: BASDAI 4.6 (SD 2.5), BASFI 3.9 (SD 2.6), BASMI 3.6 (SD 2), ASQoL 7.5 (SD 5.7), and median HAQ 0.50 (0.3, 0.9).

Data on pregnancy was collected from 118 women with axSpA. Overall, 98 women reported a history of pregnancy with a total of 335 pregnancies resulting in 279 live births. Of these pregnancies 51.6% (173) were uncomplicated and 48.5% (162) were complicated, with 13.1% (44) encountering multiple complications (Figure 9.1). An additional 20 women denied any previous history of pregnancy or attempting to conceive.

Figure 9.1: Prevalence of complications per pregnancy in pregnancies of women with axSpA



9.4.1 Pregnancy Complications

Miscarriage prevalence was high, affecting 16.7% (56) of pregnancies in 34.7% (34) of women with a history of pregnancy. Of the live births, the most common pregnancy complication was caesarean section in 13.3% (37) followed by preterm birth in 12.5% (35) (table 9.3). Infection requiring hospitalisation was the last commonly encountered complication occurring in 2.9% (8) of pregnancies resulting in live births.

Two complications were significantly more prevalent in axSpA pregnancies compared to GRN: pre-eclampsia (6.8% vs 2.8%, $p<0.01$) and preterm birth (12.5% vs 5.2%, $p<0.01$). Calculation of odds ratios for these complications in axSpA pregnancies revealed pre-eclampsia to have a 2.48 times greater prevalence in this population (95% CI 1.61 to 3.83), while the odds of preterm birth prevalence was 2.52 times more likely (95% CI 1.85 to 3.43) (table 9.3). There was also a trend towards an increased prevalence of gestational diabetes in axSpA pregnancies (7.5% vs 5.8, $p=0.21$), but this difference did not reach significance.

Unfortunately, it was not possible to compare miscarriage prevalence from the ASRI to the GRN as there was limited data available on this outcome in the GRN. This is detailed further in the discussion below.

Prevalence of caesarean sections was the only pregnancy outcome which occurred less often in axSpA pregnancies (13.3% vs 18.6%, $p=0.27$), although this difference did not reach significance.

Table 9.3: Prevalence of pregnancy and fetal complications between women with axSpA compared to GRN

	AxSpA Women	GRN*	*p value*	OR	95% CI
n	279	1,224,348			
Pregnancy Complications					
Pre-eclampsia	6.8% (19)	2.8% (34,217)	***<0.01***	2.48	1.61, 3.83
Gestational diabetes	7.5% (21)	5.8% (52)	*0.21*	1.37	0.84, 2.36
Preterm Birth	12.5% (35)	5.2% (64,226)	***<0.01***	2.52	1.85, 3.43
Caesarean section	13.3% (37)	18.6% (225,359)	*0.27*	0.85	0.63, 1.14
Miscarriage	16.7% (56)				
Infection	2.9% (8)				
Fetal Complications					
Low Birthweight	8.2% (23)	2.9% (467)	***<0.01***	2.88	1.93, 4.30
NICU admission	12.2% (34)	11.9% (90)	*0.47*	1.15	0.79, 1.66
Small for Gestational Age	5.4% (15)	11% (132,515)	***0.01***	0.54	0.33, 0.89

Abbreviations: *AxSpA -axial spondyloarthritis; GRN -global reference norms; OR -odds ratio; CI -confidence interval; NICU -neonatal intensive care unit*

**Expressed as weighted pooled means, Prevalence of complications expressed as % (frequency counts)*

9.4.2 Fetal Complications

The most common fetal complication was NICU admission in 12.2% (34) (table 9.3), however no significant difference was noted between axSpA and GRN (12.2% vs 11.9%, p=0.47). Low birthweight (LBW) was significantly more prevalent in axSpA pregnancies (8.2% vs 2.9%, p<0.01), with the odds of low birthweight 2.88 times more common in axSpA pregnancies (95% CI 1.93 to 4.30).

Small for gestational age (SGA) was the only fetal outcome to be significantly less prevalent in axSpA pregnancies (5.4% vs 11%, p<0.01). Further analysis revealed the odds of SGA following an axSpA pregnancy were 0.54 (95% CI 0.33 to 0.89) compared to pregnancies in the general population.

9.4.3 Breastfeeding

Breastfeeding was reported in 33.7% (94) of live births. Prevalence of breastfeeding from GRN was not available to allow comparison.

9.4.4 Fertility

Of the women with a history of pregnancy 14.3% (14) reported difficulty conceiving, defined as regular unprotected sex for more than one year without resulting in pregnancy. 9 women (9.2%) went on to consult a fertility specialist with 4.1% (4) requiring IVF. Of the axSpA women with no prior history of pregnancy no fertility issues were reported.

9.4.5 Disease Activity in Pregnancy

Level of disease activity in pregnancy was recorded at three time points: prior to conception, during pregnancy and postpartum. The majority of patients (72.4%) reported no change or stable disease prior to conception (Table 9.4). There was a high rate of increased disease activity during the course of pregnancy in 31.6% (31) with only 18.4% (18) reporting improved disease activity during this time. Rates of disease remission improved in the postpartum period (56.1% vs 40.8%) compared to during pregnancy. However, an increase in disease activity during the postpartum period was frequent, as reported in 26.5% (26).

