

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

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Appendix A Publications from Thesis

Published Manuscripts

- A.1 Sinead Maguire, Raj Sengupta, Finbar 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
- A.2 Sinead Maguire, Finbar 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
- A.3 Sinead Maguire, Tom O'Dwyer, David Mockler, Finbar O'Shea, Fiona Wilson. "Pregnancy in Axial Spondyloarthropathy: a Systematic Review and Meta-Analysis." *Seminars in Arthritis & Rheumatism*. 2020 Dec; 50(6): 1269-1279. DOI: 10.1016/j.semarthrit.2020.08.011
- A.4 Sinead Maguire, Finbar O'Shea. "Management of Pregnancy in Rheumatic Disease." *EMJ Rheumatology*. 2021 Jul; 8(1): 86-93
- A.5 Sinead Maguire, Phil Gallagher, Finbar 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
- A.6 Sinead Maguire, Fiona Wilson, Phil Gallagher, Finbar 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
- A.7 Sinead Maguire, Finbar 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
- A.8 Sinead Maguire, Fiona Wilson, Phil Gallagher, Finbar 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
- A.9 Sinead Maguire, Phil Gallagher, Finbar 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
- A.10 Sinead Maguire, Fiona Wilson, Phil Gallagher, Finbar O'Shea. "Central Obesity in Axial Spondyloarthritis: the Missing Link to Understanding Worse Outcomes in Women?" *The Journal of Rheumatology*. 2022 Mar; 49 (3); DOI: 10.3899/jrheum.211062
- A.11 Sinead Maguire, Fiona Wilson, Phil Gallagher, Muhanad MS Mohamed, Senan Maher, Finbar O'Shea. "What to Expect When Women with Axial Spondyloarthropathy are Expecting: Prevalence of Complications in Women with Axial Spondyloarthropathy." *Seminars in Arthritis & Rheumatism*. 2022 Mar 10; 54:151993. DOI: 10.1016/j.semarthrit.2022.151993.
- A.12 Sinead Maguire, Gillian Fitzgerald, Phil Gallagher, Finbar 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

Published Conference Abstracts

A.13 S Maguire, G Fitzgerald, C Sheehy, F O’Shea. “High Unemployment Rates in Patients with Ankylosing Spondylitis.” April 2019. *Rheumatology (Oxford)*. 58 (Suppl 2) 1038-1039; DOI: 10.1093/rheumatology/kez107.063

A.14 S Maguire, G Fitzgerald, C Sheehy, F O’Shea. “The Association of Ankylosing Spondylitis and Unemployment.” June 2019. *Annals of the Rheumatic Diseases* 78 (Suppl 2) 1038-1039; DOI: 10.1136/annrheumdis-2019-eular.2501

A.15 S Maguire, G Fitzgerald, C Sheehy, F O’Shea. “Worse outcomes for Females with Spondyloarthropathy.” November 2019. *Arthritis & Rheumatology*. 71(Suppl 10)

A.16 S Maguire, P Gallagher, F O’Shea. “Understanding Joint Replacement Surgery in Axial Spondyloarthropathy.” June 2020. *Annals of the Rheumatic Diseases*. 79 (Suppl 1)

A.17 S Maguire, P Gallagher, F O’Shea. “The Same but Different? Analysis of a Cohort of Patients with Late Onset Ankylosing Spondylitis.” June 2020. *Annals of the Rheumatic Diseases*. 79 (Suppl 1) 1139-1140

A.18 S Maguire, P Gallagher, F O’Shea. “Prescribing Practices in Axial Spondyloarthropathy.” June 2020. *Annals of the Rheumatic Diseases*. 79 (Suppl 1) 1647

A.19 S Maguire, T O’Dwyer, D Mockler, F Wilson, F O’Shea. “Pregnancy in Axial Spondyloarthropathy: a Systematic Review & Meta-analysis.” November 2020. *Arthritis & Rheumatology*. 72 (Suppl 10)

A.20 S Maguire, P Gallagher, F O’Shea. “Spinal Mobility & Function: How closely do they associate in axial spondyloarthropathy?” November 2020. *Arthritis & Rheumatology*. 72 (Suppl 10)

A.21 S Maguire, F O’Shea. “Undiagnosed Depression in Axial Spondyloarthropathy Negatively affects Disease Activity and Quality of Life.” April 2021. *Rheumatology (Oxford)*. 60 (Suppl 1)

A.22 S Maguire, P Gallagher, F O’Shea. “Examining BASDAI by Gender: Differing Scores but Similar Patterns of Disease.” April 2021. *Rheumatology (Oxford)*. 60 (Suppl 1)

A.23 S Maguire, P Gallagher, F O’Shea. “Looking Beyond BASDAI Total Scores: Analysis of the BASDAI on the Basis of Sex.” June 2021. *Annals of the Rheumatic Diseases*. 80 (Suppl 1): 27

A.24 S Maguire, F Wilson, P Gallagher, F O’Shea. “High Prevalence of Abdominal Obesity in Females with Axial Spondyloarthropathy.” June 2021. *Annals of the Rheumatic Diseases*. 80 (Suppl 1):738

A.25 S Maguire, F O’Shea. “Negative Impact of Undiagnosed Depression in Axial Spondyloarthropathy: Results of a Screening Study.” June 2021. *Annals of the Rheumatic Diseases*. 80 (Suppl 1): 734

A.26 S Maguire, P Gallagher, F O'Shea. "Sex differences in correlation of Spinal Mobility and Functional Impairment in Axial Spondyloarthritis." September 2021. *Clinical and Experimental Rheumatology*. 39 (5): 1185

A.27 S Maguire, P Gallagher, F Wilson, F O'Shea. "Negative Impact of Unemployment in Axial Spondyloarthritis: Results from the Ankylosing Spondylitis Registry of Ireland." September 2021. *Clinical & Experimental Rheumatology*. 39 (5): 1186

A.28 S Maguire, F Wilson, P Gallagher, F O'Shea. "Identifying Predictors of Unemployment in Axial Spondyloarthritis: Data from the Ankylosing Spondylitis Registry of Ireland." November 2021. *Arthritis & Rheumatology*. 73 (Suppl 10)

A.29 S Maguire, F Wilson, P Gallagher, F O'Shea. "High Frequency of Pregnancy Complications in Axial Spondyloarthritis: Emerging Data from the Ankylosing Spondylitis Registry of Ireland." November 2021. *Arthritis & Rheumatology*. 73 (Suppl 10)

A.30 S Maguire, P Gallagher, F O'Shea. "Undiagnosed Depression in Axial Spondyloarthritis and the Negative Impact on Patient Outcomes: Results of a Screening Study." November 2021. *Arthritis & Rheumatology*. 73 (Suppl 10)

A.31 S Maguire, F Wilson, P Gallagher, F O'Shea. "Body Mass Index (BMI) Underestimates Obesity in Females with Axial Spondyloarthritis." November 2021. *Arthritis & Rheumatology*. 73 (Suppl 10)

A.32 S Maguire, F Wilson, P Gallagher, F O'Shea. "Complications in Pregnancy are Common in Women with Axial Spondyloarthritis: data from the Ankylosing Spondylitis Registry of Ireland." April 2022. *Rheumatology (Oxford)*. 61 (Suppl 1)

The Future of Axial Spondyloarthritis Treatment



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KEYWORDS

• Spondyloarthritis • Axial spondyloarthritis • Therapy • Ankylosing spondylitis

KEY POINTS

- Secukinumab, an IL-17 inhibitor, is an effective therapy option for patients with axSpA and has been shown to be associated with decreased radiographic progression of disease.
- Ixekizumab and tofacitinib are approved for treating other forms of inflammatory arthritis and show promise in the treatment of axSpA
- New agents in trials inhibiting IL-17, IL-23, and JAK have shown improved outcomes in axSpA—further trials are needed.

INTRODUCTION

There have been significant developments in the availability of new therapeutic options in axial spondyloarthritis (axSpA) over the last number of years. Different recommendations have been published to reflect this changing landscape. In 2016, the Assessment of SpondyloArthritis International Society/European League Against Rheumatism (ASAS/EULAR) updated their management recommendations for patients with axSpA.¹ More recently, the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (ACR/SPARTAN) have updated their recommendations for the treatment of ankylosing spondylitis (AS) and nonradiographic axSpA.²

Recommendation 9 of the ASAS/EULAR recommendations confirms the use of an anti-tumor necrosis factor (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 the treatment landscape in the last few years has been the development of medications that work on an alternative pathway to the anti-TNF agents. Evidence now suggests that interleukin-17 (IL-17) plays a role as an

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inflammatory mediator in AS. Since 2016, anti-IL-17 medications have also been included in the ASAS/EULAR recommendations for initial biologic therapy in the management of axSpA. 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 axSpA patients for the last 3 years. A significant body of evidence exists for the benefit of secukinumab in axSpA across a series of trials—MEASURE 1 to 5 study program^{3–6} (Table 1).

This series of studies now has 5-year data demonstrating efficacy of secukinumab in axSpA.⁷ In addition, the MEASURE 1 study has shown a low rate of radiographic progression in this cohort. In fact, no radiographic progression (modified Stoke Ankylosing Spondylitis Spine Score change from baseline of <2 units) was seen in 79% of patients receiving secukinumab over 4 years.⁸

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 go on to say that in patients with a primary nonresponse to the first anti-TNF agent it may be a more rational approach to switch to another class (specifically an anti-IL-17 agent).

NEW TO MARKET TREATMENTS

TNF blockers have been the cornerstone of treatment of axSpA over the last 2 decades. Aside from biological disease-modifying antirheumatic drugs (bDMARDs), new treatments in the form of small-molecule treatments (targeted synthetic DMARDs) are showing promise in this disease area. One of the first targeted synthetic DMARDs being assessed in axSpA is a Janus kinase (JAK) inhibitor—tocacitinib—which preferentially inhibits signaling via JAK 1 and 3. A preliminary phase II study showed 63% of patients receiving 5 mg bd of tofacitinib achieved an ASAS20 response compared with 40% of patients receiving placebo at 12 weeks⁹ (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 that 18% patients treated with tofacitinib 5 mg bd achieved MIC (minimal important change) for the Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint and spine scores compared with 0% of patients receiving placebo. There was a trend for greater clinical improvements in the tofacitinib patients who achieved MIC SPARCC scores.¹⁰ Although no treatment-related serious adverse events were identified in the phase II study, the Food and Drug Administration have recently issued a safety alert regarding an increased risk of pulmonary embolism with tofacitinib 10 mg bd in patients with rheumatoid arthritis.

Table 1 MEASURE 4 study outcomes						
	Week	Placebo (%)	Secukinumab 150 mg (%)	P Value	Secukinumab 150 mg + Loading (%)	P Value
ASAS 20	4	39	53.8	.36	49.1	.36
	16	47	61.5	.05	59.5	.06
	52	—	72	—	71.7	—
	104	—	77.5	—	74	—
ASAS40	4	17.9	26.5	.36	29.3	.36
	16	28.2	35.9	.36	38.8	.19
	52	—	54.1	—	51.3	—
	104	—	58.9	—	51.9	—

Table 2
Comparative Assessment of SpondyloArthritis International Society outcomes in trials for tofacitinib and ixekizumab

	Treatment	Placebo ASAS20 (%)	Tx Group ASAS20 (%)	Tx ASAS40 (%)	Placebo ASAS40 (%)	P Value
Tofacitinib						
van der Heijde et al, ⁹ 2017	2 mg bd	41–	52–	42.30–	20–	<.05
	5 mg bd	—	81–	46.20–	—	<.01
	10 mg bd	—	56–	38.50–	—	<.05
Ixekizumab						
COAST-V trial	q2 weeks	40–	69–	52–	18–	<.0001
	q4 weeks	—	64–	48–	—	<.001
COAST-W trial	q2 weeks	30–	50–	31–	13–	.003
	q4 weeks	—	48–	25	—	.017

Note these are not head to head trials. Tx, Treatment

There is a growing body of evidence suggesting that IL-17 is one of the key cytokines in the pathogenesis of axSpA.¹¹ As previously stated, secukinumab, a monoclonal antibody against IL-17A, has had market authorization 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 psoriatic arthritis (PsA). Three phase III studies have assessed the efficacy of ixekizumab in axSpA. The COAST-V study assessed the efficacy of ixekizumab 80 mg every 2 or 4 weeks in patients with AS who were DMARD and TNF naive compared with adalimumab or placebo (see [Table 2](#)).¹² Fifty two percent of patients receiving 80 mg ixekizumab achieved an ASAS40 response compared with placebo. The COAST-W study specifically assessed the efficacy of ixekizumab 80 mg in patients who either failed or were intolerant to TNF blockers as first-line therapy. Thirty one percent of patients treated with ixekizumab 80 mg every 2 weeks exhibited an ASAS40 response at 16 weeks ([Fig. 1](#)). The COAST-X study is an ongoing phase III study assessing the efficacy of ixekizumab in bDMARD naive nr-axSpA.¹³ Preliminary top line data have shown significant improvements in ASAS40 response in patients treated with ixekizumab at weeks 16 and 52 compared with placebo.

TREATMENTS IN TRIALS

Anti-Interleukin-17

Brodalumab

Brodalumab is a human monoclonal antibody against the IL-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 was published in 2014 examined the efficacy and safety profile of brodalumab in psoriatic arthritis.¹⁴ One hundred and sixty eight patients were randomized into 2 treatment arms (brodalumab 140 or 280 mg) and 1 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 140 mg dose group and 39% ($P = .03$) in the 280 mg dose group ($P = .02$). 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 280 mg group than the 140 mg group (64% vs 51%). ACR50 and ACR70 response rates continued to improve through to week 52 in the 140 mg group

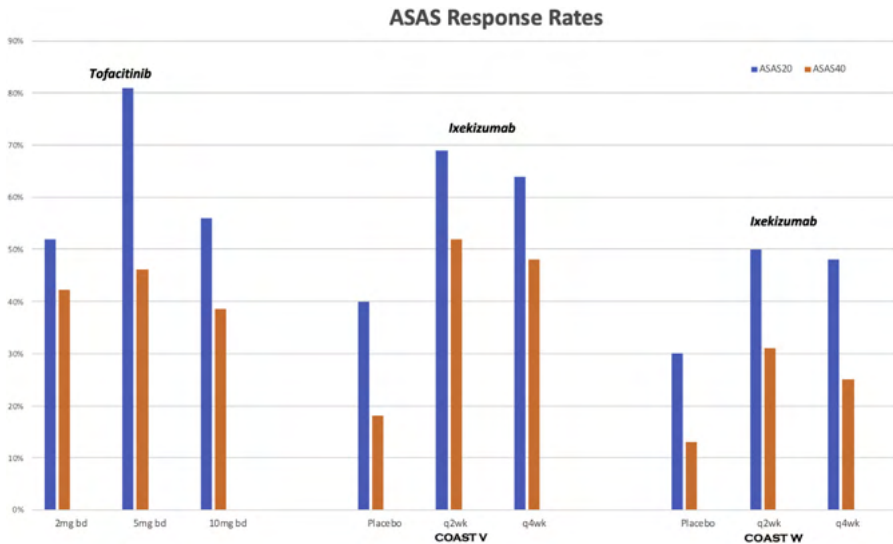


Fig. 1. Comparative ASAS outcomes in trials for tofacitinib and ixekizumab. Note these are not head-to-head trials.

Following this phase III trial, a multicenter, randomized, double-blinded, placebo-controlled study was commenced in axSpA.¹⁵ A total of 159 patients was randomized into a placebo group or a group receiving brodalumab 210 mg and treated at weeks 1, 2, and then every 2 weeks up to week 16. Primary outcome was ASAS40 at week 16, which was found to be higher in the brodalumab group than the placebo group (43.8% vs 24.1%, $P = .018$). Change in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores were also noted in the treatment group, it is unknown if this was statistically significant. Adverse events rate was comparable between the 2 groups, and no suicidal attempts or ideation was noted during the trial period, which had previously been a concern during the drug's development for psoriasis.

Netakimab

Netakimab is a humanized monoclonal antibody targeting IL-17A. Results of a phase II, randomized, placebo-controlled trial was published out of Russia focusing on safety and pharmacokinetics in patients with active AS. Eighty-nine patients were randomized to receive 40, 80, or 120 mg of subcutaneous netakimab or placebo up to week 12. Rates of ASAS20 response in treatment groups (40/80/120 mg) were 73%, 82%, and 91% versus 43% in placebo group. No dose-dependent toxicity or serious adverse events were recorded.¹⁶

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 the netakimab group compared with the placebo group (40% vs 2.6%; $P < .0001$).¹⁷ Results also demonstrated significant improvement in BASDAI, BASFI, Work Productivity and Activity Impairment response compared with placebo at week 16 ($P < .0001$).¹⁸ Further analysis of the ASTERA patients focused on spinal and sacroiliac inflammation as seen on MRI at baseline and at week 16. Significant improvements with treatment in the Berlin spine score ($P < .0001$) and

SPARCC score ($P < .01$) were found in the netakimab group compared with the placebo group.¹⁹ Plans for an extension trial to collect data up to 52 weeks are ongoing.

Bimekizumab

Bimekizumab is a monoclonal antibody targeting both IL-17A and IL-17F. Initially trialed in psoriasis, recent trials have been focusing on axSpA. A phase IIb, randomized, double-blind, placebo-controlled, dose-ranging study was done on 303 patients with active AS to assess efficacy and safety.²⁰ Primary outcome was an ASAS40 dose-response relationship at week 12, which was achieved ($P < .01$) in this study. Significantly more bimekizumab patients achieved ASAS40 at week 12 than placebo across all doses ($P < .05$). Patients in the treatment arm also had greater reductions in their BASDAI and AS Disease Activity Score (ASDAS) based on C-reactive protein than those in the placebo arm ($P < .001$). Similar rates of adverse events were noted in both groups.

Following on from this, a phase IIb, randomized, double-blind, placebo-controlled, dose-ranging study was carried out to assess the impact of bimekizumab on quality of life and patient-reported outcomes²¹ in patients with active AS. This 48-week study included 303 patients with active AS randomized 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 the placebo group. All treatment dose groups also reported greater reductions in BASDAI, BASFI, Ankylosing Spondylitis Quality of Life Scale (ASQoL), and Patient's Global Assessment of Disease Activity compared with the placebo group at week 12. Rates of adverse events were similar in both groups.