Table 9.4: Changes in Disease Activity throughout Pregnancy

	Prior to conception	During Pregnancy	Postpartum
No change	72.4% (71)	40.8% (40)	56.1% (55)
Increased activity	13.3% (13)	31.6% (31)	26.5% (26)
Decreased activity	6.1% (6)	18.4% (18)	7.1% (7)
Cannot recall	8.2% (8)	9.2% (9)	10.2% (10)

9.5 Discussion

This study of pregnancy data from the ASRI, demonstrates the high overall prevalence of pregnancy and fetal complications in women with axSpA. Furthermore, it also highlights specific complications which are more prevalent in axSpA compared to pregnancies in the general population. Recognition of this increased risk of complications is an essential first step in optimising pregnancy and fetal outcomes in axSpA.

Complications in pregnancy have serious implications for fetal viability, maternal mortality and long-term health of the neonate. Our study noted a high prevalence of complications in axSpA pregnancies overall with nearly half of axSpA pregnancies involving at least one complication. This finding alone is cause for alarm and highlights the need for further focused research in pregnancy and axSpA.

Both preterm birth and pre-eclampsia were significantly more prevalent in axSpA pregnancies compared to GRN. The findings regarding preterm birth are similar to studies in Denmark[582] and the United States[586]. Although individual studies failed to detect a difference in prevalence of pre-eclampsia, pooling of data via meta-analyses demonstrated an increased risk of this complication in axSpA pregnancies[400,587]. Many pregnancy complications, including pre-eclampsia, can increase the risk of preterm birth[588]. In Ireland, the increasing average maternal age at delivery has been identified as one of the key contributors to the rising rates of pre-eclampsia nationally[589]. However, increasing maternal age is not a challenge unique to Ireland with similar trends noted in many developed countries[590,591]. Advanced maternal age is a risk factor for preterm birth in the general population, although there are numerous additional risk factors to also consider[592]. This includes systemic inflammation[588], with a previous study in axSpA demonstrating preterm birth risk to be increased in mothers with increased disease activity during pregnancy[593]. Preterm birth can lead to both short and long-term health consequences for the neonate, as well as causing a considerable burden on the healthcare system[571]. Recognition of the higher prevalence of preterm birth in axSpA pregnancies is crucial to advancing monitoring of these patients to minimise this risk in the future. Hopefully this will lead to further studies identifying risk factors and examining the pathogenesis of preterm birth, as improved understanding would facilitate rapid identification and treatment of at risk axSpA women.

The prevalence of caesarean sections (CS) is a particularly interesting outcome of pregnancy due to evolution of societal perception and medical practices over time. In this study, differences in caesarean section rates did not reach significance between axSpA pregnancies and GRN. This is in contrast with previous studies which reported an increased prevalence in axSpA studies[400,587]. This may reflect the small sample size of the study but could also reflect differences in Obstetric practices in Ireland. Globally the prevalence of CS has been rising at a

rapid pace, resulting in increased healthcare costs and increasing the potential for maternal gynaecological complications[594]. Alarmed at this trend, the World Health Organisation (WHO) issued a consensus statement encouraging caesarean sections to be performed only when medically indicated and encouraged use of the Robinson system to standardise data collection to further study this phenomenon[595]. This was supported by the lack of evidence for non-medically indicated CS as detailed by a 2012 Cochrane review[596]. Although rates of CS are currently on the rise in Ireland[597,598], older comparative research indicates CS rates in Ireland were previously significantly lower than those reported in the United States[599]. This emphasises the importance of local data collection in pregnancy outcomes which may vary between populations and over time.

Miscarriage prevalence can be difficult to capture as women who experience miscarriage early in pregnancy do not always seek medical attention. As a consequence, studies that rely on data extracted from hospital records will result in an underestimation of the overall prevalence as this will only reflect miscarriages requiring hospitalisation. Thus, the low prevalence of miscarriage in the GRN is much lower than the globally reported pooled risk of 15.3% [600]. Of the available on the data on miscarriage in the general population of Ireland, overall prevalence has been noted to decrease over time from 70.6 per 1,000 deliveries in 2005 to 51.5 per 1,000 deliveries in 2016[601]. A controlled prospective study is needed to determine if women with axSpA face an increased risk of miscarriage. Until that time, pregnancy planning and optimisation of disease control prior to conception should be encouraged to increase chances of a successful pregnancy.

Complications in pregnancy can significantly impact the health of the neonate as well as the mother. Of the three fetal outcomes captured in this study, two showed significant differences in axSpA pregnancies. Low birthweight (LBW) was significantly more prevalent in axSpA pregnancies while small for gestational age (SGA) was less prevalent. It is well established that LBW infants face significant risk of both mortality and morbidity[602]. However, the impact of LBW extends beyond early life, as affected infants also have an increased risk of insulin resistance as well as associated comorbidities in adulthood[603,604]. This is mediated by adaptive changes in utero to optimise nutritional extraction resulting in permanent changes in metabolism and fat storage after delivery[605]. A common cause of LBW is preterm birth, which was noted to be more prevalent in axSpA pregnancies in this study. Thus, is it possible that the higher prevalence of LBW observed in axSpA pregnancies reflects the high prevalence of preterm birth.

Small for gestational age (SGA) refers to fetal weight below the 10^{th} centile for the corresponding gestational age[606]. During pregnancy this is monitored by interval ultrasounds to track fetal growth. While fetal birthweight is a single definitive measurement, SGA is a more

complex calculation. In a retrospective study there is a risk this outcome may have been under reported due to recall bias or lack of patient understanding of this term. For these reasons, our data reporting SGA prevalence in this patient population should be interpreted with caution. Regardless, recent data suggests monitoring for SGA during pregnancy is not a reliable method to identify high risk infants upon delivery and that gestational age was a more reliable predictor[607]. Results from individual studies are divergent, with pooled results suggesting a non-significant trend towards increased prevalence in axSpA pregnancies[400]. Further large-scale research is needed to fully explore the risk of SGA in axSpA pregnancies.