Anti-Interleukin-23

Guselkumab

Guselkumab is an IgG1 monoclonal antibody that selectively binds to the p19 subunit of IL-23, resulting in inhibition of IL-23 signaling. Several phase III trials have demonstrated guselkumab's efficacy in psoriasis, leading to the development of trials in PsA of which there are currently results available 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 compared with placebo.²² The other trial was a randomized, phase II, placebo-controlled trial, which showed a significant decrease of Routine Assessment of Patient Index Data 3 scores in the guselkumab group at week 24 compared with placebo.²³ Further pharmacodynamic studies have also demonstrated that treatment with guselkumab resulted in rapid reduction in IL-17A and IL-17F. IL-17F changes at weeks 4 and 16 were significantly associated with ACR20 responses at week 24, and IL-17A changes at week 4 and 16 were associated with PASI75 response at week 24 in the guselkumab group.

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 safety of tildrakizumab. The axSpA trial's primary outcome is to achieve a 40% improvement in a visual analogue scale score from baseline to 24 weeks with a secondary endpoint at 52 weeks.²⁴ Although the study is now completed, no results are currently available.

Janus Kinase Inhibitors

Filgotinib

Filgotinib is an oral selective JAK 1 inhibitor that has been theorized to have potential therapeutic benefits in many autoimmune conditions. TORTUGA was the first

randomized, placebo-controlled, phase II study to examine the efficacy of filgotinib in patients with active radiographic AS.²⁵ This study recruited 116 adult patients with AS with an inadequate response or intolerance to nonsteroidal anti-inflammatory drugs. Patients were required to have active AS at the time of study commencement for inclusion. The treatment arm received filgotinib 200 mg 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 ($P < .001$). In the filgotinib group ($n = 58$) versus placebo the following outcomes were achieved at week 12: ASAS20 = 76% versus 40%; ASAS40 = 38% versus 19%; ASAS partial remission 12% versus 3%. Significant improvements in ASQoL, BASDAI, BASFI, Bath Ankylosing Spondylitis Metrology Index (BASMI), SPARCC spine and sacroiliac joint scores were noted in the treatment group compared with the placebo group.

The EQUATOR trial was a randomized, double-blinded, placebo-controlled, phase II trial investigating the efficacy and safety profile of filgotinib in patients with active psoriatic arthritis.²⁶ Those recruited had previously failed or shown intolerance of at least 1 conventional DMARD before study commencement. The primary endpoint was ACR20 at week 16, which was reached by 80% of the treatment group and 33% of placebo group ($P < .001$). The filgotinib group also demonstrated significantly higher rates of achieving secondary outcomes compared with the placebo group: ACR50 = 48% versus 15%; ACR70 23% versus 6%. No significant difference was detected in rates of adverse events.

Upadacitinib

Upadacitinib is another selective JAK1 inhibitor that has shown efficacy in rheumatoid arthritis. At present there is a phase IIb/III randomized, double-blind, placebo-controlled trial ongoing.²⁷ This trial is evaluating both efficacy and safety profile in active radiographic axSpA with a primary endpoint of ASAS40 response at week 14. This trial is due to be completed in November 2020.

Unsuccessful Treatments in Axial Spondyloarthritis

Abatacept

Abatacept is a cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin that has been shown to selectively modulate CD80 costimulatory signaling needed for full T-cell activation. A phase II, prospective, open-label study was carried out in patients with active AS.²⁸ The 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.

Tocilizumab

Tocilizumab is a humanized monoclonal antibody that binds to IL-6 receptors. BUILDER-1 was a 2-part, phase II/III trial assessing tocilizumab in patients with AS naïve to anti-TNF therapy.²⁹ Patients were randomized into tocilizumab 8 mg/kg or placebo for 12 weeks. ASAS20 response rates at week 12 were similar between treatment and placebo groups ($P = .28$), as was ASAS40 response rates ($P = .27$). 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.

Apremilast

A phase II, double-blind, placebo-controlled, single-center study was carried out in patients with active radiographic axSpA treated with an oral phosphodiesterase

4 inhibitor, apremilast.³⁰ 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, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating apremilast in the treatment of active radiographic axSpA.³¹ The treatment group failed to achieve a superior ASAS20 response rate at week 16 over placebo and the study was terminated.

Ustekinumab

This humanized 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.³² 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.³³ Because of 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.

Risankizumab

Risankizumab is a humanized monoclonal antibody against the p19 subunit of IL-23. A phase II, randomized, double-blind, placebo-controlled study was commenced in active patients with AS.³⁴ Treatment groups did not demonstrate significantly higher proportions of ASAS40 response over placebo leading to trial discontinuation.

SUMMARY

Significant advances have been made in the treatment of axSpA. Improved understanding of the IL-17 pathway has led to the development many medications, including secukinumab, which has been shown to improve patient outcomes in addition to decreasing radiographic progression. Ongoing drug development is focused on the IL-17/IL-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.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017; 76:978–91.
2. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/Spondylitis Research and Treatment Network Recommendations for the treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol* 2019;71(10):1599–613.
3. Blair HA. Secukinumab: a review in ankylosing spondylitis. *Drugs* 2019;79(4): 433–43.
4. Marxo-Ortega H, Sieper J, Kivitz A, et al. Secukinumab provides sustained improvements in the signs and symptoms of active ankylosing spondylitis with high retention rate: 3 year results from the phase III trial; MEASURE 2. *RMD Open* 2017;3(2):e000592.

5. Pavelka K, Kivitz A, Dokoupilova E, et al. Efficacy, safety and tolerability of secukinumab in patients with active ankylosing spondylitis: a randomised, double-blind phase 3 study, MEASURE 3. *Arthritis Res Ther* 2017;19(1):285.
6. Kivitz A, Wagner U, Dokoupilova E, et al. Efficacy and safety of Secukinumab 150 mg with and without loading regimen in ankylosing spondylitis: 104 week results from MEASURE 4 study. *Rheumatol Ther* 2018;5(2):447–62.
7. Baraliakos X, Braun J, Deodhar A, et al. Long term efficacy and safety of secukinumab 150 mg in ankylosing spondylitis: 5 year results from the phase III MEASURE I extension study. *RMD Open* 2019;5(2):e001005.
8. Braun J, Baraliakos X, Deodhar A, et al. Secukinumab shows sustained efficacy and low structural progression in ankylosing spondylitis: 4 years results from the MEASURE 1 study. *Rheumatology (Oxford)* 2019;58(5):859–68.
9. van der Heijde D, Deodhar A, Wei JC, et al. Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2017;76(8):1340–7.
10. Maksymowych W, van der Heijde D, Baraliakos X, et al. Tofacitinib is associated with attainment of the minimally important reduction in axial magnetic resonance imaging inflammation in ankylosing spondylitis patients. *Rheumatology* 2018;57:1390–9.
11. McGonagle D, McInnes I, Kirkham B, et al. The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: recent advances and controversies. *Ann Rheum Dis* 2019;1–12. <https://doi.org/10.1136/annrheumdis-2019-215356>.
12. van der Heijde D, Cheng-Chung W, Dougados M, et al. Ixekizumab, an interleukin-17A antagonist in the treatment of ankylosing spondylitis or radiographic axial spondyloarthritis in patients previously untreated with biological disease-modifying anti-rheumatic drugs (COAST-V): 16 week results of a phase 3 randomised, double-blind, active-controlled and placebo-controlled trial. *Lancet* 2018;392(10163):2441–51.
13. A study of Ixekizumab (LY2439821) in Participants with Non-Radiographic Axial Spondyloarthritis (COAST-X) (2019). Available at: www.Clinicaltrials.gov/Ct2/Show/NCT02757352. Identification number NCT02757352. Accessed 31 Oct 2019.
14. Mease P, Genovese M, Greenwald M, et al. Brodalumab, an anti-IL1RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med* 2014;370(24):2295–306.
15. Wei JC, Kim TH, Kishimoto M, et al. Efficacy and safety of Brodalumab, an anti-interleukin-17 receptor A monoclonal antibody in patients with axial spondyloarthritis: a 16-week results of a phase 3, multicentre, randomised, double blind, placebo-controlled study. *Ann Rheum Dis* 2019;78:195.
16. Erdes S, Nasonov E, Kunder E, et al. Primary efficacy of Netakimab, a novel interleukin-17 inhibitor, in the treatment of active ankylosing spondylitis in adults. *Clin Exp Rheumatol* 2020;38:27–34.
17. Gaydukova I, Mazurov V, Erdes S, et al. OP0232 Netakimab reduces the disease activity of radiographic axial spondyloarthritis. Results of the ASTERA study. *Ann Rheum Dis* 2019;78:193–4.
18. Gaydukova I, Mazurov V, Erdes S, et al. FRI0391 Netakimab improves patient related outcomes in patients with radiological axial spondyloarthritis: results from randomised phase 3 trial (ASTERA). *Ann Rheum Dis* 2019;78:880–1.
19. Smirnov A, Gaydukova I, Mazurov V, et al. FRI0412 spinal and sacroiliac joints inflammation in patients with radiographic axial spondyloarthritis treated with Netakimab—16 weeks results of multicentre, randomised, double blinded, placebo controlled, phase III ASTERA study. *Ann Rheum Dis* 2019;78:893–4.
20. Van der Heijde D, Gensler LS, Deodhar A, et al. Dual neutralisation of IL-17A and IL-17F with Bimekizumab in patients with active ankylosing spondylitis

- (AS): 12-week results from a phase 2b, randomised, double-blind, placebo-controlled, dose-ranging study. *Ann Rheum Dis* 2018;77:70.
21. Van der Heijde D, Gensler LS, Deodhar A, et al. Dual neutralisation of IL-17A and IL-17F with bimekizumab was associated with improvements in patient reported and quality of life outcomes in patients with active ankylosing spondylitis: results from a phase 2B, randomized, double blind, placebo controlled, dose ranging study. *Ann Rheum Dis* 2019;78:193.
 22. Helliwell P, Deodhar A, Gottlieb A, et al. Comparing composite measures of disease activity in psoriatic arthritis: results from a randomized phase 2 trial with guselkumab. *Ann Rheum Dis* 2019;78:1843.
 23. Deodhar A, Kirkham L, Rahman P, et al. Assessment of disease activity using RAPID3 and evaluation of treatment effect of Guselkumab in patients with PsA: results from a randomized placebo-controlled phase 2 clinical trial. *Ann Rheum Dis* 2019;78:1838.
 24. Efficacy and safety study of SUNPG1622(2019). Available at: <https://clinicaltrials.gov/ct2/show/NCT02980705>. Identification number NCT02980705. Accessed 31 Oct 2019.
 25. van der Heijde D, Baraliakos X, Gensler L, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392(10162):2378–87.
 26. Mease P, Coates LC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. *Lancet* 2018;392:2367e77.
 27. A Study Evaluating the Safety and Efficacy of Upadacitinib in Subjects with Active Ankylosing Spondylitis (SELECT Axis 1) (2019). Available at: <https://clinicaltrials.gov/ct2/show/NCT03178487>. Identification number NCT03178487. Accessed 31 Oct 2019.
 28. Song IH, Heldmann F, Rudwaleit M, et al. Treatment of active ankylosing spondylitis with abatacept: an open-label, 24-week pilot study. *Ann Rheum Dis* 2011;70:1108e10.
 29. Sieper J, Porter Brown B, Thompson L, et al. Assessment of short-term symptomatic efficacy of tocilizumab in ankylosing spondylitis: results of randomised, placebo-controlled trial. *Ann Rheum Dis* 2014;73(1):95.
 30. Pathan E, Abraham S, Van Rossen E, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis. *Ann Rheum Dis* 2013;72(9):1475–80.
 31. Celgene Corporation. Study of apremilast to treat subjects with active ankylosing spondylitis (POSTURE). Bethesda (MD): ClinicalTrials.gov National Library of Medicine; 2000. NLM Identifier: NCT01583374.
 32. Poddubny D, Hermann KG, Callhoff J, et al. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). *Ann Rheum Dis* 2014;73(5):817–23.
 33. Deodhar A, Gensler LS, Sieper J, et al. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol* 2019;71(2):258–70.
 34. Baeten D, Østergaard M, Wei JC, et al. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. *Ann Rheum Dis* 2018;77:1295–302.



Social isolation due to the COVID-19 pandemic has led to worse outcomes in females with inflammatory arthritis

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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).

Aim To capture the level of psychological distress for patients with IA following prolonged social isolation.

Methods A survey was sent out to patients with a confirmed diagnosis of IA. 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.

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. Evaluating the mean PHQ-4 scores, no significant difference was noted between genders (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%, $p = 0.13$). Subanalysis of patients with axSpA found high rates of moderate to severe distress in both genders.

Conclusions 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.

Keywords Arthritis · COVID-19 · Females · Isolation · Psychological distress

Introduction

Quarantine and social isolation are public health measures used to contain and prevent the spread of an infectious disease [1]. 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 recent mandated quarantines for the SARS and Ebola outbreaks [2]. The 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 EU, the social isolation has now gone on for over 3 months. Although

restrictions are slowly being lifted, it is 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 unrecognized, 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.

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Table 1 Overall outcomes by gender

	Males	Females	<i>p</i> value
<i>n</i>	62.5% (50)	37.5% (30)	
Age	50.1	50.5	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

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. Axial spondyloarthritis (axSpA) is a form of IA affecting the sacroiliac joints and the spine [3]. Patients with axSpA have been previously shown to have increased rates of depression [4] and there is a trend towards higher levels of disease activity in patients with depression [5]. 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 aims of this study are to capture the level

of psychological distress for patients with inflammatory arthritis and understand how this is affecting their disease and general health.

Methods

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

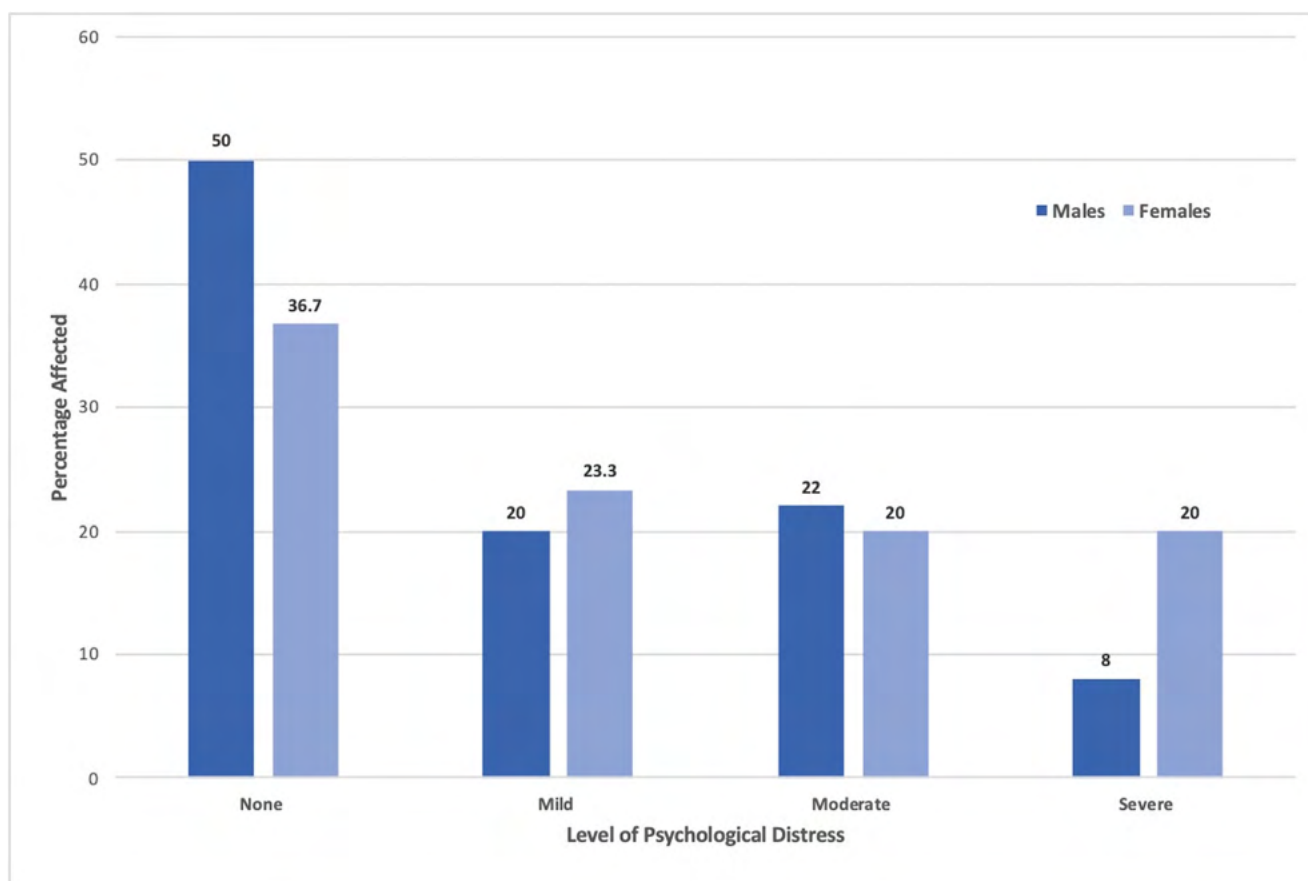


Fig. 1 PHQ-4 outcomes by gender

including axSpA. Participation was voluntary. Results of the survey were analysed on the basis of gender 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 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.

Data analysis

Analysis was performed using IBM SPSS version 26. An independent sample *t* test was used to test for significance in differences of means between groups, including age and PHQ-4 scores. A Chi² 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.

Results

In total, 88 completed surveys were returned, of these 80 contained data on gender and were included in this analysis. Patients were 37.5% (30) females and 62.5% (50) males with a mean age of 50.7 years (Table 1). Population was predominantly axSpA patients, 73.8% (59) with 26.3% (21) patients with inflammatory arthritis. Fifty percent (40) were currently employed; 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. Mean PHQ-4 score was 4.10, 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, *p* = 0.02).

Eighty responses contained data on gender. Overall, females reported significantly higher rates of mood disturbance (43.4%

Table 2 Outcomes in AxSpA by gender

	Males	Females	<i>p</i> value
<i>n</i>	69.5% (41)	30.5% (18)	
Age	49.6	45.6	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

vs 26%, $p = 0.03$) and increased disease activity (50% vs 16%, $p = 0.01$) compared to males (Table 1). 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.

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%, $p = 0.13$) (Fig. 1).

Further analysis focused on axSpA patients alone on the basis of gender. Of the 59 axSpA patients included in the analysis, 30.5% (18) were female and 69.5% (41) male (Table 2). 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.

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 (Fig. 2).