There are numerous well-established benefits of breastfeeding for both mother and baby following pregnancy[608]. This includes improved cognitive development and decreased risk of many chronic diseases in children who are breastfed, while for mothers breastfeeding can decrease risk of obesity and certain cancers[609]. Public health initiatives have continued to campaign to raise public awareness of breastfeeding however, rates globally remain below 50%[610]. Within the ASRI the prevalence of breastfeeding was notably lower at 33.7% compared to the national Irish prevalence of 59.9%[611]. Although there is scant published data on this issue in axSpA, a similar trend has also been reported in rheumatoid arthritis[612]. A major contributing factor to this issue may be related to medication use. Fortunately, recent guidelines have been published by the American College of Rheumatology clearly outlining medication safety at each stage of pregnancy including lactation[457]. Patient education including a discussion of medication safety while breastfeeding prior to delivery could be a prime opportunity to address patient concerns and encourage a trial of breastfeeding upon delivery.

In the discussion of pregnancy, it is important to also consider women who struggled to become pregnant. Although there is limited data available on this topic, axSpA women have previously been shown to have a diminished ovarian reserve[613]. It is important to note that in the general population this has not been proven to result in reduced fertility[614]. However, prolonged time to conception can place significant additional burden on axSpA women due to desire to come off certain medication prior to conception and avoidance of non-steroidal anti-inflammatory drugs (NSAIDs)[615]. Infertility in the general population is estimated to affect 8-12% of couples worldwide[616], in line with results of this study. Pregnancy planning in axSpA women is key to optimising disease control prior to conception to create the best possible chance of successful conception. This also creates a window of opportunity to educate women with axSpA on the importance of disease control at all stages of pregnancy and provide education on safety of medication, especially biologic therapies, during pregnancy. Early initiation of conversations around pregnancy planning or fertility struggles would also allow provision of reliable evidence-based resources for patients to obtain further information.

Previous research on disease activity during pregnancy in axSpA women has been complicated by a multitude of issues, which may explain the differences in reported results. One of the main issues encountered was the lack of standard outcome measures used to quantify disease activity prior to the development of the BASDAI in 1994[115]. Since then, several additional clinical tools have been developed to also quantify disease activity, making comparison between studies and pooling of data difficult due to the variety in outcome measures used. Despite this, it has been suggested that disease activity in axSpA increases during pregnancy with a high rate of flares in the postpartum period. Data from this study supports this finding, with increased disease activity reported during pregnancy in 31.6% of axSpA women and over 25% of women reporting flares postpartum. A seminal study on this topic indicated that disease activity is likely a significant risk factor for pregnancy complications overall in women with axSpA[593]. However, larger prospective studies are needed to capture changes in disease activity in more detail throughout pregnancy and corroborate these findings.

9.5.1 Limitations

As the collection of pregnancy data was retrospective, there was the potential for recall bias. To limit this risk the pregnancy questionnaire (Table 9.1) specifically focused on commonly encountered complications in pregnancy with the trained investigator explaining each outcome in lay terminology to all involved participants. For all recorded complications if a patient was unsure no answer was recorded. However, certain terms with medical definitions such as SGA this may have resulted underreporting of the outcome. Secondly, the nature of the data collection within the ASRI resulted in cross-sectional study design. For this reason, it is not possible to assess for presence of a causal relationship between disease activity and prevalence of pregnancy outcomes at this time. Plans are in place to develop longitudinal data collection within the ASRI which would include collection of pregnancy data. Lastly, Irish national data on pregnancy outcomes is published on a yearly basis. This reflects pregnancy outcomes over a single year, while data from the ASRI reflects pregnancy outcomes over multiple years. It is important that these differences in reporting time are considered when comparing results.

9.6 Conclusion

This study details pregnancy outcomes of women with axSpA from a large, well characterised national registry. During pregnancy, women with axSpA face a high prevalence of complications overall. Specifically, preterm birth, pre-eclampsia and low birthweight are significantly more prevalent in pregnancies of axSpA women compared to the general population. Additionally, rates of breastfeeding are notably lower than that of the general population, which can have significant health implications for both mother and neonate. Although prevalence of infertility was similar to the general population, it is important to ensure disease remission and patient education of medication compatibility with pregnancy to optimise chance of conception. Lastly, there is a high rate of increased disease activity both during pregnancy and in the postpartum period for axSpA women. Thus, continuation of pregnancy compatible medications during this time is vital. These results provide much needed insight into the impact of axSpA in pregnancy and highlight the need for further research to understand the pathogenesis of these complications.

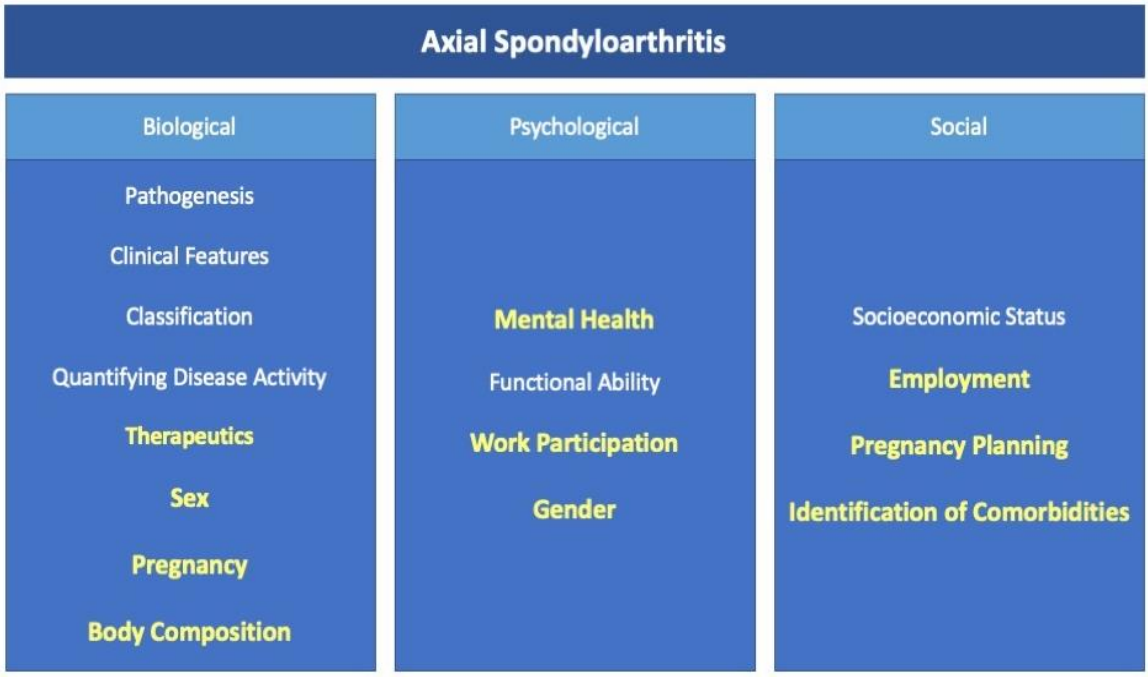
Chapter 10. Conclusions & Clinical Implications

10.1 Background

This concluding chapter highlights the clinical implications of the research carried out as part of this thesis. In addition to summarising data presented in previous chapters, this section focuses on how these findings fit into current clinical understanding of axial spondyloarthritis (axSpA). Building on this information, the chapter will finish with a discussion of future directions and additional questions which have been raised by these results.

The work contained within this thesis aimed to not only demonstrate the clinical utility of a high-quality national registry such as the Ankylosing Spondylitis Registry of Ireland (ASRI), but also to examine subpopulations of patients with axSpA who are currently underrepresented in the published literature. To fully comprehend these subpopulations and their unique challenges in axSpA, it is critical they are evaluated from a biopsychosocial perspective (figure 10.1). The most obvious of these groups is women with axSpA, who have long been neglected in the discussion of clinical outcomes and monitoring of axSpA. This research strives to draw attention to these populations while also addressing clear knowledge gaps in their identification and monitoring.

Figure 10.1: Biopsychosocial aspects to be considered in the management of patients with axSpA. Topics highlighted in yellow are areas of focus within this thesis.



10.2 Clinical Implication of Findings

10.2.1 New Treatments in AxSpA

The review of new and upcoming treatments in axSpA outlines the significant advances in therapeutic options over the past two decades. While other forms of inflammatory arthritis have a multitude of biologic therapies licensed for treatment, previous trials in axSpA have failed to demonstrate response to newer biologic agents beyond anti-tumour necrosis factor (anti-TNF) agents. Newer therapeutic agents targeting interleukin-17 (IL-17), such as Secukinumab, have recently proven to be effective treatment options in the management of axSpA.

Three additional agents: Ixekizumab (another IL-17 inhibitor), Tofacitinib and Upadacitinib (both JAK inhibitors) have also demonstrated significant clinical benefit in advanced clinical trials. However, use of JAK inhibitors has been slowed by ongoing safety concerns related to risk of thromboembolism, major cardiovascular adverse events, and malignancy.

Several ongoing clinical trials are also discussed within Chapter 2, indicating both the level of interest and need for additional therapies in axSpA. Ongoing re-evaluation of treatment guidelines is undertaken to reflect the rapid rate of development of newer therapeutic options for axSpA. Thus, large scale collection of real-world data via national registries on patient experience is crucial during this period of treatment evolution.

10.2.2 Utility of the ASRI

National registries for specific diseases are a rich source of epidemiologic information for a given geographic area. Maintenance of such registries and ongoing enrolment also allows for capture of changes in practice to be reflected in clinical outcomes. Since being established in 2013, the Ankylosing Spondylitis Registry of Ireland (ASRI) has been steadily recruiting patients with a confirmed diagnosis of axSpA from all major geographic regions of Ireland. All recruited patients must meet the ASAS classification criteria for axSpA prior to enrolment, which created a reliable representation of axSpA patients in Ireland and allowed comparison with other international axSpA cohorts.

Data from the ASRI revealed that patients with axSpA have a high prevalence of comorbidities, with over 40% of the ASRI recording at least one comorbidity. Hypertension and hyperlipidaemia were the most commonly encountered. Given the young mean age of the ASRI this is highly concerning, especially as presence of comorbidities has previously been associated with worse patient outcomes.

Further cause for concern is the high rate of current or past smokers in the ASRI, with the current smokers noted to be considerably younger than the rest of the population. While the prevalence of current smokers is similar to that reported in other registries, the trend for younger patients to be current smokers suggests public health campaigns against smoking need to target teenagers and young adults to encourage a tobacco free lifestyle. This is crucial in axSpA for two reasons. Firstly, smoking can accelerate atherosclerotic deposits and increase risk of cardiovascular events; in a population with a high burden of cardiac related comorbidities this is highly concerning. Secondly, smoking in axSpA is known to be associated with persistent disease activity and poorer response to treatment. Inversely, it is very possible that the high prevalence of smoking was a major contributing factor to the high frequency of comorbidities in the ASRI. As the data collection of the ASRI resulted in cross-sectional data a causal relationship between smoking and presence of comorbidities could not be drawn. Regardless of the direction of this relationship, the need to proactively educate and encourage smoking cessation to improve overall health in patients with axSpA is evident.