Discussion

The COVID-19 global pandemic led to an abrupt and prolonged period of social isolation to stem spread of the

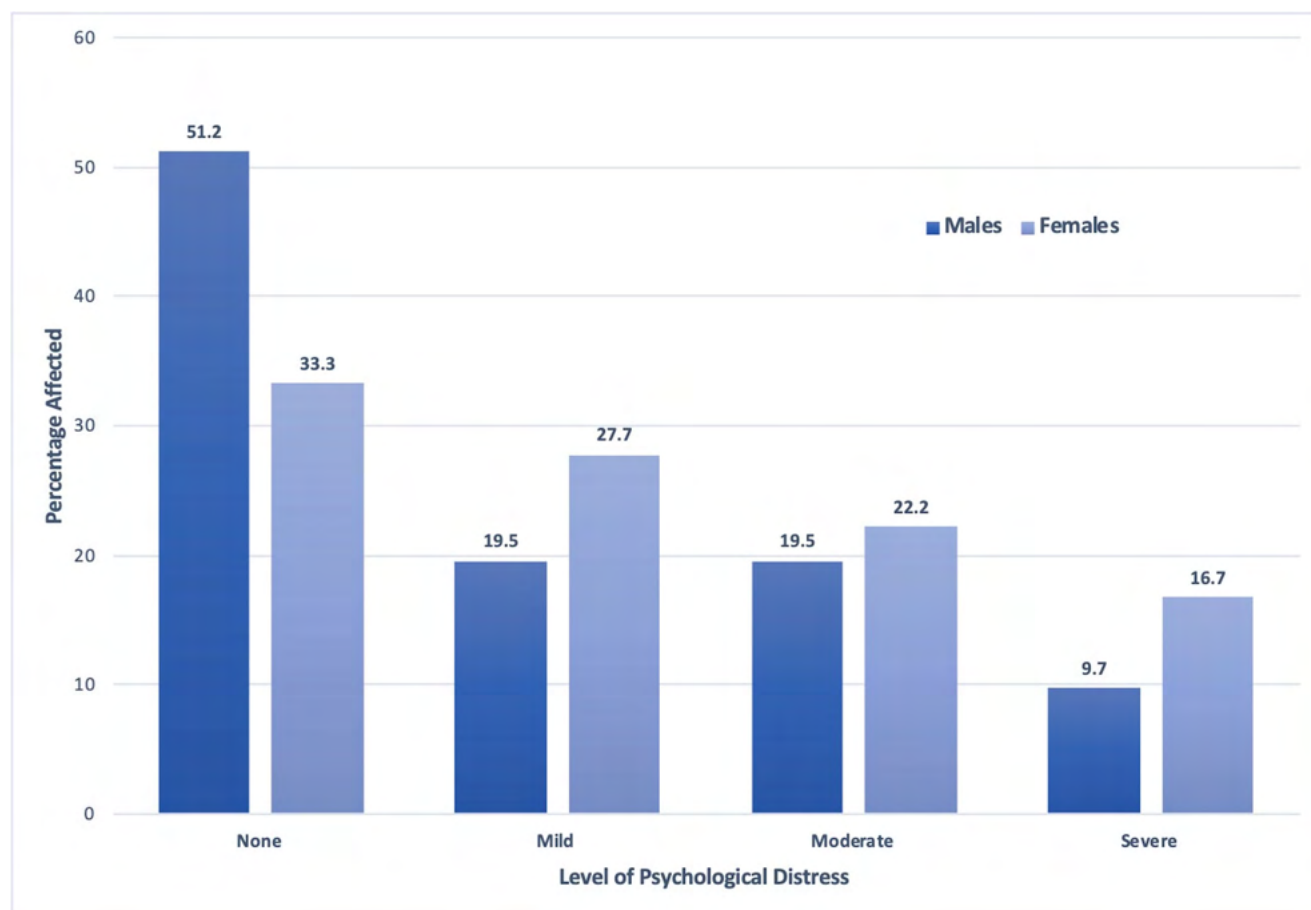


Fig. 2 PHQ-4 outcomes in AxSpA by gender

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 moderate to severe psychological distress in females compared to males. Subgroup analysis of the axSpA patients alone reached demonstrated similar findings but did not reach significance in variation of mood disturbance.

Previous studies have shown that prolonged social isolation can lead to decreased work performance and increased risk of mental health disorders [6]. 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 [7]. Encouraging regular exercise [8], increased reliance on digital communication [9] and social integration [10] are strategies

proposed to decreased 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 [11, 12].

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

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Authors' contributions All authors contributed to the study concept and design. Data collection, analysis and manuscript composition was performed by all authors. All authors read and approved final version of the manuscript prior to submission.

Data availability Anonymized data available upon request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Project was reviewed and approved by the St James' Hospital/Tallaght University Hospital Joint Research Ethics Committee.

Consent to participate Participation in the survey following review of the patient information leaflet was taken as implied consent. Participation in the study was voluntary.

Consent for publication Prior to participation in this study, all patients were provided with an information leaflet detailing how results would be published in a medical journal. As stated within this leaflet, participation implied consent for publication.

References

- Giubilini A, Douglas T, Maslen H, Savulescu J (2018) Quarantine, isolation and the duty of easy rescue in public health. *Dev World Bioeth* 18(2):182–189. <https://doi.org/10.1111/dewb.12165>
- Barbisch D, Koenig KL, Shih FY (2015) Is there a case for quarantine? Perspectives from SARS to Ebola. *Disaster Med Public Health Prep* 9(5):547–553. <https://doi.org/10.1017/dmp.2015.38>
- Zhu W, He X, Cheng K et al (2019) Ankylosing spondylitis: etiology, pathogenesis, and treatments. *Bone Res* 7:22. <https://doi.org/10.1038/s41413-019-0057-8>
- Park JY, Howren AM, Zusman EZ et al (2020) The incidence of depression and anxiety in patients with ankylosing spondylitis: a systematic review and meta-analysis. *BMC Rheumatol* 4:12. <https://doi.org/10.1186/s41927-019-0111-6>
- Webers C, Vanhoof L, Leue C et al (2019) Depression in ankylosing spondylitis and the role of disease-related and contextual factors: a cross-sectional study. *Arthritis Res Ther* 21(1):215. <https://doi.org/10.1186/s13075-019-1995-7>
- Torales J, O'Higgins M, Castaldelli-Maia JM, Ventriglio A (2020) The outbreak of COVID-19 coronavirus and its impact on global mental health. *Int J Soc Psychiatry* 66(4):317–320. <https://doi.org/10.1177/0020764020915212>
- World Health Organisation (2020) Mental health and psychosocial considerations during the COVID-19 outbreak. WHO
- Matias FDT, Marks DF (2020) Human needs in COVID-19 isolation. *J Health Psychol* 25(7):871–882. <https://doi.org/10.1177/1359105320925149>
- Razai MS, Oakeshott P, Kankam H et al (2020) Mitigating the psychological effects of social isolation during the covid-19 pandemic. *BMJ* 369:m1904. <https://doi.org/10.1136/bmj.m1904>
- Banerjee D, Rai M (2020) Social isolation in Covid-19: the impact of loneliness. *Int J Soc Psychiatry* 20764020922269. <https://doi.org/10.1177/0020764020922269>
- Research AAFPO Response Rates - An Overview
- Phillips AW, Reddy S, Durning SJ (2016) Improving response rates and evaluating nonresponse bias in surveys: AMEE Guide No. 102. *Med Teach* 38(3):217–228. <https://doi.org/10.3109/0142159x.2015.1105945>

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Pregnancy in axial spondyloarthritis: A systematic review & meta-analysis

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ABSTRACT

Background: Axial spondyloarthritis (axSpA) is an inflammatory arthritis which affects the sacroiliac joints and the spine. Many females affected are of childbearing age. Studies on effects of pregnancy on axSpA disease activity and medication use have been limited, with divergent conclusions.

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

Methods: A systematic review of case-control trials, observational studies, cross sectional studies and case series ($n > 5$) on axSpA in pregnancy. EMBASE, Medline (OVID), CINAHL, Maternity and Infant Care (MIDIRS online), and Web of Science were searched for keywords. Two reviewers reviewed articles to determine suitability for inclusion. The Newcastle Ottawa Scale was used to assess risk of bias. Data extraction was performed using a standardized template to streamline data to allow comparison and meta-analysis.

Results: Search strategy returned 884 records, 130 full text articles were assessed for eligibility. Eighteen studies with a total of 3,166 axSpA participants were eligible for inclusion. There was an increased prevalence of pre-eclampsia (OR 1.3, 95% CI 0.92–1.82) and IUGR (OR 1.17, 95% CI 0.26–5.17) and a statistically significant increase in cesarean sections (OR 1.85, 95% CI 1.46–2.30) in axSpA females, with an especially high prevalence of elective cesarean sections (OR 2.26, 95% CI 1.74, 2.93). There was a trend towards increased prevalence of fetal complications 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 1.34, 95% CI 0.63–1.24; NICU admissions OR 1.55, 95% CI 0.96–2.51) which did not reach significance.

Conclusion: AxSpA females have an increased prevalence of cesarean sections compared to the general population. There is a trend towards increased prevalence of pre-eclampsia, IUGR and certain fetal complications. Ongoing development of national registries could help to better understand axSpA in pregnancy.

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Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory arthritis affecting the sacroiliac joints and the spine. This SpA is described as radiographic axSpA, previously known as ankylosing spondylitis (AS), which has sacroiliitis on x-ray, and non-radiographic SpA which has sacroiliitis on MRI only [1]. Symptoms typically begin in young adulthood with peak incidence in the second and third decade of life [2]. Although previously thought to predominantly affect males, recent studies have shown the incidence in females to be as high as 1:2 [3]

It is important to recognize that many females with axSpA are of childbearing age during the early course of the disease. The priority when managing a pregnant woman with inflammatory arthritis is to ensure a healthy, uncomplicated pregnancy [4]. This includes close monitoring of disease activity, a healthy lifestyle, monitoring medication usage and regular reviews with both Rheumatology and Obstetrics [5]. A narrative review discussed this topic as part of a broader scoping article [6]. One of the main issues highlighted was the lack of data specific to individuals with axSpA, as many studies included low numbers of women with axSpA within a broader inflammatory arthritis cohort. There is currently no published synthesis and meta-analysis of data in this area to guide practice.

In recent years, the development of national registries has led to an increase in published pregnancy data for women with axSpA [7–10]. Increased use of standardized outcome measures within

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registries has increased the comparability of data. Pooling of recently published registry data could increase the power to detect significant differences in pregnancy outcomes among women with axSpA.

Pregnancy related complications include any adverse health outcome encountered during the course of the pregnancy. Commonly discussed complications include stillbirth [11], miscarriage [12], cesarean sections [13] and pre-eclampsia [14]. Fetal outcomes, including low birth weight (LBW) [15], small for gestational age (SGA) [16] and congenital abnormalities [17] are important additional considerations. Disease activity in axSpA during the course of pregnancy is an area of recent research interest. Lui et al. [18] found high rates of disease improvement in pregnancy while van den Brandt et al. [19] reported high rates of flare in disease during pregnancy especially in females taken off anti-TNF (tumor 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 post-partum period [20]. 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 there is an increased risk of complications. Secondary objectives were to explore fetal outcomes, disease activity, medication usage and breastfeeding among women with axSpA during pregnancy. This will inform guidance for the monitoring and management of women with axSpA during pregnancy.

Methods

The protocol for this review was prospectively registered with an international registry for systematic reviews (PROSPERO, Ref: CRD42020147814). The 'Preferred Reporting Items for Systematic Reviews and Meta-analysis' (PRISMA) guidelines [21] were followed in completing this review.

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 participants were excluded.

Studies documenting the frequency of pregnancy related complications in females with axSpA were included in analysis. The primary outcome of this review was frequency of pregnancy related complications including: miscarriage, pre-eclampsia, cesarean section, intra-uterine growth restriction, gestational diabetes, premature rupture of membranes (PPROM), pre-term delivery and stillbirth. The prevalence of these complications was compared between groups and pooled for analysis. Presence of a primary outcome was a prerequisite for consideration of secondary outcomes, including fetal outcomes, disease activity (BASDAI, BASFI, HAQ, ASQoL and BASMI), medication usage (NSAIDs, sDMARD or biologic agents) and breastfeeding.

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 (MID-IRS online) from time of inception to September 2019. Electronic databases 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 completed. Search terms were adapted for use within each database and consisted of common key words and medical headings related to pregnancy, pregnancy outcomes, pregnancy complications, ankylosing spondylitis, and axial spondyloarthritis. No language or date restrictions were placed on the searches. An experienced librarian (DM) conducted the search strategy (Appendix 1 of online supplement).

In cases where only abstracts were available for relevant records, authors were contacted requesting full text manuscripts. Authors were contacted twice, after which the abstract was excluded if no response was received.

Two reviewers (SM and TOD) independently screened titles, abstracts and keywords for potential eligibility. Full texts of potentially eligible studies were retrieved and assessed for inclusion (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. One study was identified during the course of manuscript preparation [10]. Due to the high-quality study design and outcome measures assessed, reviewers selected to include this as grey literature.

Data extraction and analysis

A data extraction template was developed based on Cochrane recommendations [22]. 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. 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 synthesis

For all outcomes included in analyses, 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 Chi² test ($p < 0.1$ indicating significant heterogeneity), and output of the I² statistic ($> 75\%$ indicating significant heterogeneity requiring sensitivity analysis). A weighted pooled means was calculated for primary outcomes.

Risk of bias assessment

Two independent reviewers (SM and FW) performed independent assessment of risk of bias for each of the included studies. The ROB-INS-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 [23]. 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

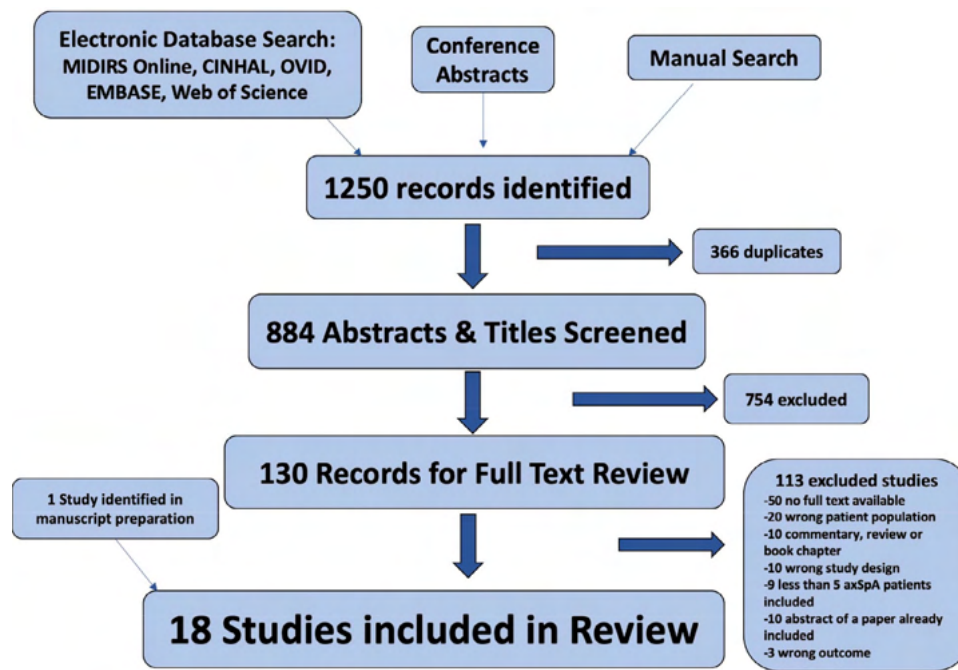


Fig. 1. PRISMA Study Selection.

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.

Results

Study selection

Eighteen studies were selected for inclusion in this review (Fig. 1). These 18 studies, published between 1980 and 2019, present data from thirteen countries; seventeen of the studies were based within a single country, with one study [24] collecting data from 13 countries. Three articles were not published in English and were translated from Icelandic [8], Hungarian [25] and Croatian [26].

Study design & characteristics

Thirteen retrospective studies and five prospective studies were included. Of the retrospective studies, eight included matched controls [7, 8, 10, 18, 25, 27–29]. Of the prospective studies, three studies [30–32] included matched controls (Table 1). There were differences in control groups, with ten studies including healthy controls [7, 8, 10, 27–32] and other studies including control groups with psoriasis [18] and other musculoskeletal diagnosis [25].

Study participants

The number of participants with axSpA in each study varied from 9 [33] to 996 [27] (Table 2). Median number of participants was 63

[IQR 20 – 129]. In total 4881 pregnancies in 3166 females with axSpA were included in the pooled data of this review.

Risk of bias within studies

The risk of bias assessment for all studies is detailed in Table 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 ($p < 0.01$). Funnel plots were constructed for cesarean sections and preterm birth (online supplement: appendix 2). Visual inspection revealed no obvious bias in cesarean sections, but Park et al. was an outlier in PTB which could suggest publication bias.

Primary outcome: pregnancy outcomes in axSpA

Cesarean sections were recorded in 12 studies [7,8,10,24,27,29–35] with 1163 recorded in axSpA pregnancies and 225,299 in controls (Table 4). Moderate heterogeneity was noted between studies ($I^2 = 72\%$, $p = 0.001$). A random effects model was used to calculate a significant overall odds ratio (OR) of 1.85 (95% CI 1.46–2.30) indicating increased prevalence in axSpA pregnancies (Fig. 2). 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 [7, 8, 10, 27, 30] with data on elective and emergency cesarean sections (Fig. 2). Emergency cesarean 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 cesarean sections were recorded in 203 axSpA pregnancies. Low heterogeneity was noted between studies ($I^2 = 37\%$, $p = 0.17$), a random effects model calculated an overall OR of 2.26 (95% CI 1.74–2.93) indicating significant increased prevalence in axSpA pregnancies. Weighted pooled means revealed a prevalence of 16.7% in axSpA pregnancies versus 10.8% in control pregnancies.

Table 1
Study Description.

Authors	Publication	Data Source Period	Country	Study Type	Data Source	Control Population
Retrospective Studies						
Gomor et al. [25]	1980	not stated	Hungary	Cross-sectional	Not stated	Other MSK disorders
Ostensen et al. [34]	1982	1974–1980	Norway	Cross-sectional	Single center	None
Jajic et al. [26]	1995	not stated	Croatia	Cross-sectional	Not stated	None
Ostensen et al. [24]	1998	prior to 1994	Norway & 12 other countries	Cross-sectional	Multi-center	None
Sampaio-Barros et al. [36]	2005	1990–2004	Brazil	Cross-sectional	Single center	None
Lui et al. [18]	2011	prior to 2010	Canada	Cross-sectional	Single center	Females with Psoriasis
Zhou et al. [35]	2012	2004–2011	China	Cross-sectional	Single center	None
Jakobsson et al. [7]	2016	2001–2009	Sweden	Cross-sectional	National Register	Healthy controls
Timur et al. [29]	2016	2007–2015	Turkey	Case control	Single center	Healthy controls
Kristjandottir et al. [8]	2019	1981–2017	Iceland	Cross-sectional	National Register	Healthy controls
Park et al. [27]	2019	1994–2017	Korea	Cross-sectional	Multi-center	Healthy controls
Strouse et al. [28]	2019	2007–2012	USA	Case control	Multi-center	Healthy controls
Mork et al. [10]	2019	1997–2016	Denmark	Cross-sectional	National Register	Healthy controls
Prospective Studies						
Ostensen et al. [32]	1983	1979–1982	Norway	Case control	Single center	Healthy controls
Ostensen et al. [33]	2004	not stated	Switzerland	Cohort	Single center	None
Ursin et al. [9]	2018	2006–2016	Norway	Cohort	National Register	None
Zbinden et al. [30]	2018	2000–2016	Switzerland	Case control	Single center	Healthy controls
Smith et al. [31]	2019	2004–2018	USA	Case control	Multi-center	Healthy controls

Pre-term birth prevalence was documented in 11 studies [7,8,10,24,25,27–31,35], with 172 documented cases in axSpA pregnancies. Very high heterogeneity was noted between studies ($I^2 = 93\%$). For this reason, a sensitivity analysis was performed which demonstrated removal of data from Park et al. resulting in improved homogeneity of data ($I^2 = 34\%$, $p = 0.16$). A random effects model calculated an overall OR of 1.24 (95% CI 0.94–1.64) indicative of a non-significant trend towards increased prevalence in axSpA pregnancies

(online supplement: appendix 3). Weighted pooled means calculation resulted in a weighted mean of 5.5% in axSpA pregnancies and 5.3% in control pregnancies (Fig. 3).

Pre-eclampsia was documented in 7 studies [7, 10, 24, 27, 30, 31, 34] with 4 of the studies controlled. In total 81 pregnancies in the axSpA group were affected. Moderate heterogeneity was noted between studies ($I^2 = 81\%$). A sensitivity analysis demonstrated removal of data from Jakobsson et al. improved homogeneity ($I^2 = 2\%$).

Table 2
Study Participants.

Study	Group; axSpA Classification Criteria	N	Age at Conception, year	Disease Duration, year	Primiparous% (n)	Number of Pregnancies
Retrospective Studies						
Gomor et al. 1980 [25]	axSpA; mNY	65	Not reported	Not reported	Not reported	65
	Control	65	Not reported	N/A	Not reported	65
Ostensen et al. 1982 [34]	axSpA; mNY	50	26.3	7.5	56% (28)	120
Jajic et al. 1995 [26]	axSpA; Amor	20	20	6	Not reported	20
Ostensen et al. 1998 [24]	axSpA; not specified	939	Not reported	Not reported	Not reported	1586
Sampaio-Barros et al. 2005 [36]	axSpA; mNY	40	Not reported	15.5	Not reported	83
Lui et al. 2011 [18]	axSpA; mNY	19	27.5	Not reported	Not reported	35
	Control	33	28.4	N/A	Not reported	77
Zhou et al. 2012 [35]	axSpA; mNY	12	32.6	7.7	91.7% (11)	12
Jakobsson et al. 2016 [7]	axSpA; mNY	301	30–34 ¹	Not reported	Not reported	388
	Control	698	30–34 ¹	N/A	43% (465)	1082
Timur et al. 2016 [29]	axSpA; mNY	20	30.2	6.6	Not reported	20
	Control	40	27	N/A	Not reported	40
Kristjandottir et al. 2019 [8]	axSpA; not specified	60	26–30 ¹	Not reported	Not reported	132
	Control	Not reported	26–30 ¹	N/A	Not reported	3214
Park et al. 2019 [27]	axSpA; mNY	996	32	4.2	57.9% (749)	1293
	Control	Not reported	32	N/A	49.5% (6903)	12,926
Strouse et al. 2019 [28]	axSpA; not specified	128	Not reported	Not reported	Not reported	128
	Control	Not reported	> 34 ¹	N/A	Not reported	10,244
Mork et al. 2019 [10]	axSpA; ASAS	129	30.5	Not reported	Not reported	590
	Control	Not reported	31	N/A	44.6% (526,519)	1195,882
Prospective Studies						
Ostensen et al. 1983 [32]	axSpA; mNY	13	28	7.2	38% (5)	13
	Control	31	26.3	N/A	42% (13)	31
Ostensen et al. 2004 [33]	axSpA; ESSG ²	9	31	9	60% (6)	10
Ursin et al. 2018 [9]	axSpA; ASAS	166	30.6	5.9	92.7% (154)	179
Zbinden et al. 2018 [30]	axSpA; ASAS	70	32	Not reported	64.3% (45)	78
	Control	70	32.3	N/A	61.4% (43)	70
Smith et al. 2019 [31]	axSpA; not specified	129	32.6 ³	6.1	51.2% (66)	129
	Control	Not reported	32.2 ³	N/A	34.4% (247)	717

Abbreviations: axSpA: axial spondyloarthritis; mNY: modified New York criteria; ASAS: Assessment of Spondyloarthritis International Society; N/A -not applicable.

¹ Most common reported age

² European Spondyloarthritis Study Group (ESSG) criteria for AS

³ Age at delivery.

Table 3
Risk of Bias Assessment.

	Selection	Comparability	Outcome	Overall
Retrospective Studies				
Gomor et al. 1980 [25]	Fair	Good	Poor	Poor
Ostensen et al. 1982 [34]	Fair	Good	Fair	Fair
Jajic et al. 1995 [26]	Poor	Poor	Poor	Poor
Ostensen et al. 1998 [24]	Fair	Good	Poor	Poor
Sampaio-Barros et al. 2005 [36]	Fair	Good	Fair	Fair
Lui et al. 2011 [18]	Fair	Good	Poor	Poor
Zhou et al. 2012 [35]	Fair	Good	Fair	Fair
Jakobsson et al. 2016 [7]	Good	Good	Good	Good
Timur et al. 2016 [29]	Good	Good	Good	Good
Kristjandottir et al. 2019 [8]	Good	Good	Good	Good
Park et al. 2019 [27]	Good	Good	Good	Good
Strouse et al. 2019 [28]	Good	Good	Good	Good
Mork et al. 2019 [10]	Good	Good	Good	Good
Prospective Studies				
Ostensen et al. 1983 [32]	Good	Good	Good	Good
Ostensen et al. 2004 [33]	Fair	Good	Good	Fair
Ursin et al. 2018 [9]	Good	Good	Good	Good
Zbinden et al. 2018 [30]	Good	Good	Good	Good
Smith et al. 2019 [31]	Good	Good	Good	Good

A random effects model calculated an overall OR of 1.3 (95% CI 0.92–1.82) indicative of a non-significant trend towards increased prevalence in axSpA pregnancies. Weighted pooled means calculation resulted in a weighted mean of 2.8% in axSpA pregnancies versus 2.5% in control studies.

PPROM was recorded in two studies [30,35] with 78 affected pregnancies in axSpA females, with no control results available for comparison. A weighted pooled means calculation resulted in a weighted mean of 6.7% for axSpA pregnancies.

Miscarriage was recorded in 5 studies [9,24,32,34,36] with 56 total events in axSpA pregnancies. Only one study [32] 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 recorded in the two studies [27,29], with only two axSpA pregnancies affected in total. Heterogeneity was not noted between studies ($I^2 = 0\%$, p value = 0.4). A random effects model was used to calculate an overall OR of 1.17 (95% CI 0.26–5.17), indicating no significant difference in axSpA pregnancies compared to controls. A weighted pooled means calculation showed a weighted means of 4.3% in axSpA compared to 4.7% in controls.

Stillbirth was documented in 5 studies [7,24,30,32,33] of which four were controlled, with six affected axSpA pregnancies and 30 affected control pregnancies. Heterogeneity was low between studies ($I^2 = 0\%$, $p = 0.68$). A random effects model was used to calculate an overall OR of 0.70 (95% CI of 0.26–1.85) 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.

Gestational diabetes was recorded in three studies (27, 30, 31) and affected ten axSpA pregnancies and 51 controls. Heterogeneity was not noted between the studies ($I^2 = 41\%$, $p = 0.18$). A random effects model was used to calculate an overall OR of 0.88 (95% CI 0.24–3.21), indicating no significant difference in incidence between groups. A weighted pooled means showed a weighted mean of 4.3% in axSpA pregnancies and 5.7% in control pregnancies.

Secondary outcomes

Fetal outcomes

Low birth weight (LBW) was documented in eight studies [7,8,24,25,27–29,31] of which seven were controlled. Overall LBW occurred in 94 neonates delivered to axSpA females. Heterogeneity was low between the studies ($I^2 = 34\%$, p value = 0.17) (Table 5). A random effects model was used to calculate an overall OR of 1.47 (95% CI 0.98–2.21) indicating a non-significant trend towards increased prevalence in axSpA pregnancies (Figure 4). Calculation of weighted pooled means equaled 6.3% in axSpA pregnancies and 2.9% in controls.

Congenital abnormalities were documented in five studies [24,27,28,30,34], three of which were controlled. In total this

Table 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
Cesarean Sections	1163	225,299	1.85 (1.46–2.30)	72% (0.008)	37.3	18.6	(7, 8, 10, 24, 27, 29–35)
Total							
Emergency CS ^{1,2}	145	129,407	1.29 (1.06–1.56)	0% (0.58)	11.9	10.8	(7, 8, 10, 27, 30)
Elective CS ^{1,2}	203	90,656	2.26 (1.74–2.93)	37% (0.17)	16.7	7.6	(7, 8, 10, 27, 30)
Preterm birth	172	64,243	0.84 (0.39–1.81)	93% (<0.001)	5.5	5.3	(7, 8, 10, 24, 25, 27–31, 35)
Sensitivity Analysis	154	64,069	1.24 (0.94–1.64)	34% (0.16)	8	5.3	(7, 8, 10, 24, 25, 28–31, 35)
Miscarriage	56	1	0.75 (0.03–19.7)	N/A	3	3.2	(9, 24, 32, 34, 36)
Pre-eclampsia	81	30,606	1.74 (0.85–3.54)	81% (0.001)	2.8	2.5	(7, 10, 24, 27, 30, 31, 34)
Sensitivity Analysis	53	30,589	1.3 (0.92–1.82)	2% (0.36)	2.1	2.5	(10, 24, 27, 30, 31, 34)
Gestational Diabetes	10	51	0.88 (0.34–3.21)	41% (0.18)	4.3	5.7	(27, 30, 31)
IUGR	2	7	1.17 (0.26–5.17)	0% (0.4)	4.3	4.7	(27, 29)
PPROM	78	N/A	N/A	N/A	6.7	N/A	(30, 35)
Stillbirth	6	30	0.7 (0.26–1.85)	0% (0.68)	0.7	1.1	(7, 24, 30, 32, 33)

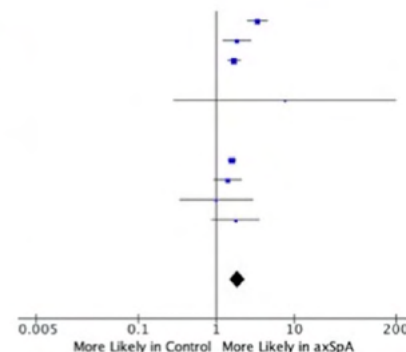
¹ CS: cesarean section.

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.

Total Cesarean Sections

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Jakobsson et al 2016	112	388	117	1082	17.3%	3.35 [2.50, 4.48]
Kristiansdottir et al 2019	31	132	460	3214	13.5%	1.84 [1.21, 2.78]
Mork et al 2019	162	590	219395	1195882	20.9%	1.68 [1.41, 2.02]
Ostensen et al 1982	4	87	0	0		Not estimable
Ostensen et al 1983	1	13	0	31	0.5%	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	22.7%	1.59 [1.41, 1.78]
Smith et al 2019	43	129	188	717	13.8%	1.41 [0.94, 2.10]
Timur et al 2016	11	20	22	40	3.8%	1.00 [0.34, 2.94]
Zbinden et al 2018	31	78	19	70	7.5%	1.77 [0.88, 3.55]
Zhou et al 2012	7	12	0	0		Not estimable
Total (95% CI)		3117		1213962	100.0%	1.83 [1.46, 2.30]
Total events	1163		225299			

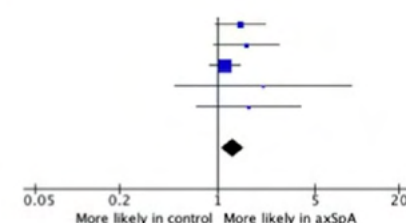
Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 24.82$, $df = 7$ ($P = 0.0008$); $I^2 = 72\%$



Emergency Cesarean Sections

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Jakobsson et al 2016	38	388	75	1082	21.7%	1.46 [0.97, 2.19]
Kristiansdottir 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 Cesarean Sections

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Jakobsson et al 2016	74	388	102	1082	30.8%	2.26 [1.64, 3.13]
Kristiansdottir et al 2019	15	132	205	3214	16.1%	1.88 [1.08, 3.28]
Mork et al 2019	91	590	90334	1195882	41.1%	2.23 [1.78, 2.79]
Park et al 2019	9	27	6	108	4.8%	8.50 [2.70, 26.79]
Zbinden et al 2018	14	78	9	70	7.3%	1.48 [0.60, 3.68]
Total (95% CI)		1215		1200356	100.0%	2.26 [1.74, 2.93]
Total events	203		90656			

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 6.36$, $df = 4$ ($P = 0.17$); $I^2 = 37\%$

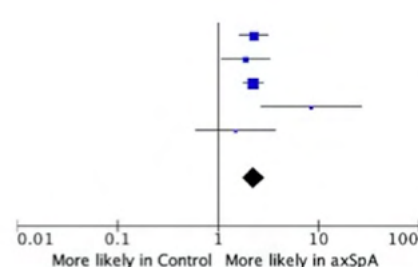


Fig. 2. Analysis of Cesarean Section by type.

occurred in 23 neonates from females with axSpA. Heterogeneity was not noted between the studies ($I^2 = 0\%$, p value = 0.94). A random effects model was used to calculate an overall OR of 1.34 (95% CI 0.63–2.84), 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.

NICU admission prevalence was discussed in two studies [29,31], with 26 neonates requiring neonatal intensive care unit (NICU) admission post-delivery in axSpA pregnancies. Heterogeneity was not found between the studies ($I^2 = 0\%$, p value = 0.86). A random effects model was used to calculate an overall OR of 1.55 (95% CI of 0.96–2.51), indicating a non-significant 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.

Small for gestational age (SGA) was recorded in five controlled studies [7,10,27,28,30] with 106 affected neonates of axSpA females. Moderate heterogeneity was noted between the studies ($I^2 = 72\%$). A random effects model was used to calculate an overall OR of 1.66 (95% CI 0.93–2.95), indicative of a non-significant trend towards increased risk in axSpA pregnancies. A weighted pooled means calculation showed a weighted means of 8.7% in axSpA pregnancies and 11% in control pregnancies.

Disease activity of axSpA

In eight studies [9,18,29–34], pre-defined criteria were used to assess changes in disease activity. In three studies [24,26,35], 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.

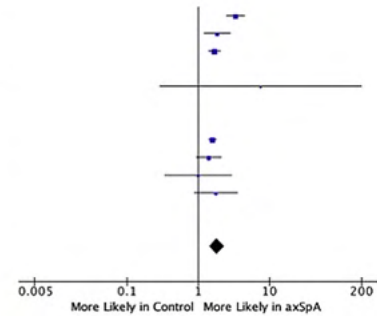
Standardized outcomes. Six of the eleven studies discussing disease activity in pregnancy used standardised outcome measures (Table 6). Outcome measures used (BASDAI [9,33], HAQ [31], ASDAS-CRP [29,30], Roland Morris Questionnaire [18]) are validated and accepted measures for the assessment of individuals with axSpA.

Data on active disease via assessment with standardised outcomes during pregnancy was pooled. Overall, 47.8% of patients (211 of 451) had increased disease activity during pregnancy with three studies [9,30,33] identifying the 2nd trimester as peak of disease activity.

Non-Standardised outcomes. Five [7,9,26,32,35] of the eleven studies used non-standardised outcomes to explore disease activity in pregnancy (Table 6). Four studies [24,26,32,34] used data on patients recorded prior to the early 1990s, during which time a number of standardised outcome measures were developed for axSpA [37,38].