The period of recruitment that followed the launch of the ASRI captured a time of considerable change in the field of axSpA. In addition to advances in biologic therapies as detailed above, increased use of the ASAS classification criteria led to recognition of non-radiographic axSpA (nr-axSpA). This resulted in recognition of the disease in a larger percentage of the population, as well as allowing identification and treatment at an earlier stage in the disease process.

This evolution in axSpA is explored further in the medication analysis in **Chapter 3**. This analysis examined characteristics and outcomes of patients in four treatment categories: no treatment, NSAIDs, biologics or combination therapy. The most interesting findings of this analysis highlighted the changes in practice over time in the use of NSAID therapy compared to biologics. The NSAID-use cohort was found to represent older patients with longer delay to diagnosis and worse patient reported outcomes compared to those on biologic therapy. Meanwhile the biologic-use cohort averaged a shorter delay in diagnosis with significantly better disease activity and quality of life scores. Not surprisingly the oldest cohort was those on no treatment, which fit the more classical phenotype of ankylosing spondylitis. Although these patients reported the longest delay in diagnosis and worst overall spinal mobility, their outcome scores were lower than expected likely as a result of burnt-out disease. These treatment groups nicely depict the evolution of the treatment of axSpA and the impact on patient outcomes. While significant advances have been made, further efforts to reduce delay to diagnosis and identify additional therapies are needed to continue to improve quality of life for these patients.

As part of this effort to improve disease recognition, a sub-analysis in **Chapter 3** examined patients with late onset of axSpA symptoms after the age of 45 years. Traditionally

axSpA has long been defined as onset of symptoms prior to this age, however numerous publications have described small cohorts with late onset axSpA. Evaluation of the ASRI population identified 6.3% of the population qualified as late onset disease. Furthermore, these patients were found to have similar patterns of disease and radiographic findings consistent with current classification criteria. While there are numerous causes for low back pain later in life, presence of inflammatory symptoms should trigger consideration of axSpA as a possible diagnosis. Currently there is no set criteria for late onset axSpA, limiting comparison with other studies. Ongoing registry development and recognition of this sub-type of disease would aid in further studies of this cohort.

10.2.3 Unemployment

The first set of analyses of **Chapter 4** highlighted the strikingly higher prevalence of unemployment in patients with axSpA compared to national Irish unemployment rates during the same period (2013-2020). Ability to actively participate in the workforce is directly indicative of a person's functional ability and essential for income. However, the benefits of employment also include socialisation, improved sense of self-worth and skill development.

This is supported by the worse patient outcome scores noted in unemployed compared to employed axSpA patients in the ASRI. This reflected worse disease activity as well as poorer overall quality of life. Worse spinal mobility as captured by the BASMI was associated with higher likelihood of unemployment, highlighting the need for prompt treatment initiation with an aim to limit disease progression. Male sex was the most significant factor associated with unemployment and unemployment was noted to affect a higher proportion of men than women with axSpA.

This outlines the impact of unemployment on patient outcomes in axSpA and furthermore identifies factors associated with likelihood of unemployment. As discussed in **Chapter 4**, use of these factors could be used in combination with tools to monitor work productivity. This would allow creation of a window of opportunity to identify those at risk of decreased productivity or work instability, allowing an opportunity for occupational supports and preventing progression to unemployment. Improving an axSpA patient's ability to actively participate in the workforce would have benefits for the patient, their families and healthcare systems. Thus, regular monitoring of risk factors for unemployment as well as use of tools to monitor work productivity should be incorporated into routine clinical care for axSpA patients.

10.2.4 Depression

Building on the previous analyses of **Chapter 4** where depression was noted to be more prevalent in unemployed participants with axSpA, the subsequent sections of the chapter focused on depression and mental health. Between the prolonged delay in diagnosis and high burden of comorbidities in patients with axSpA, this population faces considerable risk factors for depression. The series of analyses were unique in capturing the prevalence and impact of depression in both those with known depression and those at risk of undiagnosed depression.

The prevalence of depression was high in the ASRI with males and females equally affected, however females with depression were noted to have the worst overall patient reported outcomes. Although this interaction between sex and depression did not reach statistical significance, it does highlight the different impact of depression between sexes. This was also seen in the prospectively screened cohort with significantly higher HADs-D scores noted in axSpA women.

Presence of depression or abnormal scores on depression screening questionnaires were associated with worse patient outcomes reflecting worse quality of life and disease activity. These findings suggest Rheumatologists should consider screening for depression and consider mental health issues in patients with poor patient reported outcomes despite treatment. Both depression and axSpA are clinical diagnoses that can go undetected for many years. Although it is not clear from this data if depression drives higher disease activity or vice versa, prompt identification and management of both axSpA and depression are crucial to improve outcomes and overall quality of life in affected patients. Recognition of the high prevalence of depression in axSpA is the first step, but active screening with simple tools such as the HADs-D or PHQ-9 would actively aid identification of at risk axSpA patients.

The final section of **Chapter 4** studied the impact of prolonged social isolation due to the COVID-19 pandemic on those with inflammatory arthritis and specifically on axSpA patients. A high proportion of participants overall reported some level of psychological distress during this time. Interestingly women, especially those with axSpA reported higher levels compared to men. Additionally, they also reported worse disease activity and greater decline in general health, despite having a higher rate of employment during this time compared to men. Factors identified as contributing to these findings are higher rates of remote working and a trend towards more frequent sleep disturbance noted in axSpA women.