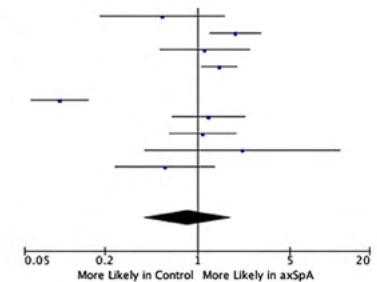
Cesarean Sections

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Jakobsson et al 2016	112	388	117	1082	17.3%	3.35 [2.50, 4.48]
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Mork et al 2019	162	590	219395	1195882	20.9%	1.68 [1.41, 2.02]
Ostensen et al 1982	4	87	0	0		Not estimable
Ostensen et al 1983	1	13	0	31	0.5%	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	22.7%	1.59 [1.41, 1.78]
Smith et al 2019	43	129	188	717	13.8%	1.41 [0.94, 2.10]
Timur et al 2016	11	20	22	40	3.8%	1.00 [0.34, 2.94]
Zbinden et al 2018	31	78	19	70	7.5%	1.77 [0.88, 3.55]
Zhou et al 2012	7	12	0	0		Not estimable
Total (95% CI)		3117		1213962	100.0%	1.83 [1.46, 2.30]
Total events	1163		225299			
Heterogeneity: Tau ² = 0.06; Chi ² = 24.82, df = 7 (P = 0.0008); I ² = 72%						



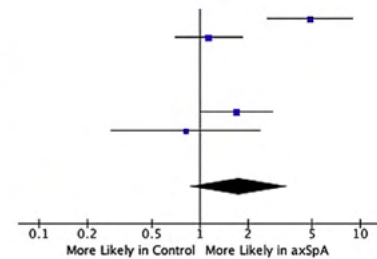
Preterm Birth

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Gomor et al 1980	5	76	13	113	10.1%	0.54 [0.18, 1.59]
Jakobsson et al 2016	35	388	53	1082	12.1%	1.93 [1.24, 3.00]
Kristiansdottir et al 2019	7	132	152	3214	11.2%	1.13 [0.52, 2.46]
Mork et al 2019	44	590	62807	1198882	12.4%	1.46 [1.07, 1.98]
Ostensen et al 1998	25	366	0	0		Not estimable
Park et al 2019	18	1293	174	1296	12.0%	0.09 [0.06, 0.15]
Smith et al 2019	13	129	61	717	11.6%	1.21 [0.64, 2.26]
Strouse et al 2019	13	128	962	10244	11.8%	1.09 [0.61, 1.94]
Timur et al 2016	3	20	3	40	7.8%	2.18 [0.40, 11.92]
Zbinden et al 2018	9	78	18	96	10.9%	0.57 [0.24, 1.34]
Zhou et al 2012	0	12	0	0		Not estimable
Total (95% CI)		3212		1215684	100.0%	0.84 [0.39, 1.81]
Total events	172		64243			
Heterogeneity: Tau ² = 1.23; Chi ² = 119.30, df = 8 (P < 0.00001); I ² = 93%						



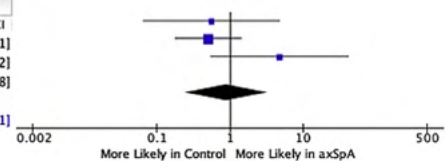
Pre-eclampsia

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Jakobsson et al 2016	28	388	17	1082	25.9%	4.87 [2.64, 9.01]
Mork et al 2019	17	590	30461	1195882	28.0%	1.14 [0.70, 1.84]
Ostensen et al 1982	3	50	0	0		Not estimable
Ostensen et al 1998	10	366	0	0		Not estimable
Park et al 2019	17	1293	101	12926	27.5%	1.69 [1.01, 2.84]
Smith et al 2019	4	129	27	717	18.6%	0.82 [0.28, 2.38]
Zbinden et al 2018	2	70	0	0		Not estimable
Total (95% CI)		2886		1210607	100.0%	1.74 [0.85, 3.54]
Total events	81		30606			
Heterogeneity: Tau ² = 0.41; Chi ² = 15.74, df = 3 (P = 0.001); I ² = 81%						



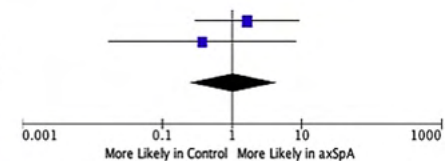
Gestational Diabetes

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Park et al 2019	1	27	7	108	24.7%	0.55 [0.07, 4.71]
Smith et al 2019	4	129	43	717	51.2%	0.50 [0.18, 1.42]
Zbinden et al 2018	5	78	1	70	24.2%	4.73 [0.54, 41.48]
Total (95% CI)		234		895	100.0%	0.88 [0.24, 3.21]
Total events	10		51			
Heterogeneity: Tau ² = 0.56; Chi ² = 3.42, df = 2 (P = 0.18); I ² = 41%						



IUGR

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Park et al 2019	2	27	5	108	52.8%	1.65 [0.30, 8.99]
Timur et al 2016	0	20	2	40	47.2%	0.38 [0.02, 8.20]
Total (95% CI)		47		148	100.0%	1.05 [0.24, 4.49]
Total events	2		7			
Heterogeneity: Chi ² = 0.70, df = 1 (P = 0.40); I ² = 0%						



Stillbirth

Study or Subgroup	axSpA		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Jakobsson et al 2016	1	388	1	1082	12.4%	2.79 [0.17, 44.77]
Ostensen et al 1983	0	13	1	31	8.9%	0.75 [0.03, 19.70]
Ostensen et al 1998	3	366	27	1586	66.4%	0.48 [0.14, 1.58]
Ostensen et al 2004	1	9	0	0		Not estimable
Zbinden et al 2018	1	78	1	96	12.3%	1.23 [0.08, 20.05]
Total (95% CI)		854		2795	100.0%	0.70 [0.26, 1.85]
Total events	6		30			
Heterogeneity: Tau ² = 0.00; Chi ² = 1.53, df = 3 (P = 0.68); I ² = 0%						

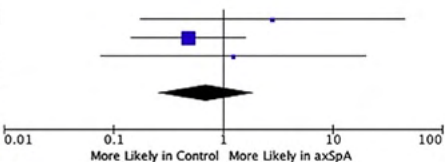
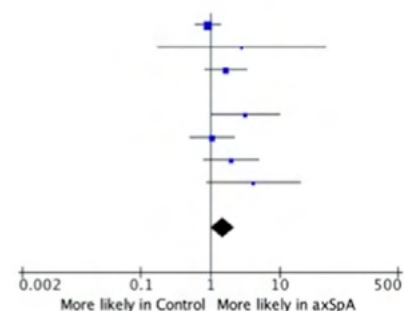


Fig. 3. Pooled Data of Pregnancy Complications.

Low Birth Weight

Study or Subgroup	axSpA Females		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Gomor et al 1980	42	327	61	437	30.6%	0.91 [0.60, 1.39]
Jakobsson et al 2016	1	388	1	1082	2.0%	2.79 [0.17, 44.77]
Kristiansdottir et al 2019	9	132	137	3214	19.4%	1.64 [0.82, 3.30]
Ostensen et al 1998	17	366	0	0		Not estimable
Park et al 2019	6	27	9	108	10.0%	3.14 [1.01, 9.78]
Smith et al 2019	9	129	48	717	18.2%	1.05 [0.50, 2.19]
Strouse et al 2019	5	128	208	10244	13.9%	1.96 [0.79, 4.85]
Timur et al 2016	5	20	3	40	5.9%	4.11 [0.87, 19.41]
Total (95% CI)		1517		15842	100.0%	1.47 [0.98, 2.21]
Total events	94		467			

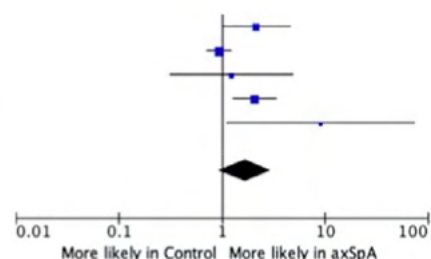
Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 9.10$, $df = 6$ ($P = 0.17$); $I^2 = 34\%$



Small for Gestational Age

Study or Subgroup	axSpA Females		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Jakobsson et al 2016	12	388	16	1082	21.7%	2.13 [1.00, 4.54]
Mork et al 2019	61	590	131596	1195882	32.2%	0.93 [0.72, 1.22]
Park et al 2019	3	27	10	108	11.8%	1.23 [0.31, 4.80]
Strouse et al 2019	21	128	892	10244	28.1%	2.06 [1.28, 3.30]
Zbinden et al 2018	9	78	1	70	6.3%	9.00 [1.11, 72.97]
Total (95% CI)		1211		1207386	100.0%	1.66 [0.93, 2.95]
Total events	106		132515			

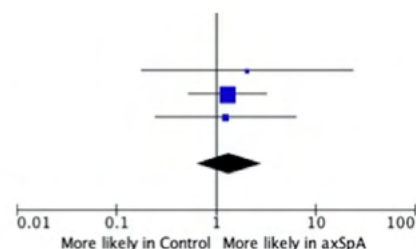
Heterogeneity: $\tau^2 = 0.25$; $\chi^2 = 14.23$, $df = 4$ ($P = 0.007$); $I^2 = 72\%$



Congenital Abnormalities

Study or Subgroup	axSpA Females		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Ostensen et al 1982	3	87	0	0		Not estimable
Ostensen et al 1998	11	366	0	0		Not estimable
Park et al 2019	1	27	2	108	9.5%	2.04 [0.18, 23.35]
Strouse et al 2019	5	128	311	10244	69.3%	1.30 [0.53, 3.20]
Zbinden et al 2018	3	78	3	96	21.2%	1.24 [0.24, 6.32]
Total (95% CI)		686		10448	100.0%	1.34 [0.63, 2.84]
Total events	23		316			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.13$, $df = 2$ ($P = 0.94$); $I^2 = 0\%$



NICU Admissions

Study or Subgroup	axSpA Females		Control		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Smith et al 2019	22	129	85	717	88.8%	1.53 [0.92, 2.55]
Timur et al 2016	4	20	5	40	11.2%	1.75 [0.41, 7.40]
Total (95% CI)		149		757	100.0%	1.55 [0.96, 2.51]
Total events	26		90			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.03$, $df = 1$ ($P = 0.86$); $I^2 = 0\%$

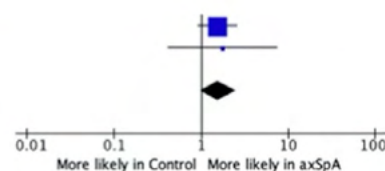


Fig. 4. Pooled data of Fetal Complications.

Table 5
Summary of Fetal Outcomes.

	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	15,842	1.47 (0.98–2.21)	34% (0.17)	6.3	2.9	(7,8,24,25,27–29,31)
SGA	106	132,515	1.66 (0.93–2.95)	72% (0.007)	8.7	11	(7,10,27,28,30)
Congenital abnormalities	23	316	1.34 (0.63–2.84)	0% (0.94)	3.4	3	(24,27,28,30,34)
NICU admissions	26	90	1.55 (0.96–2.51)	0% (0.86)	17.4	11.9	(29,31)

Table 6
Summary of Disease Activity in Pregnancy by Outcome Measure.

Study	Outcome Measure	Findings
Standardised Outcome Measures		
Ostensen et al. 2004 (33)	BASDAI	Pain and stiffness scores peaked in the 2nd trimester Pain and stiffness scores lowest in the 3rd trimester
Lui et al. 2011 (18)	Roland Morris Questionnaire	51% decreased disease activity in pregnancy 26% increased disease activity 23% no change
Timur et al. 2016 (29)	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 (9)	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 (30)	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 (31)	HAQ	34.5% had active disease at study initiation Mean HAQ increased over the course of the pregnancy
Non-standardised Outcome Measures		
Ostensen et al. 1982 (34)	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 (32)	Not reported	Active disease in 61.5% throughout pregnancy 100% of patients flared 4–8 weeks postpartum
Jajic et al. 1995 (26)	Not reported	65% of patients have increased disease activity in pregnancy 35% noted no change in activity during pregnancy
Ostensen et al. 1998 (24)	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 (35)	Not reported	No change in disease activity in 66.7% Aggravation of symptoms throughout pregnancy in 25%

Abbreviations: BASDAI -Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP -Ankylosing Spondylitis Disease Activity Score with C reactive protein; HAQ -Health Assessment Questionnaire.

Table 7
Medication Usage in Pregnancy.

	NSAIDs	sDMARDs	Corticosteroids	anti-TNF	Other
<i>Ostensen et al. 1983 (32)</i>	93%	Not reported	Not reported	Not reported	no tx 7%
<i>Timur et al. 2016 (29)</i>	20%	Not reported	35%	Not reported	Not reported
<i>Ursin et al. 2018 (9)</i>	18/23/8%*	16/13/10%*	6/5/8%*	6/4/1%*	no tx 58/55/69%*
<i>Smith et al. 2019 (31)</i>	24%	7.8%	38%	81.4%	Not reported

Abbreviations: Anti-TNF: anti-tumor 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 (%).

Medication usage in pregnancy

Medication usage was recorded during pregnancy in four studies [9,29,31,32] (Table 7). 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.

Breastfeeding

Breastfeeding was reported in four studies. Rates of breastfeeding showed considerable variation from 0.8% to 50% to 81.3% to 90% (26, 27, 30, 33).

Discussion

This review systematically identified published research on pregnancy outcomes in women with axSpA and, when appropriate, synthesizes data through meta-analysis. 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.

Increased cesarean section rate was the most significant finding within this analysis (OR 1.85), with studies of women with axSpA consistently reporting a higher prevalence of cesarean section than control groups, with weighted pooled means of 37.3% and 18.6% respectively. Women with axSpA are almost twice as likely as pregnant women without axSpA to deliver by cesarean section; both elective and emergency cesarean sections were more common in axSpA pregnancies than in control pregnancies. Variation in clinical guidelines and obstetric practices over time and between countries should be considered when interpreting this information [39,40]. Rates of cesarean section deliveries has increased [41] and current research suggests reasons for this are multifold [42]. The increased rate of elective cesarean section could represent physician concerns regarding vaginal delivery in women with axSpA, or increased preference of women with axSpA for this mode of delivery. However, this review did not uncover any evidence of increased risk of vaginal delivery versus cesarean section in axSpA pregnancies. So why is the prevalence of elective cesarean sections so high in axSpA pregnancies? Further research focusing on indications for cesarean sections in axSpA pregnancies would provide significant insight into this complex issue.

Pregnancy related complications were the primary outcome assessed in this analysis. There was a trend towards increased prevalence of IUGR and pre-eclampsia in axSpA pregnancies as compared to non-axSpA pregnancies. Preterm birth also showed a trend towards increased prevalence in axSpA pregnancies on sensitivity analysis, not overall. Additional studies are needed to confirm these findings. Understanding why these complications may be occurring with greater frequency in axSpA pregnancies will be the next challenge. Stillbirth, gestational diabetes and miscarriage all demonstrated non-significant trends to occur less frequently in axSpA pregnancies. Variations in frequency of pregnancy checks and criteria for both complications between centers and countries must be controlled for before conclusions can be drawn on the effects of axSpA on these outcomes.

Review of fetal outcomes showed low birth weight, 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 [7,31] 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 cesarean section? Or are pregnancy complications such as pre-eclampsia the driving factor in rate of cesarean section which could be associated with low birth weight 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 [20,43]. Studies in axSpA have not shown consistent patterns of disease in pregnancy [6]. Individual study results range from improved disease control in pregnancy [33] especially noted in the first trimester [18], to high risk of flares late in pregnancy [19]. Pooled data of publications using standardized outcomes from this analysis show a high rate (47.8%) of increased disease activity in axSpA, which tends to peak in the second trimester.

Many women 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[4]. Pooled data from this analysis shows significant variation in medication usage in pregnancy, however this was only documented in four [9,29,31,32] studies which represent a 36-year time span in treatment. Advances in treatments beyond NSAIDs, changes in prescribing guidelines, and increased use of medication in pregnancy following development of dedicated pregnancy guidelines, may explain these observed variations.

The WHO states that breastfeeding “is the most effective way to ensure child health and survival” [44]. However, it was documented in only four studies [26,27,30,33] with significant variation in prevalence and no discussion. Reasons for this could be multifold, but further research is needed.

This analysis included a large number of women 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 center 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, with included women 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.

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 axSpA 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 standardized 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.

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.

Clinical impact and further research

Going forward, the results of this analysis could aid in educating and managing women with axSpA planning to conceive. Given the trend towards increased prevalence of certain complication, regular communication between Rheumatology and Obstetrics is essential from conception through to the postpartum period. This would ensure close monitoring of women, rapid recognition of disease activity and increased awareness of concerns from both specialties. 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 cesarean sections in women with axSpA. Further research on indications of these deliveries would better characterize these deliveries and understand why women with axSpA require cesarean section deliveries more frequently. A collaborative effort with Obstetrics would provide valuable insight into this topic.

Conclusion

Women with axSpA have significantly higher prevalence of cesarean sections, than the general population. This analysis suggests a trend towards increased prevalence of pre-eclampsia, IUGR and a number of fetal complications in women with axSpA. 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 women with axSpA, however there are conflicting reports of disease activity throughout the course of pregnancy. As national registries and pregnancy registries continue to develop, larger cohorts could help to better understand the true impact of axSpA on pregnancy outcomes.

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Declaration of Competing Interest

None.

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None

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.semarthrit.2020.08.011](https://doi.org/10.1016/j.semarthrit.2020.08.011).