This study highlights the interplay between employment and mental health as a complex, multifaceted interaction when considered in the setting of outcomes in axSpA. Longitudinal studies within large axSpA registries capturing further data on these issues will

improve understanding of the driving factors of these relationships. This will aid in development of a targeted multidisciplinary approach in the management of patient with axSpA that considers mental health, functional ability, employment and patient outcomes.

10.2.5 Women with AxSpA

Despite the recent advances in the field of axSpA, much of what is known about the disease is derived from studies of men with radiographic axSpA. Additionally, data from the studies in **Chapters 3 and 4** demonstrated clear sex differences in the axSpA population. To explore these issues further, a focused analysis of the women of the ASRI was carried out.

In line with results of other international cohorts, women with axSpA reported worse quality of life and disease activity compared to men. However, the most surprising result came from the focused analysis of the BASDAI. This revealed that although axSpA women reported worse scores for each component of the BASDAI, the pattern of symptom severity was strikingly similar in both sexes. In fact, the main difference was due to which symptom was rated the most problematic, which for women was fatigue and for men spinal pain. Fatigue can be driven by a multitude of factors, but this analysis highlights the higher prevalence of many intra- and extra-articular manifestations noted in women with axSpA which would contribute to a greater burden of inflammatory symptoms.

Another factor to consider, was the similar rate of medication usage despite the higher burden of disease manifestations and worse outcome scores. This raises many questions including: are women with axSpA being undertreated? If so, why are they less likely to be offered medication? Or escalation of therapy? Certain symptoms, such as fatigue, in axSpA women may be more likely to be put down to underlying fibromyalgia and chronic widespread pain. However, in a patient with known inflammatory disease it is crucial to ensure thorough investigation and treatment of symptoms prior to dismissing them as chronic widespread pain.

While the BASDAI has recently come under increased scrutiny with the introduction of newer tools to capture disease activity, the simple elegance of the BASDAI has led to its continued use in clinical practice. Results of this study prove the information captured within the BASDAI still provides valuable insights into disease activity in axSpA. However, given the demonstrated variation in disease manifestations between sexes, we must question if the time has come to re-evaluate how disease activity is evaluated and captured in both sexes. Are certain tools more sensitive in axSpA men with more axial disease or vice versa for women with more peripheral involvement? Or do we need to re-define active disease with sex specific cut offs for tools currently in use?

Lastly, when considering variation in outcomes between sexes in axSpA the influence of hormones remains an obvious but poorly understood contributing cause. While this study did

not include hormonal analysis, the discussion of **Chapter 5** highlights the limitations of current knowledge of the impact of hormonal fluctuations over the course of a female lifetime on patient outcomes in axSpA.

10.2.6 Central Obesity in AxSpA

The high prevalence of comorbidities in axSpA discussed in **Chapter 3**, combined with the considerable sex differences outlined in **Chapter 5**, led to further examination of anthropometric data of the ASRI participants. Although the detrimental effects of obesity in axSpA is well established, there is little data describing central obesity in this population. This is of clear relevance in axSpA as central obesity is a known driver of systemic inflammation. Research from the general population has highlighted the many dangers of central obesity as well as validating screening tools such as the waist to hip ratio (WtHpR). However, there is scant discussion of how various measures of obesity including body mass index (BMI) and WtHpR perform between men and women. Given the recognised differences in body shape between sexes, we felt it important that this be evaluated.

Results of this study were most notable in two regards. Firstly, was the dramatically higher prevalence of central obesity found in axSpA women compared to men. Epidemiological data from the general population has clearly demonstrated this to be more common in men due to visceral fat deposition. As presence of excess adipose tissue can create a persistent low inflammatory state and the worse outcomes observed in axSpA patients with central obesity, could this modifiable risk factor account for the worse outcomes noted in women with axSpA? Furthermore, could targeted efforts to address central obesity result improve outcomes in axSpA? While the nature of this study did not allow for determination of a causal relationship between central obesity and patient outcomes, it certainly raised many interesting questions for future longitudinal studies.

The second notable finding of concern was the discordance in detection of obesity between WtHpR and BMI in women with axSpA. Although BMI is a tool that was developed to describe the average man, it remains one of the most frequently used anthropometric measures to assess physical health. Results of this study confirmed that BMI performs similarly to WtHpR for men with axSpA. However, for axSpA women it was a very different story with BMI failing to detect obesity in a significant proportion of the population. Further investigation revealed this is not the first study to demonstrate the poor performance of BMI in women. Previous studies have demonstrated BMI to be unreliable in postmenopausal women as well as women of varying ethnic backgrounds. This highlights the urgent need to improved recognition of obesity in women by reconsidering sole reliance on BMI.

Recognition is a critical first step needed to address this modifiable risk factor which is known to be associated with numerous long term health issues. Public health campaigns and regular monitoring of physical measurements offer significant opportunities to help axSpA patients at risk of developing central obesity to lead a healthier lifestyle.

10.2.7 Management of Pregnancy in Rheumatic Disease

The high prevalence of central obesity in women with axSpA discussed in **Chapter 6**, highlights one area of women's health that needs to be explored further in the context of axSpA. During the consideration of these results, the issue of the changing demands on the female body over the course of a lifetime arose. One of the most commonly encountered periods of change is that of pregnancy which is a period of significant hormonal, physical and physiological fluctuation. As such we felt a discussion of sex differences in axSpA would be incomplete without addressing pregnancy in women with axSpA.