References

- [1] Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, et al. Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis research and treatment network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol* 2019;71(10):1599–613 2019.
- [2] Joachim Sieper DP. Axial Spondyloarthritis. *Lancet* 2017;390:73–84.
- [3] Lee W, Reveille JD, Weisman MH. Women with ankylosing spondylitis: a review. *Arthritis Rheumatol* 2008;59(3):449–54.
- [4] Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, Marder W, Guyatt G, Ware Branch D, Buyon J, Christopher-Stine L, Crow-Hercher R, Cush J, Druzin M, Kavanaugh A, Laskin CA, Plante L, Salmon J, Simard J, Somers EC, Steen V, Tedeschi SK, Vinet E, White CW, Yazdany J, Barbhuiya M, Bettendorf B, Eudy A, Jayatilake A, Shah AA, Sullivan N, Tarter LL, Talabi MB, Turgunbaev M, Turner A, D'Anci KE. American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol* 2020;67(4):1–28.
- [5] Sammaritano LR, Bermas BL. Management of pregnancy and lactation. *Best Pract Res Clin Rheumatol* 2018;32(6):750–66.
- [6] Giovannopoulou E, Gkasdaris G, Kapetanakis S, Kontomanolis E. Ankylosing spondylitis and pregnancy: a literature review. *Curr Rheumatol Rev* 2017;13(3):162–9.
- [7] Jakobsson GL, Stephansson O, Askling J, Jakobsson LTH. Pregnancy outcomes in patients with ankylosing spondylitis: a nationwide register study. *Ann Rheum Dis* 2016;75(10):1838–42.
- [8] Kristjansdottir SR, Steingrimsdottir T, Grondal G, Bjarnadottir RI, Einarsdottir K, Gudbjornsson B, et al. Pregnancy outcomes in Icelandic female patients with inflammatory arthritides. Nationwide results from the ICEBIO and the Icelandic Medical Birth Register. *Laeknabladid* 2019;105(6):267–75.
- [9] Ursin K, Lydersen S, Skomsvoll JF, Wallenius M. Disease activity during and after pregnancy in women with axial spondyloarthritis: a prospective multicentre study. *Rheumatology* 2018;57(6):1064–71.
- [10] Mork S, Voss A, Moller S, Bliddal M. Spondyloarthritis and outcomes in pregnancy and labor: a nationwide register-based cohort study. *Arthritis Care Res (Hoboken)* 2019.
- [11] Lawn JE, Blencowe H, Waiswa P, Amouzou A, Mathers C, Hogan D, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016;387(10018):587–603.
- [12] Dugas C, Slane VH. Miscarriage. StatPearls. Treasure IslandFL: StatPearls Publishing; 2020 Copyright ©StatPearls Publishing LLC.; 2020.
- [13] Sung S, Mahdy H. Cesarean Section. StatPearls. Treasure IslandFL: StatPearls Publishing; 2020 Copyright ©StatPearls Publishing LLC.; 2020.
- [14] National Guideline A. National Institute for Health and Care Excellence: clinical guidelines. Hypertension in pregnancy: diagnosis and management. LondonUK: National Institute for Health and Care Excellence; 2019 Copyright © NICE2019.
- [15] Hughes MM, Black RE, Katz J. 2500-g low birth weight cutoff: history and implications for future research and policy. *Matern Child Health J* 2017;21(2):283–9.
- [16] Hong YH, Chung S. Small for gestational age and obesity related comorbidities. *Ann Pediatr Endocrinol Metab* 2018;23(1):4–8.
- [17] DeSilva M, Munoz FM, McMillan M, Kawai AT, Marshall H, Macartney KK, et al. Congenital anomalies: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2016;34(49):6015–26.
- [18] Lui NL, Haroon N, Carty A, Shen H, Cook RJ, Shanmugarajah S, et al. Effect of pregnancy on ankylosing spondylitis: a case-control study. *J Rheumatol* 2011;38(11):2442–4.
- [19] van den Brandt S, Zbinden A, Baeten D, Villiger PM, Ostensen M, Forger F. Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. *Arthritis Res Ther* 2017;19.
- [20] Jethwa H, Lam S, Smith C, Giles I. Does rheumatoid arthritis really improve during pregnancy? A systematic review and metaanalysis. *J Rheumatol* 2019;46(3):245–50.
- [21] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.
- [22] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from: www.training.cochrane.org/handbook.
- [23] Wells GSB., O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed February 2020.
- [24] Ostensen M, Ostensen H. Ankylosing spondylitis—the female aspect. *J Rheumatol* 1998;25(1):120–4.
- [25] Gomor B, Izsak J. Epidemiological characteristics of ankylosing spondylitis. *Magyar Reumatologia* 1980;21(4):199–206.
- [26] Jajić Z, Jajić I, Bilić A. The effect of pregnancy on the course of ankylosing spondylitis. *Reumatizam* 1995;42(1):11–4.
- [27] Park EH, Lee SL, Kim YJ, Lee SM, Jun JK, Lee EB, et al. Pregnancy outcomes in Korean women with ankylosing spondylitis. *Korean J Internal Med* 2019;922–3.
- [28] Strouse J, Donovan BM, Fatima M, Fernandez-Ruiz R, Baer RJ, Nidey N, et al. Impact of autoimmune rheumatic diseases on birth outcomes: a population-based study. *RMD Open* 2019;5(1).
- [29] Timur H, Tokmak A, Turkmen GG, Inal HA, Uygur D, Danisman N. Pregnancy outcome in patients with ankylosing spondylitis. *J Mater-Fetal Neonat Med* 2016;29(15):2469–73.
- [30] Zbinden A, van den Brandt S, Ostensen M, Villiger PM, Forger F. Risk for adverse pregnancy outcome in axial spondyloarthritis and rheumatoid arthritis: disease activity matters. *Rheumatology* 2018;57(7):1235–42.
- [31] Smith CJF, Bandoli G, Kavanaugh A, Chambers CD. Birth outcomes and disease activity during pregnancy in a prospective cohort of women with psoriatic arthritis and ankylosing spondylitis. *Arthritis Care Res (Hoboken)* 2020;72(7):1029–37.
- [32] Ostensen M, Husby G. A prospective clinical study of the effect of pregnancy on rheumatoid arthritis and ankylosing spondylitis. *Arthritis Rheum* 1983;26(9):1155–9.
- [33] Ostensen M, Fuhrer L, Mathieu R, Seitz M, Villiger PM. A prospective study of pregnant patients with rheumatoid arthritis and ankylosing spondylitis using validated clinical instruments. *Ann Rheum Dis* 2004;63(10):1212–7.
- [34] Ostensen M, Romberg O, Husby G. Ankylosing spondylitis and motherhood. *Arthritis Rheum* 1982;25(2):140–3.
- [35] Zhou Q, Bian XM, Liu JT. Management of pregnancy with ankylosing spondylitis. *Chin Med Sci J* 2012;27(1):46–9.
- [36] Sampaio-Barros PD, Barros Bértolo M, Muhib Samara A. Pregnancy profile in ankylosing spondylitis. *Rev Bras Reumatol* 2005;45(3):103–6.
- [37] Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index. *J Rheumatol* 1994;21(12):2286–91.
- [38] Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care Res (Hoboken)* 2011;63:S47–58 Suppl 11.
- [39] Thuillier C, Roy S, Peyronnet V, Quibel T, Nlandu A, Rozenberg P. Impact of recommended changes in labor management for prevention of the primary cesarean delivery. *Am J Obstet Gynecol* 2018;218(3):341. e1–e9.
- [40] Mylonas I, Friesse K. Indications for and risks of elective cesarean section. *Dtsch Arztebl Int* 2015;112(29–30):489–95.
- [41] Declercq E, Menacker F, Macdorman M. Maternal risk profiles and the primary cesarean rate in the United States, 1991–2002. *Am J Public Health* 2006;96(5):867–72.
- [42] Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. *Obstet Gynecol* 2011;118(1):29–38.
- [43] Ursin K, Lydersen S, Skomsvoll JF, Wallenius M. Psoriatic arthritis disease activity during and after pregnancy: a prospective multicenter study. *Arthritis Care Res* 2019;71(8):1092–100.
- [44] WHO. Guidelines Approved by the Guidelines Review Committee. Guideline: protecting. Promoting and supporting breastfeeding in facilities providing maternity and newborn services. Geneva: World Health Organization; 2017 Copyright World Health Organization 2017.

Management of Pregnancy in Rheumatic Disease

**EDITOR'S
PICK**

The Editor's Pick is the review paper by Maguire et al. Managing patients with rheumatic musculoskeletal disorders (RMD) during pregnancy and the postpartum period is challenging. Disease activity in some RMDs, such as rheumatoid arthritis, improve during the course of pregnancy and in others, such as systemic lupus erythematosus, it worsens. Then there is the issue of drug treatment during pregnancy to maintain remission and the potential undesirable effects on the fetus. This complex subject area is reviewed as well as the current American College of Rheumatology (ACR) guidelines on pregnancy and RMDs.

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Abstract

Managing patients with rheumatic diseases (RMD) during pregnancy and the postpartum period can be a challenge for both rheumatologists and obstetricians. While disease activity during the course of pregnancy varies with regard to the presence of underlying conditions, 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 a successful conception while decreasing the risk of flares during pregnancy. For this reason, discussion of pregnancy in females with RMDs should begin prior to conception with risk stratification and pregnancy planning. This allows for the 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 the risk to the pregnancy. Systemic lupus erythematosus and axial spondyloarthritis can present diagnostic dilemmas due to overlap of symptoms of disease activity and normal pregnancy. Patients with end-organ involvement, such as systemic lupus erythematosus or systemic sclerosis, face a higher risk of adverse pregnancy outcomes and disease progression. Close monitoring of patients with RMD should be done by both obstetrics and rheumatology, with regular communication between specialties. Medications should be reviewed at each stage of pregnancy to ensure compliance with the current American College of Rheumatology (ACR) guidelines and the adequate treatment of RMDs.

INTRODUCTION

Many patients with rheumatic diseases (RMD) are diagnosed during their childbearing years.¹ Historically, females with RMDs were advised to avoid pregnancy due to potential risk to both mother and fetus.² Because of advances in detection of disease activity and therapeutics, this is no longer the case and most females with RMDs can safely become pregnant;³ however, they may face an increased risk of a number pregnancy-related complications and require closer monitoring during their pregnancy.⁴

Pregnancy with RMD should involve a period of planning between the patient and rheumatologist prior to actively trying to conceive.^{5,6} The primary objective in managing a 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 1).⁷ Pregnancy planning to risk assess and address these issues allows the rheumatologist to help their patients safely navigate both the pregnancy and postpartum period.

During pregnancy, the female body undergoes a series of significant physiological and

hormonal changes, which can affect disease activity.⁸ During pregnancy, these patients can pose a challenge to rheumatologists as flares can be confused with complications or physiological changes of pregnancy. Advances in understanding of the 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.^{9,10} A number of disease activity scores have been modified for use in pregnancy; however, most are focused around rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), with a considerable paucity of tools for other RMDs.¹¹ For this reason, close monitoring by both rheumatology and obstetrics is necessary during the course of pregnancy.

SEARCH STRATEGY

For this review, PubMed, Cochrane, and EMBASE were searched for articles related to pregnancy in RMD, with more specific searches for each RMD.¹² Preference was given to more recently published literature to reflect most recent research. Bibliographies of included articles were also searched for additional sources.

Table 1: Factors of rheumatic diseases involved in pregnancy outcome.

Positive impact	Negative impact
Pregnancy planning and counselling	Active diseases§
Disease remission*	End-organ damage:
Known autoantibody status	• Lupus nephritis • Pulmonary hypertension • Restrictive lung disease
Medication adherence	Unplanned pregnancy
Use of pregnancy-safe medications†	Unplanned cessation of treatment**
Close monitoring of disease activity‡	
Optimisation of general health	

*Remission of disease for at least 6 months prior to conception and throughout pregnancy.

†Adjusted for each stage of pregnancy.

‡With outcome measures adjusted for pregnancy where possible.

§Both prior to conception and during pregnancy.

**Without consultation with a rheumatologist due to risk of disease activity.

PRIOR TO CONCEPTION

Counselling and Planning

For females 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 cannot be understated. Lack of pregnancy planning in the general population has been associated with increased incidence of low birth weight and even neonatal mortality.^{13,14} Unplanned pregnancies are also associated with increased rates of smoking, stress, and lack of prenatal care.¹⁵ 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.¹⁶

This issue is correctable with improved patient education and increased physician-led discussion of family planning during rheumatology consultations.¹⁷ Barriers to these conversations discussed in a SLE focus group include busy clinic schedules and difficulty initiating pregnancy conversations.¹⁸ 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.

Disease Control

Control of maternal disease during pregnancy is associated with improved pregnancy outcomes and lower risk of fetal complications.^{5,9} The importance of disease control begins in the pre-conception stage, as females with active disease are advised to wait for remission prior to actively trying to conceive.^{6,7} Patients planning for pregnancy should be in remission for at least 6 months prior to conception.¹⁰ Patients with significant end-organ damage should be counselled on their risk stratification prior to conception.¹⁹ In cases of severe disease, including advanced pulmonary arterial hypertension (PAH), chronic renal impairment Stage IV/V, or in cardiac failure, there is considerable risk of maternal morbidity and mortality. In such cases, individuals should be advised against pregnancy (Table 2).^{10,17,20}

Table 2: Relative and absolute contraindications to pregnancy in patients with rheumatic diseases.^{12,19,21}

Relative contraindications	Absolute contraindications
Severe SLE flare within the past 6 months*	Advanced pulmonary hypertension
Stroke in the past 6 months	End-stage renal disease
Pulmonary hypertension	Severe cardiac failure
Severe restrictive lung disease	
Moderate to severe cardiac failure	
Severe valvular disease	
CKD stage 4-5	
Uncontrolled hypertension	
Previous early-onset pre-eclampsia or HELLP†	

*Including renal flare.

†Despite therapy with aspirin and heparin.

CKD: chronic kidney disease; HELLP: haemolysis, elevated liver enzymes, and low platelets.

Table 3: Summary of the American College of Rheumatology (ACR) guidelines on medication for rheumatic disease usage during conception, pregnancy, and lactation.⁹

Conception			
Safe to continue	Conditionally recommend to continue	Stop prior to conception	Unknown
Hydroxychloroquine Sulfasalazine Colchicine Azathioprine Certolizumab pegol Cyclosporine Tacrolimus	Prednisolone ^a Cyclosporine NSAIDs Infliximab Etanercept Adalimumab Golimumab Rituximab ^b Anakinra ^b Belimumab ^b Abatacept ^b Tocilizumab ^b Secukinumab ^b Ustekinumab ^b	Methotrexate Leflunomide Mycophenolate mofetil Cyclophosphamide Thalidomide	Tofacitinib Apremilast Baricitinib
Pregnancy			
Safe to continue	Conditionally recommend to continue	Stop prior to conception	Unknown
Hydroxychloroquine Sulfasalazine Colchicine Azathioprine Certolizumab pegol Cyclosporine Tacrolimus	Prednisolone ^a Cyclosporine NSAIDs ^c Infliximab ^d Etanercept ^d Adalimumab ^d Golimumab ^d Cyclophosphamide ^e Rituximab ^f	Methotrexate Leflunomide Mycophenolate mofetil Thalidomide Anakinra ^g Belimumab ^g Abatacept ^g Tocilizumab ^g Secukinumab ^g Ustekinumab ^g	Tofacitinib Apremilast Baricitinib
Lactation			
Hydroxychloroquine Sulfasalazine Colchicine Certolizumab pegol Infliximab Etanercept Adalimumab Golimumab Rituximab	Azathioprine ^h Prednisolone ⁱ Cyclosporine ^h Tacrolimus ^h NSAIDs ^j Anakinra ^k Belimumab ^k Abatacept ^k Tocilizumab ^k Secukinumab ^k Ustekinumab ^k	Methotrexate ^l Leflunomide Mycophenolate mofetil Cyclophosphamide Thalidomide	Tofacitinib ^m Apremilast ^m Baricitinib ^m

^aMinimise dose to <20 mg/day with use of alternative pregnancy-compatible immunosuppressant.

^bDiscontinue at conception.

^cAvoid after 32 weeks to prevent premature closure of PDA.

^dDiscontinue in the third trimester several half-lives prior to delivery.

^eOnly to be used in life- or organ-threatening disease, in the second or third trimester only.

^fLife- or organ-threatening disease only.

^fLife- or organ-threatening disease only.

^gConditionally recommend to discontinue in pregnancy.

^hLow transfer in breastmilk.

ⁱIn doses >20 mg, breastfeeding should be delayed by 4 hours following consumption.

^jPreferably use ibuprofen when needed.

^kNo data currently available but due to large size of molecule, minimal transfer in breastmilk anticipated.

^lLimited data available, which suggests low transfer in breastmilk.

^mNo data available but small size of molecule suggests transfer into breastmilk likely.

NSAIDs: Non-steroidal anti-inflammatory drugs; PDA: patent ductus arteriosus.

Medication

One of the main causes of patient and physician concern during pregnancy is around medication usage. Certain medications used to treat RMDs are not safe in pregnancy;²² however, this is not true for all medications as outlined by the American College of Rheumatology (ACR) guidelines (Table 3).⁷ Despite this, many females with RMDs stop their RMD medication prior to conception or in the early stages of pregnancy.²³ 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-RMD medication is restarted.²¹ 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 could also be an opportunity to ensure that the patient has commenced a prenatal vitamin. Females on folic acid antagonists including sulfasalazine will require higher doses of folic acid of 5 mg/day when trying to conceive through to the completion of the first trimester to decrease risk of neural tube defects.²⁴

Many people with RMDs are treated with medications that are not compatible with pregnancy or have limited data for use in pregnancy.²² For these patients, a period of transition to pregnancy-safe medications should take place prior to conception. It is important to remind those taking medications such as methotrexate and mycophenolate mofetil that these medications are not safe in pregnancy and to remind of the importance of using reliable contraception.

Autoantibody Status

Assessment for the presence of autoantibodies such as anti-Ro/SS-A, anti-La/SS-B, and 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 females during pregnancy with hydroxychloroquine significantly reduces this risk.²⁵

Patients with SLE, history of recurrent miscarriage, or other severe pregnancy outcomes should be evaluated for presence of antiphospholipid antibodies (aPL).²⁰ This includes screening for β -2 glycoprotein 1, lupus anticoagulant, and anti-cardiolipin antibodies. Use of low-dose aspirin is recommended for patients with aPL to decrease risk of pre-eclampsia in pregnancy.²⁶ 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.^{7,27}

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 effect on disease activity in RMD. Monitoring for signs of active disease is an essential component of care for the patient who is pregnant with RMD; however, accuracy of conventional tools to detect active disease can be limited by physiologic changes of pregnancy. An article outlining these challenges highlighted that a number of instruments have

been developed to more accurately assess disease activity in RMD pregnancies.¹¹

While there are no specific guidelines for how often these patients should be seen by a rheumatologist during pregnancy, clinical assessment once per trimester allows 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 patients with RMD who are pregnant and regular communication between obstetrics and rheumatology can help to safely manage these challenging cases.

Systemic Lupus Erythematosus

Pregnancy in SLE is commonly encountered as this disease has a strong female predominance, with many diagnosed during their childbearing years. SLE can be difficult to monitor and manage due to the multi-organ involvement of autoimmune disease. This is further complicated by physiological changes of pregnancy, which can mimic disease activity, such as observed increases in erythrocyte sedimentation rate²⁸ or development of thrombocytopenia.²⁹ Other common pregnancy issues, including fatigue and proteinuria, can also be signs of active disease and confuse measures of disease monitoring. However, pregnancy has not been shown to affect presence of autoantibodies.

Disease activity is the most important predictor of pregnancy outcome in SLE, with 23.5% of patients experiencing active disease during pregnancy.³⁰ Pattern of organ involvement prior to conception accurately predicts organ involvement in pregnancy flares and can be helpful for targeted monitoring of disease activity.³¹ There are a number of SLE scores that have been adapted for pregnancy including SLE Pregnancy Disease Activity Index (SLEPDAI),³² Systemic Lupus Activity Measure (SLAM)-Revised, Lupus Activity Index in Pregnancy (LAI-P),³³ and the British Isles Lupus Assessment Group (BILAG) 2004 for pregnancy.³⁴

Patients with lupus nephritis or renal impairment have an increased risk of further renal deterioration and adverse pregnancy outcomes.³⁵ This risk remains even in patients with previous lupus nephritis in remission at the time

of conception.⁴ Patients should be assessed for presence of hypertension, proteinuria, and raised serum creatinine >100 µmol/L routinely because of association with increased risk of adverse outcomes.³⁶ Risk for renal flare during pregnancy is associated with active renal disease at the time of conception, with a relative risk of 9.0 in cases of non-remission and a relative risk of 3.0 in partial remission.³⁷ To reduce risk of flare, disease activity should be controlled throughout pregnancy. This involves use of immunosuppressive medication, adequate blood pressure control, and use of low-dose aspirin to decrease risk of pre-eclampsia.³⁸ 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 patients with no previous history of connective tissue disease. Such cases have higher rates of thrombocytopenia, pregnancy loss, and active disease in pregnancy as compared to those with a previous diagnosis.³⁹ Higher rates of adverse maternal complications have also been seen in this population.⁴⁰ Prompt recognition and treatment is critical but can be a challenge due to the overlap of symptoms with that of normal pregnancy. Monitoring levels of complement and anti-double-stranded DNA antibodies can identify new-onset SLE in a patient who is pregnant. Certain clinical features, such as onset of renal impairment and hypertension prior to 20 weeks' gestation, are suggestive of SLE rather than pre-eclampsia.¹⁷

Autoantibody status is crucial for management of SLE pregnancies. In patients with SLE who have not had antibody status assessed prior to conception, this should be done as soon as possible in pregnancy along with an ECG. In cases of corrected QT prolongation or previous history of cardiac involvement, a baseline echocardiogram is useful to assess cardiac function. Females known to have anti-Ro or anti-La antibodies should be commenced on hydroxychloroquine to decrease risk of congenital heart block and neonatal lupus.⁴¹ 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.⁴² Presence of anti-Ro antibodies will require serial fetal echocardiograms from Weeks 16–26 as per ACR guidelines.⁷

Pregnancy is a naturally prothrombotic event, requiring evaluation of need for additional anti-coagulation during this period. All patients with SLE should be screened for 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.⁴³ Positive aPL with no previous history can be managed with low-dose aspirin alone and close monitoring due to increased risk of pre-eclampsia.⁷

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. 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 Ig (IVIG) due to limited evidence of benefit;⁷ however, it has been previously deemed compatible with all stages of pregnancy including breastfeeding.²¹ The European League Against Rheumatism (EULAR) guidelines also recommend consideration of IVIG in cases of severe refractory maternal disease in pregnancy.⁴⁴ Belimumab is the first biologic agent approved for use in the treatment of SLE, but unfortunately pregnancy data is not yet available to comment on its safety.