Chapter 7 evaluated the management of pregnancy not only in axSpA but in the context of rheumatic disease (RMD) as a whole. Although this included detailed discussion of disease specific issues, the several core principles for the effective management of both the RMD and pregnancy emerged. One of the most important areas of focus was around pregnancy planning, which should occur months prior to conception to ensure disease stabilisation or remission and use of pregnancy compatible medication. Although seemingly simple in concept, this period is crucial to a successful pregnancy. **Chapter 7** outlines the numerous benefits of pregnancy planning but also highlights the need for Rheumatologists to initiate conversations regarding family planning.

Excellent guidelines are in place to guide management once a patient becomes pregnant; however, optimisation of the preconception period is an area that requires greater emphasis in clinical practice and research. Patients may not feel that conception is a topic to discuss with their Rheumatologist, thus is it our job to actively seek this information. The more comfortable a Rheumatologist is discussing conception and pregnancy, the more comfortable our patients will be raising questions related to these issues.

10.2.8 Pregnancy in AxSpA

Following review of the issues related to management of pregnancy in RMD overall and challenges in the management of these patients, **Chapter 8** was dedicated to pregnancy in axSpA. This chapter contained a systematic review and meta-analysis which included all eligible published research on pregnancy outcomes in axSpA representing a 40-year time span in the literature. We felt this was the best way to assess current level of knowledge on the topic as results of individual studies have been divergent, with no clear consensus on if women with

axSpA are at a higher risk of pregnancy complications compared to women of the general population.

This analysis was the first published meta-analysis of pregnancy outcomes in women with axSpA. Notable findings included a trend towards higher prevalence of pre-eclampsia, as well as a significantly higher prevalence of both caesarean section (CS) and preterm birth in pregnancies of women with axSpA compared to controls.

Regarding fetal complications, although the trend towards increased prevalence in axSpA pregnancies did not reach significance it is notable that this trend was present in all four complications. These findings establish a pattern of increased risk of certain adverse outcomes in pregnancies of women with axSpA. The reason for this occurrence is not immediately apparent, although numerous possible contributing factors are discussed in **Chapter 8**. This includes disease activity in pregnancy, medication usage as well as social and cultural influences.

Fluctuation in axSpA disease activity over the course of pregnancy remains poorly understood, although this review suggested a peak in activity in the second trimester. Large prospective studies would certainly improve the data available on this issue. However, development of tools adapted for use in pregnancy are desperately needed to improve the quality of information recorded. Combined with regular recording of medication use at each stage of pregnancy, from preconception to postpartum, this would provide a more complete picture of how axSpA disease activity changes in response to pregnancy.

To fully assess social and cultural influences, ongoing national data collection is essential to document variation in outcomes prevalence. This information will be key to create international evidence-based consensus guidance on the management of axSpA in pregnancy to minimise the risk of adverse pregnancy outcomes in women with axSpA. Additionally, it will also identify key areas in need of additional patient and physician education to aid optimisation of outcomes.

10.2.9 Pregnancy Outcomes from the Ankylosing Spondylitis Registry of Ireland

While the systematic review of **Chapter 8** benefited from including studies from 13 countries around the world, there was a notable lack of data on Irish women with axSpA. Additionally, findings from this review highlighted variations between countries for certain outcomes such as breastfeeding which may be due to differences in social and cultural norms.

For these reasons, the final study of the thesis contained in **Chapter 9** was focused on Irish pregnancy outcomes in axSpA using data from the ASRI. This study represented the first Irish data ever collected or published on pregnancy in axSpA. This chapter also documented the expansion of a national registry to create a dedicated section on pregnancy and fertility. The roll

out of this new section was met with enthusiasm and interest from participating women with axSpA, many of whom requested to be involved in further research in this area.

The study was descriptive in nature and designed to capture as many aspects as possible of pregnancy for women with axSpA. Selection of pregnancy outcomes included was guided by those commonly encountered in the systematic review of **Chapter 8**. Data was also gathered on breastfeeding, disease activity throughout pregnancy and fertility. Although data on disease activity was potentially limited by recall bias, this was included as a narrative discussion point to provide context of the issues facing women with axSpA during pregnancy.

One of the most important findings of this study was the high overall prevalence of complications encountered by axSpA women during their pregnancy. Specific outcomes such as preterm birth, pre-eclampsia and low birth weight were found to be more prevalent in axSpA women compared to women of the general population. Interestingly, prevalence of caesarean sections in the ASRI was lower than global reference norms reflecting the slower increase in frequency of caesarean sections in Ireland relative to North America.

In line with previous studies, an increase in disease activity was noted to be most common during pregnancy with a high frequency of postpartum flares. This supports the need for proactive medication planning for the postpartum period. As part of this process, medication safety during lactation should also be addressed to encourage breastfeeding, if possible, in women with axSpA. Increased patient education and breastfeeding promotion is key to optimising the health of both the mother and neonate in the immediate postpartum period.

The inclusion of data on miscarriage and fertility highlighted the limited comparison data available on these topics in other axSpA populations. While both issues would be generally considered to be directly linked to pregnancy, they are commonly excluded from published axSpA pregnancy studies. However, for women with axSpA trying to conceive or in the early stages of pregnancy these topics are of the utmost importance. The data from the ASRI on miscarriage and fertility in axSpA women represents an important first step in increasing the available evidence of knowledge basis in this area.

In addition to providing valuable information on pregnancy outcomes in women with axSpA in Ireland, this study outlined the interwoven biopsychosocial aspects which need to be considered in the management of pregnancy in these patients. This provides an essential resource for future data collection, as well as a springboard for future prospective studies to identify risk factors for complications, barriers to breastfeeding, monitoring disease activity in pregnancy and collaboration with other international axSpA registries.