Rheumatoid Arthritis

Research in RA has demonstrated that the inflammatory arthritis commonly goes into remission during the course of pregnancy.⁴⁵ A recent meta-analysis reported improved disease activity in 60% of individuals during pregnancy, with 46.7% developing a flare in the postpartum period.⁴⁶ This is driven by a series of modifications of the maternal immune system, including downregulation of effector T-cell activity with an increase in regulatory T cells, to allow placentation and fetal growth.⁴⁷ Following delivery, these immunomodulatory effects dissipate with the decrease of pregnancy hormones, resulting in postpartum flares.

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,²⁸ fatigue, weight gain, and anaemia can all affect commonly used indexes such as the Disease Activity Score in 28 joints (DAS28) and Health Assessment Questionnaire (HAQ).⁴⁸ However, the DAS28-C-reactive protein 3, which excludes the global health score, has been shown to be the best clinical metric to detect active disease in patients with RA who are pregnant.⁴⁹ Ongoing research has shown that additional indices also perform well in this population, including the Rheumatoid Arthritis Disease Activity Index (RADAI) and the Clinical Disease Activity Index (CDAI).⁵⁰

Risk of flare during pregnancy is commonly associated with medication cessation and active disease prior to conception.²³ There is no clear consensus on antibody presence and risk of flare in pregnancy. The Dutch Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) study demonstrated a decreased risk of flare in people with RA who were pregnant and who did not carry autoantibodies.⁵¹ However, a smaller study showed females with RA with active disease in pregnancy had higher levels of anti-citrullinated protein antibodies compared to those with lower disease activity.⁵² Further studies are needed to characterise the relationship between RA antibodies and risk of flare in pregnancy.

Flare in RA 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 treatment or had not been on treatment, discussion of treatment initiation with a pregnancy-safe medication ([Table 1](#)) is required.⁷

Spondyloarthropathy

Spondyloarthropathy (SpA) includes both axial SpA and psoriatic arthritis. Unfortunately, research on pregnancy in SpA is not as abundant as other RMDs. Research in axial SpA has revealed 47.8% of patients experience active disease in pregnancy,⁵³ with a peak in disease activity in the second trimester. Studies in psoriatic arthritis report quiescent disease during pregnancy with increased disease activity 6 months postpartum.⁵⁴ Similar to other RMDs, 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.⁵⁵ 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 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 focus on improving data collection on people with RMDs who are pregnant.⁵⁶ 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 are used to treat flares in SpA; however, these should be avoided beyond 32 weeks due to risk of premature closure of the ductus arteriosus.⁵⁷ Biologics such as 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 pegol, which can continue into the postpartum period.⁷

Systemic Sclerosis

Pregnancy in systemic sclerosis is uncommon as onset is typically after childbearing years. The primary concern in pregnancy is presence of PAH, which is the leading cause of maternal mortality.⁵⁸ Those considering pregnancy should be evaluated for PAH as part of monitoring and counselled when considering pregnancy. In cases of established PAH, patients should be strongly advised against pregnancy.⁵⁹ Patients with systemic sclerosis who achieve pregnancy have a higher prevalence of adverse pregnancy outcomes (odds ratio [OR]: 1.9 for miscarriage; 3.8 for low birth weight; 2.4 for preterm birth). However, optimisation of disease control prior to conception decreases this risk,⁶⁰ although progression of disease during pregnancy was observed in 14.3%. Close monitoring in specialist centres with support from obstetrics, rheumatology, and respiratory can aid in optimising outcomes.

Although now uncommon due to angiotensin-converting enzyme (ACE) inhibitors, there is a risk of scleroderma renal crisis in pregnancy. To avoid this, ACE inhibitors should be continued during pregnancy.⁶¹ Prior to conception, a trial period on an alternative antihypertensive agent could be considered to optimise blood pressure control. In cases of hypertension, despite alternative medication, ACE inhibitors should be restarted. Low-molecular-weight heparin can reduce thrombotic risk, while sildenafil and epoprostenol are additional therapeutic options in pregnancy.⁶² In cases of disease acceleration or rapid progression during pregnancy, additional life-saving therapies need to be considered, including preterm labour induction to allow use of additional medications not compatible with pregnancy.

Vasculitis

There are limited data on pregnancy in vasculitis because age of onset is typically beyond childbearing years, with a male predominance in most types of vasculitis. Disease activity in pregnancy varies by diagnosis, but all females 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;⁶³ however, improved disease control prior to conception can improve outcomes.⁶⁴

Patients with a new diagnosis or active disease prior to pregnancy are at higher risk of flares during pregnancy. Transitioning to pregnancy-safe treatment is essential to ensure stable disease during pregnancy. This is especially important as flares in eosinophilic granulomatosis with polyangiitis and microscopic polyangiitis can have high fatality rates.⁶⁵ 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 because of associations with adverse pregnancy outcomes, with increased reliance on low-risk medications including azathioprine and TNF inhibitors.⁶⁴

Inflammatory Myopathies

The most common types of inflammatory myopathies are polymyositis and dermatomyositis. One study reported that 4–11% of females with these diseases had an onset age between 25 and 34 years.⁶⁶ Pregnancy complications in this population were associated with active disease during pregnancy (OR: 435.4) and onset of disease prior to pregnancy (OR: 9.36).⁶⁷ Relative risk of obstetric and fetal complications was 7.6 and 2.7, respectively, and were noted to occur more frequently following disease onset.⁶⁸ Hypertensive disorders in pregnancy have also been found to occur more commonly (OR: 2.90).⁶⁹ One analysis reported remission of disease during pregnancy, with active disease observed in 12.5%, but with notably 56.2% reporting postpartum flares.⁷⁰ Treatment in pregnancy is with IVIG and azathioprine, with limited use of glucocorticoids.⁷¹

POSTPARTUM

During the postpartum period, the mother's body again undergoes significant hormonal and physiological transitions as it recovers from the birth while adapting to breastfeeding.

This is compounded by the physical strain and sleep deprivation that comes with caring for a new infant. All of these factors can contribute to risk of postpartum flare. To minimise this risk, prompt re-evaluation of therapy is required.

A EULAR consensus statement in 2016 encouraged decisions on medication use during the postpartum period to maximise maternal benefit while minimising infant exposure.⁴⁴ The 2020 ACR guidelines includes a section on postpartum use and lactation,⁷ highlighting the range of therapeutic options that can be safely offered to those breastfeeding to optimise disease control (Table 3).

CONCLUSION

Risk stratification and pregnancy planning are key to ensuring individuals with RMD 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 that 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.

References

1. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev.* 2003;2(3):119–25.
2. Tincani A et al. Autoimmune diseases and pregnancy. *Best Pract Res Clin Endocrinol Metab.* 2019;33(6):101322.
3. Tincani A et al. Pregnancy in patients with autoimmune disease: a reality in 2016. *Autoimmun Rev.* 2016;15(10):975–7.
4. Bramham K et al. Pregnancy and renal outcomes in lupus nephritis: an update and guide to management. *Lupus.* 2012;21(12):1271–83.
5. Andreoli L et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis.* 2017;76(3):476–85.

6. Østensen M. Preconception counseling. *Rheum Dis Clin North Am*. 2017;43(2):189-99.
7. Sammaritano LR et al. 2020 American college of rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol*. 2020;72(4):529-56.
8. Somers EC. Pregnancy and autoimmune diseases. *Best Pract Res Clin Obstet Gynaecol*. 2020;64:3-10.
9. Clowse ME et al. The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum*. 2005;52(2):514-21.
10. Soh MC, Nelson-Piercy C. High-risk pregnancy and the rheumatologist. *Rheumatology (Oxford)*. 2015;54(4):572-87.
11. Andreoli L et al. Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies. *Autoimmun Rev*. 2019;18(2):164-76.
12. Sampson M et al. An evidence-based practice guideline for the peer review of electronic search strategies. *J Clin Epidemiol*. 2009;62(9):944-52.
13. Hall JA et al. Pregnancy intention and pregnancy outcome: systematic review and meta-analysis. *Matern Child Health J*. 2017;21(3):670-4.
14. Bearak J et al. Global, regional, and subregional trends in unintended pregnancy and its outcomes from 1990 to 2014: estimates from a Bayesian hierarchical model. *Lancet Glob Health*. 2018;6(4):e380-9.
15. Goossens J et al. The prevalence of unplanned pregnancy ending in birth, associated factors, and health outcomes. *Hum Reprod*. 2016;31(12):2821-33.
16. Rajendran AEA et al. The importance of pregnancy planning in lupus pregnancies [abstract]. *Arthritis & Rheumatology*. 2020;72.
17. Knight CL, Nelson-Piercy C. Management of systemic lupus erythematosus during pregnancy: challenges and solutions. *Open Access Rheumatol*. 2017;9:37-53.
18. Clowse MEB et al. Provider perceptions on the management of lupus during pregnancy: barriers to improved care. *Lupus*. 2019;28(1):86-93.
19. Nahal SK et al. Safety issues and recommendations for successful pregnancy outcome in systemic lupus erythematosus. *J Autoimmun*. 2018;93:16-23.
20. Sammaritano LR. Contraception and preconception counseling in women with autoimmune disease. *Best Pract Res Clin Obstet Gynaecol*. 2020;64:11-23.
21. van den Brandt S et al. Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. *Arthritis Res Ther*. 2017;19(1):64.
22. Flint J et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology (Oxford)*. 2016;55(9):1693-7.
23. Desai RJ et al. Brief report: patterns and secular trends in use of immunomodulatory agents during pregnancy in women with rheumatic conditions. *Arthritis Rheumatol*. 2016;68(5):1183-9.
24. Hernández-Díaz S et al. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol*. 2001;153(10):961-8.
25. Izmirly PM et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro-antibody-associated cardiac manifestations of neonatal lupus. *Circulation*. 2012;126(1):76-82.
26. Tektonidou MG et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. *Ann Rheum Dis*. 2019;78(10):1296-304.
27. Schreiber K, Hunt BJ. Managing antiphospholipid syndrome in pregnancy. *Thromb Res*. 2019;181(Suppl 1):S41-6.
28. van den Broe NR, Letsky EA. Pregnancy and the erythrocyte sedimentation rate. *BJog*. 2001;108(11):1164-7.
29. Cines DB, Levine LD. Thrombocytopenia in pregnancy. *Blood*. 2017;130(21):2271-7.
30. Pastore DEA et al. Systemic lupus erythematosus and pregnancy: the challenge of improving antenatal care and outcomes. *Lupus*. 2019;28(12):1417-26.
31. Tedeschi SK et al. Specific systemic lupus erythematosus disease manifestations in the six months prior to conception are associated with similar disease manifestations during pregnancy. *Lupus*. 2015;24(12):1283-92.
32. Buyon JP et al. Assessing disease activity in SLE patients during pregnancy. *Lupus*. 1999;8(8):677-84.
33. Ruiz-Irastorza G et al. Measuring systemic lupus erythematosus activity during pregnancy: validation of the lupus activity index in pregnancy scale. *Arthritis Rheum*. 2004;51(1):78-82.
34. Yee CS et al. The BILAG2004-Pregnancy index is reliable for assessment of disease activity in pregnant SLE patients. *Rheumatology (Oxford)*. 2012;51(10):1877-80.
35. Smyth A et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol*. 2010;5(11):2060-8.
36. Gladman DD et al. The effect of lupus nephritis on pregnancy outcome and fetal and maternal complications. *J Rheumatol*. 2010;37(4):754-8.
37. Imbasciati E et al. Pregnancy in women with pre-existing lupus nephritis: predictors of fetal and maternal outcome. *Nephrol Dial Transplant*. 2009;24(2):519-25.
38. Lightstone L, Hladunewich MA. Lupus nephritis and pregnancy: concerns and management. *Semin Nephrol*. 2017;37(4):347-53.
39. He X et al. Clinical features of new-onset systemic lupus erythematosus during pregnancy in Central China: a retrospective study of 68 pregnancies. *Clin Rheumatol*. 2021;40(6):2121-31.
40. Zhang C et al. Clinical features of new-onset systemic lupus erythematosus in pregnant patients. *J Obstet Gynaecol Res*. 2018;44(2):234-40.
41. Izmirly PM et al. Evaluation of the risk of anti-SSA/Ro-SSB/La antibody-associated cardiac manifestations of neonatal lupus in fetuses of mothers with systemic lupus erythematosus exposed to hydroxychloroquine. *Ann Rheum Dis*. 2010;69(10):1827-30.
42. Clowse ME et al. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum*. 2006;54(11):3640-7.
43. Mak A et al. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. *Rheumatology (Oxford)*. 2010;49(2):281-8.
44. Götestam Skorpen C et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis*. 2016;75(5):795-810.
45. Hench PS. The ameliorating effect of pregnancy on chronic atrophic (infection rheumatoid) arthritis, fibrositis and intermittent hydroarthrosis. *Mayo Clinic Proc*. 1938;13:161-7.
46. Jethwa H et al. Does rheumatoid arthritis really improve during pregnancy? a systematic review and metaanalysis. *J Rheumatol*. 2019;46(3):245-50.
47. Förger F, Villiger PM. Immunological adaptations in pregnancy that modulate rheumatoid arthritis disease activity. *Nat Rev Rheumatol*. 2020;16(2):113-22.

48. de Man YA et al. Disease activity or remission of rheumatoid arthritis before, during and following pregnancy. *Curr Opin Rheumatol*. 2014;26(3):329-33.
49. de Man YA et al. Measuring disease activity and functionality during pregnancy in patients with rheumatoid arthritis. *Arthritis Rheum*. 2007;57(5):716-22.
50. Bermas BL et al. An evaluation of the patient-administered Rheumatoid Arthritis Disease Activity Index for assessing disease activity during pregnancy. *Rheumatology (Oxford)*. 2017;56(12):2237-9.
51. de Man YA et al. Women with rheumatoid arthritis negative for anti-cyclic citrullinated peptide and rheumatoid factor are more likely to improve during pregnancy, whereas in autoantibody-positive women autoantibody levels are not influenced by pregnancy. *Ann Rheum Dis*. 2010;69(2):420-3.
52. Förger F et al. Pregnancy mediated improvement of rheumatoid arthritis. *Swiss Med Wkly*. 2012;142:w13644.
53. Maguire S et al. Pregnancy in axial spondyloarthritis: A systematic review & meta-analysis. *Semin Arthritis Rheum*. 2020;50(6):1269-79.
54. Ursin K et al. Psoriatic arthritis disease activity during and after pregnancy: a prospective multicenter Study. *Arthritis Care Res (Hoboken)*. 2019;71(8):1092-100.
55. Østensen M et al. A prospective study of pregnant patients with rheumatoid arthritis and ankylosing spondylitis using validated clinical instruments. *Ann Rheum Dis*. 2004;63(10):1212-7.
56. Meissner Y et al. European network of pregnancy registers in rheumatology (EuNeP)-an overview of procedures and data collection. *Arthritis Res Ther*. 2019;21(1):241.
57. Østensen M et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther*. 2006;8(3):209.
58. Clark KE et al. Systemic sclerosis in pregnancy. *Obstet Med*. 2020;13(3):105-11.
59. Martin SR, Edwards A. Pulmonary hypertension and pregnancy. *Obstet Gynecol*. 2019;134(5):974-87.
60. Blagojevic J et al. Pregnancy in systemic sclerosis: results of a systematic review and Metaanalysis. *J Rheumatol*. 2020;47(6):881-7.
61. Baethge BA, Wolf RE. Successful pregnancy with scleroderma renal disease and pulmonary hypertension in a patient using angiotensin converting enzyme inhibitors. *Ann Rheum Dis*. 1989;48(9):776-8.
62. Lidar M, Langevitz P. Pregnancy issues in scleroderma. *Autoimmun Rev*. 2012;11(6-7):A515-9.
63. Nguyen V et al. Pregnancy outcomes in women with primary systemic vasculitis: a retrospective study. *J Matern Fetal Neonatal Med*. 2019;1-7.
64. Machen L, Clowse ME. Vasculitis and pregnancy. *Rheum Dis Clin North Am*. 2017;43(2):239-47.
65. Sangale SR et al. Pregnancy outcome in patients with systemic vasculitis: a single-centre matched case-control study. *Rheumatology (Oxford)*. 2015;54(9):1582-6.
66. Ohta A et al. Age at onset and gender distribution of systemic lupus erythematosus, polymyositis/dermatomyositis, and systemic sclerosis in Japan. *Mod Rheumatol*. 2013;23(4):759-64.
67. Zhong Z et al. Pregnancy in polymyositis or dermatomyositis: retrospective results from a tertiary centre in China. *Rheumatology (Oxford)*. 2017;56(8):1272-5.
68. Gupta L et al. Outcomes of pregnancy in women with inflammatory myositis: a cohort study from India. *J Clin Rheumatol*. 2020;26(5):165-8.
69. Kolstad KD et al. Pregnancy outcomes in adult patients with dermatomyositis and polymyositis. *Semin Arthritis Rheum*. 2018;47(6):865-9.
70. Pinal-Fernandez I et al. "Pregnancy in adult-onset idiopathic inflammatory myopathy": report from a cohort of myositis patients from a single center. *Semin Arthritis Rheum*. 2014;44(2):234-40.
71. Munira S, Christopher-Stine L. Pregnancy in myositis and scleroderma. *Best Pract Res Clin Obstet Gynaecol*. 2020;64:59-67.