10.3 Future Directions

The studies contained within this thesis aimed to explore specific issues within axSpA in a holistic, bio-psycho-social approach to fully capture both the patient experience and the impact on outcomes. As quality research often raises as many questions as it initially sets out to answer, there are a number of future research issues to pursue following the conclusion of this thesis.

10.3.1 Registry Development

As highlighted in Chapter 3, national registries have the potential to provide a wealth of information into various aspects of axSpA. Ongoing development of these registries is essential to maintain the relevance of the data captured and adapt the registry to reflect advances in understanding of the disease. This ensures the registry will remain an effective source of information and research tool going forward.

To do this, there are several factors which need to be considered and pursued. Firstly, ongoing patient recruitment is vital for continuous growth of the registry. This ensures the cohort already captured does not become a historical cohort, which is no longer reflective of current patient populations. Building on this, the collection of longitudinal data will provide updated information on treatment patterns, patient response, outcome measures over time, development of comorbidities and morbidity. These are just a few of the potential areas that could be captured with the added benefit of multiple time points for data collection.

To limit the potential of recall bias and to collect more specific data in real time, prospective data collection for the registry should be considered. This would provide an excellent opportunity to answer specific research questions and ensure the highest quality and reliability of data collected. An expansion of the registry to include prospective data would be laborious and time intensive compared to other expansion options, however with careful planning offers a huge potential for research yield.

10.3.2 Hormones

Understanding why women with axSpA average worse outcomes compared to men is an ongoing challenge, with many additional avenues that require exploration. While the work contained within this thesis outlined variation in burden of disease, capturing disease activity and factors associated with worse outcomes between sexes, future studies would benefit from examination of previously unexplored issues which may help to explain variation in outcomes between sexes. As discussed in **Chapter 4** one of the most obvious areas that has received very limited attention to date is that of hormones.

Not only are there significant variation in levels of sex hormones between males and females with axSpA, but during the course of the female lifetime these levels fluctuate significantly from puberty to menopause. AxSpA women are also commonly prescribed hormonal supplements for the purposes of contraception and management of menopausal symptoms. Thus, there is significant potential to examine the effect of sex hormones on both disease activity, burden of disease and treatment response. Improved understanding of this area has the potential to aid in the development of sex specific guidelines to optimise management of axSpA, with an aim to improve quality of life and disease activity for women with axSpA.

Lastly, the long-term impact of differing hormone levels in axSpA patients require evaluation, in terms of effect on body composition and metabolism. Focused studies on the interplay between sex hormones and adipocytokines may provide insights into the development of central obesity and other comorbidities highly prevalent in axSpA populations.

Capturing Pregnancy in AxSpA

The systematic review of pregnancy outcomes in axSpA combined with the ASRI study of pregnancy outcomes demonstrated that certain pregnancy complications are more prevalent in women with axSpA. It was also made clear that women with axSpA have a higher risk of complications overall compared to women of the general population. Now that this has been established, the next logical question is: why is this happening? More importantly, what can be done to minimise the risk of adverse outcomes in pregnancy for women with axSpA?

To answer these critical clinical questions large scale prospective studies of pregnancy in axSpA are needed. Areas of focus for these studies would include medication usage, comorbidities prior to pregnancy, fluctuation in maternal weight, and disease activity. Collection of data for all participants at multiple time points before, throughout and after pregnancy would allow identification of patterns in fluctuation of axSpA disease activity which is currently poorly documented and understood. Furthermore, information on disease activity and medication usage could provide insights on the impact of these factors on risk of pregnancy complications.

The potential to identify risk factors for adverse pregnancy outcomes in axSpA women has huge clinical implications. Not only would this evidence be key to developing guidelines for the management of pregnancy in axSpA women, but implementation of such guidelines would improve outcomes for both mother and fetus in an axSpA pregnancy.

Capturing maternal pregnancy information prospectively would allow detailed data collection into nuanced areas including indication for caesarean section or NICU admission. Furthermore, studying this topic in a large population with appropriately matched controls would help to ensure the study is adequately powered to allow appropriate exploration of outcomes.

Ideally a study of this type would also examine trends in breastfeeding and barriers to breastfeeding in axSpA women. Prospective data collection may provide insight into axSpA women's attitude and concerns around breastfeeding their infants. This information could be used to tailor breastfeeding educational resources for pregnant axSpA women to encourage breastfeeding, provide support and address concerns prior to delivery.

There are several challenges facing a prospective axSpA study on pregnancy. This includes patient identification and recruitment, multidisciplinary involvement, funding, the prolonged duration of the study, as well as confounding variables encountered in the general population such as age and comorbidities. Several of these challenges could be addressed by a multi-centred collaborative approach. This would be aided further with ongoing registry development as outlined previously and standardisation of pregnancy data collection to allow collaboration between national axSpA registries.

10.4 Concluding Remarks

The studies within this thesis provide numerous valuable insights into the factors affecting patient outcomes in axSpA and how this varies dramatically between sexes. Many of these factors affect multiple aspects of the life of women with axSpA. This is especially evident in the discussion of pregnancy, which requires consideration beyond pregnancy outcomes to include fluctuations in disease activity during pregnancy, fertility and breastfeeding. The importance of understanding these factors and how the biopsychosocial impact varies by sex in patients with axSpA, is key to closing the gender gap in the work towards improving outcomes in axSpA.

Ongoing research into sex differences and pregnancy in axSpA has many potential avenues which require exploration. To do this most effectively ongoing registry development to capture prospective longitudinal data is essential. Future studies on sex hormones and prospective pregnancy studies would also be key to advancing understanding and management of axSpA in women.

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