Letter to the Editor

The negative impact of depression in women with Axial Spondyloarthritis



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Mental health issues such as depression, are a considerable source of disability which can impact all aspects of life. The World Health Organisation (WHO) has projected depression will be the leading cause of severe disability worldwide by 2030 [1]. However, the true prevalence is suspected to be underestimated [2] due to societal stigma, under recognition of symptoms and limited or lack of access to appropriate services [3]. Depression can often complicate chronic disease which resulting in worsening of underlying disease and decline in quality of life [4].

Depression has previously been found to be a prevalent comorbidity in axial spondyloarthritis (axSpA) with an estimated pooled prevalence of 15% [5], and is associated with increased disease activity [6]. In the general population, depression is more prevalent in women [7]. For this reason, a focused analysis examining the prevalence and impact of depression in women with axSpA was carried out using data from the Ankylosing Spondylitis Registry of Ireland (ASRI).

At enrolment in the presence of numerous comorbidities are captured, including depression. For the purposes of this analysis patients were compared based on a previous diagnosis of depression. Comparison statistical analysis including independent t test and chi² tests of independence were carried out to determine statistical significance of differences. A two-way multivariate analysis of variance (MANOVA) was performed to assess the impact of sex (males vs females) and presence of depression on patient outcome scores.

At the time of analysis, 877 patients were enrolled in the ASRI, made up of 73.4% (644) males and 21% (184) females (Table 1). Overall, 10.1% (89) of the population in the ASRI had a diagnosis of depression consisting of 70.1% (63) males and 25.8% (23) females, with a prevalence of 9.8% (63) in males and 12.5% (23) in females ($p=0.44$).

Multivariate analysis on patient outcome scores failed to detect a significant interaction effect between sex and presence of depression ($F=1.26$, Wilk's lambda = 0.99, $p=0.28$), however there were statistically significant effects on patient outcome scores from both depression ($F=7.58$, Wilk's lambda = 0.94, $p<0.01$) and sex ($F=5.43$,

Table 1

Comparison of characteristics of patients with depression to those without depression.

	Depression % (n)	No Depression % (n)
n	10.1% (89)	88.5% (776)
Males	70.1% (63)	74.6% (579)
Females	25.8% (23)	20.7% (161)
Age	47.5 (10) ^a	45.7 (12)
Age at symptom onset	25.3 (10)	26.6 (11)
Delay to dx (years)	9.4 (8)	7.8 (9)
Disease duration (years) ^b	22.3 (12)	19.1 (12)
Caucasian	96.6% (86)	91.6% (711)
HLA-B27+	91.4% (64)	89.7% (529)
r-axSpA	80.9% (72)	77.7% (603)
nr-axSpA	19.1% (17)	22.2% (173)
Articular manifestations		
Arthritis ^b	41.6% (37)	29.3% (227)
Enthesitis ^b	25.8% (23)	29% (125)
Dactylitis	5.6% (5)	6.3% (49)
EAMs		
Psoriasis ^b	23.6% (21)	15.5% (120)
Uveitis	33.7% (30)	34% (264)
Colitis	13.5% (12)	10.2% (79)
Medications		
NSAIDs ^b	61.8% (55)	49.6% (385)
DMARDs	18% (16)	18.9% (147)
Biologics	71.9% (64)	67.5% (524)
anti-TNF	69.7% (62)	67.2% (522)

Dx: diagnosis; HLA-B27: human leukocyte antigen 27; r-axSpA: radiographic axSpA; nr-axSpA: non-radiographic axSpA; MRI: magnetic resonance imaging; NSAID: non-steroidal anti-inflammatory drug; DMARD: disease modifying antirheumatic drug; anti: TNF -anti tumour necrosis factor.

^a Continuous variables expressed as: Mean (Standard Deviation).

^b Indicates P -value < 0.05.

Wilk's lambda = 0.96, $p<0.01$) when considered in a univariate two-way ANOVA (Table 2).

This analysis was unique in assessing the impact of both depression and sex on patient outcome scores in axSpA. Analysis of the effects of depression between sexes revealed a similar prevalence of depression between men and women with axSpA. Although the interaction effect between sex and depression did not reach significance, both variables significantly impacted patient outcomes with depressed axSpA women averaging worse overall patient reported outcomes.

The relationship between disease activity in axSpA and depression is difficult to decipher. Active disease contributes to functional impairment and poorer quality of life increasing the risk of developing depression. Conversely, depression may drive worse quality of life causing functional limitation and increased reporting of symptomatology. Regardless, the importance of prompt recognition and management of both axSpA and depression is crucial to improving outcomes, especially axSpA women who already face challenges in time to diagnosis [8], disease recognition [9] and poorer response to anti-tumour necrosis factor (TNF) therapies [10].

Table 2
Effects of depression and gender on patient outcome scores.

Depression vs No Depression	Mean difference (95% CI)
BASDAI	
Females ²	1.89 (0.73, 3.04)
Males ²	1.11 (0.43, 1.79)
BASFI	
Females ²	2.07 (0.74, 3.4)
Males ¹	0.88 (0.10, 1.66)
HAQ	
Females ²	0.58 (0.31, 0.85)
Males ¹	0.22 (0.06, 0.37)
ASQoL	
Females ²	5.56 (2.82, 8.28)
Males ²	3.55 (1.94, 5.17)
BASMI	
Females	0.78 (−0.25, 1.81)
Males ¹	0.62 (0.01, 1.22)
Females vs Males	Mean Difference (95% CI)
BASDAI	
No depression ²	0.69 (0.22, 1.16)
Depression ¹	1.47 (0.22, 2.72)
BASFI	
No depression	0.33 (−0.22, 0.88)
Depression ¹	1.52 (0.08, 2.96)
HAQ	
No depression	0.06 (−0.05, 0.17)
Depression ²	0.43 (0.14, 0.72)
ASQoL	
No depression	0.9 (−0.22, 2.02)
Depression	2.89 (−0.71, 5.86)
BASMI	
No depression ²	−0.65 (−1.07, −0.23)
Depression	−0.49 (−1.60, 0.63)

Reporting of p values: ¹ $p < 0.05$, ² $p < 0.01$. 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.

Disclosure of interests

The authors declare that they have no competing interest. SM is the recipient of the Gilead Inflammation Fellowship. PG & FO have no disclosures to declare. The ASRI is supported by unrestricted funding from UCB, AbbVie and Pfizer.

References

- [1] The World Health Organisation. The global burden of disease: 2004 update. Geneva: The World Health Organisation (WHO); 2004. p. 34–7.
- [2] Malhi GS, Mann JJ. Depression. *Lancet* 2018;392:2299–312.
- [3] Kohn R, Saxena S, Levav I, et al. The treatment gap in mental health care. *Bull World Health Organ* 2004;82:858–66.
- [4] DeJean D, Giacomini M, Vanstone M, et al. Patient experiences of depression and anxiety with chronic disease: a systematic review and qualitative meta-synthesis. *Ont Health Technol Assess Ser* 2013;13:1–33.
- [5] Zhao S, Thong D, Miller N, et al. The prevalence of depression in axial spondyloarthritis and its association with disease activity: a systematic review and meta-analysis. *Arthritis Res Ther* 2018;20:140.
- [6] Garrido-Cumbrera M, Delgado-Domínguez CJ, Gálvez-Ruiz D, et al. The Effect of Axial Spondyloarthritis on Mental Health: Results from the Atlas. *J Rheumatol* 2019;46:1284–9.
- [7] Salk RH, Hyde JS, Abramson LY. Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychol Bull* 2017;143:783–822.
- [8] Neuenschwander R, Hebeisen M, Micheroli R, et al. Differences between men and women with nonradiographic axial spondyloarthritis: clinical characteristics and treatment effectiveness in a real-life prospective cohort. *Arthritis Res Ther* 2020;22:233.
- [9] Garrido-Cumbrera M, Poddubnyy D, Gossec L, et al. Gender differences in patient journey to diagnosis and disease outcomes: results from the European Map of Axial Spondyloarthritis (EMAS). *Clin Rheumatol* 2021.
- [10] van der Horst-Bruinsma IE, Zack DJ, Szumski A, et al. Female patients with ankylosing spondylitis: analysis of the impact of gender across treatment studies. *Ann Rheum Dis* 2013;72(7):1221–4.

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The toll of unemployment in axial spondyloarthritis: high prevalence and negative impact on outcomes captured in a national registry

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The toll of unemployment in axial spondyloarthritis: high prevalence and negative impact on outcomes captured in a national registry

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Objective: Axial spondyloarthritis (axSpA) is an inflammatory arthritis of the axial skeleton. Persistent disease activity can result in significant disability and affect the ability to maintain employment. This study aimed to determine the prevalence of unemployment in axSpA and the impact on patient outcomes.

Method: Data from the Ankylosing Spondylitis Registry of Ireland (ASRI) were cleaned, and information on employment, demographics, and disease characteristics was extracted. Patients were analysed on the basis of employment and categorized as employed or unemployed.

Results: Of the 759 participants included in the analysis, 23.5% (178) were unemployed, higher than national averages of 6.2–13.1% during the study period. Unemployed participants reported significantly worse Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; 5.1 vs 3.6), Metrology Index (BASMI; 4.8 vs 3.4), Functional Index (BASFI; 5.2 vs 3.0), Health Assessment Questionnaire (HAQ; 0.82 vs 0.40), and Ankylosing Spondylitis Quality of Life (ASQoL; 9.4 vs 5.4) scores compared to employed (all $p < 0.01$). Male gender (odds ratio, 95% confidence interval: 2.65, 1.46–4.83), worse BASMI (1.16, 1.02–1.33), and worse HAQ scores (2.18, 1.13–4.19) were significantly associated with unemployment.

Conclusion: The prevalence of unemployment in axSpA patients is higher than in the general population, and is associated with worse quality of life, poorer levels of function, and higher levels of disease activity. Predictors of unemployment in axSpA were male gender, worse spinal mobility, and poorer level of function. Recognition of patients at risk of unemployment will improve opportunities for intervention and maintain participation in the workforce.

Axial spondyloarthritis (axSpA) is an inflammatory arthritis of the axial skeleton and sacroiliac joints (1). This term includes both radiographic axSpA, or ankylosing spondylitis (AS), and non-radiographic axSpA. Persistent disease activity can result in deformity of the spine, restriction of movement, and chronic pain (2). Onset is in the third and fourth decades of life (3), during which time many affected patients will be actively engaged in the workforce.

For many years, axSpA was associated with significant deformity and disability, issues which limited ability to maintain employment for many patients (4). With advances in treatments and diagnostics, it would be expected that unemployment levels now would be similar to those in 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.

Method

Patient population

Data were 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.

All participants met the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA, allowing data collection on both radiographic and non-radiographic axSpA. All participants were over the age of 18 years, with full capacity, and fluent in English. Written informed consent was obtained from all participants and ethical approval was received from local hospital ethics boards.

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Outcomes and assessments

Participation in the ASRI involved a single clinical visit with a trained investigator. A structured interview and medical records review captured information on demographics and patterns of disease. Self-administered questionnaires captured the following outcomes: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Health Assessment Questionnaire (HAQ), and Ankylosing Spondylitis Quality of Life (ASQoL) scores. A focused examination allowed calculation of the Bath Ankylosing Spondylitis Metrology (spinal mobility) Index (BASMI). Employment status was recorded at time of enrolment. Retirement or sick leave resulted in exclusion from the analysis.

Statistical analysis

IBM SPSS version 26 was used for statistical analysis. A series of comparison analyses was carried out to assess variation between employed and unemployed axSpA patients. Two-tailed t-tests tested for significance in differences between means of continuous variables, while a chi-squared test of independence was used for categorical variables. An alpha level of $p < 0.05$ was deemed significant. A binomial logistic regression model captured the effect of variables on the likelihood of unemployment.

Results

In total, 886 patients were enrolled in the ASRI, with 759 participants eligible for analysis. The population of the ASRI was made up of 73% ($n = 554$) males and 27% ($n = 205$) females, with 91% ($n = 690$) identifying as Caucasian. Mean $\pm$ sd age was 43.4 ± 10.7 (range 18–73) years, mean disease duration 17.8 ± 10.9 years, and mean delay to diagnosis 7.6 ± 7.7 years. Mean scores were: BASDAI 4.00, BASMI 3.76, BASFI 3.46, HAQ 0.49, and ASQoL 6.33.

Females with axSpA had worse BASDAI (4.47 vs 3.80, $p < 0.01$), HAQ (0.56 vs 0.47, $p = 0.04$), and ASQoL (7.44 vs 5.95, $p < 0.01$) scores compared to males, although females recorded better BASMI scores (3.32 vs 3.92, $p < 0.01$).

The level of unemployment in the ASRI was 23.5% ($n = 178$), with 24% of patients ($n = 182$) reporting that their employment had been affected by axSpA, resulting in unemployment, disability, or part-time employment. Unemployed axSpA patients had significantly worse ASQoL [9.4 vs 5.4, 95% confidence interval (CI) 3.11–4.88, $p < 0.01$], HAQ (0.82 vs 0.40, 95% CI 0.34–0.50, $p < 0.01$), BASDAI (5.1 vs 3.6, 95% CI 1.1–1.88, $p < 0.01$), BASFI (5.2 vs 3.0, 95% CI 1.83–2.75, $p < 0.01$), and BASMI (4.8 vs 3.4, 95% CI 1.04–1.77, $p < 0.01$) scores (Figure 1) than employed participants.

Baseline demographics were similar in both cohorts, but unemployment was more prevalent in males with axSpA than in females (26.7% vs 14.6%, $p = 0.01$) (Table 1).

A binomial logistic regression was performed to determine the effects of gender, disease duration, and patient outcomes on the likelihood of unemployment in axSpA. The model was statistically significant [$\chi^2(8) = 109.75$, $p < 0.001$], correctly classifying 79% of cases overall. Of the nine variables, only three were statistically significant: gender, BASMI, and HAQ (Table 2). The area under the receiver operating characteristics (ROC) curve was 0.776 (95% CI 0.729–0.823), which shows an acceptable level of discrimination.

Discussion

This analysis demonstrates the high prevalence (23.5%) of unemployment in axSpA. National unemployment during the same period (2013–2019) was noticeably lower, with a range of 6.2–13.1% (5–7). Compared to other axSpA cohorts, the prevalence of unemployment in our cohort was above the reported prevalence in Spain of 20.1% (8), but lower than in Argentina, at 26.2% (9), and 30% in the UK (10). These results indicate that the higher unemployment level in axSpA is an issue extending beyond Ireland and affecting axSpA patients globally.

Overall, 24% of patients reported that their employment had been affected or limited by their disease. Similar results were found in an Italian axSpA cohort, with 21% reporting work restrictions due to axSpA (11). The loss or limitation of work productivity in such a large proportion of the cohort represents a significant financial loss for axSpA patients and their dependants. Lower socioeconomic status has previously been associated with worse health outcomes in axSpA, using the ASAS health index (12). This has also been associated with a higher prevalence of depressive symptoms and worse psychological well-being (13).

AxSpA patients who were unemployed were found to have significantly worse outcomes across all measures captured in this analysis compared to those who were employed. These included higher levels of disease activity, worse functional abilities, greater limitation of spinal mobility, and worse overall quality of life. This finding was supported by the results of the regression model, which found an increased likelihood of unemployment in patients with worse BASMI and HAQ scores. This could be explained by the higher prevalence of radiographic changes in unemployed patients (81.5% vs 76%, $p = 0.24$); however, this difference did not reach significance. There was a non-significant trend towards increased use of biological disease-modifying anti-rheumatic drugs (bDMARDs) in this group, possibly representing patients with persistent disease activity, hence the increased requirement for bDMARDs and worse outcome measures. Additional research capturing longitudinal data is required to determine whether

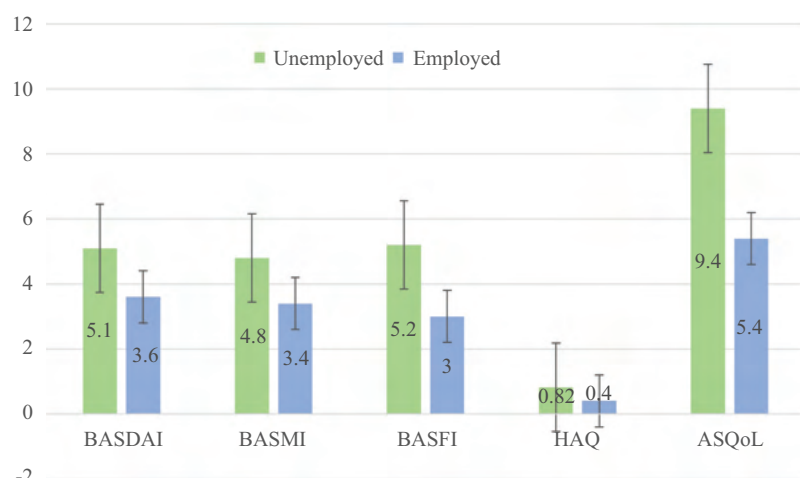


Figure 1. Comparison of mean outcomes on the basis of employment. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index; HAQ, Health Assessment Questionnaire; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire. All differences were statistically significant at the $p < 0.01$ level.

Table 1. Characteristics of the employed versus unemployed cohort in the Ankylosing Spondylitis Registry of Ireland (ASRI).

	Unemployed	Employed	p
All patients	178 (23.5)	581 (76.5)	
Males	148 (83.1)	406 (70)	< 0.01
Females	30 (16.9)	175 (30.1)	
Age (years)	46.2 $\pm$ 10	42.5 $\pm$ 10.7	< 0.01
Disease duration (years)	19.6 $\pm$ 11.5	17.2 $\pm$ 10.7	0.02
Delay to diagnosis (years)	7.6 $\pm$ 7.6	7.6 $\pm$ 7.8	1
Age at symptom onset (years)	26.7 $\pm$ 9.6	25.2 $\pm$ 9.7	0.08
Caucasian	166 (93.3)	524 (91.2)	0.25
HLA-B27 ⁺	121 of 134 (90.3)	414 of 457 (90.1)	0.92
Radiographic sacroiliitis	145 (81.5)	441 (76)	0.24
MRI sacroiliitis	68 (38.2)	280 (48.2)	0.06
Arthritis	56 (31.5)	163 (28.1)	0.68
Enthesitis	36 (20.2)	92 (15.8)	0.38
Dactylitis	13 (7.3)	35 (6)	0.67
Psoriasis	31 (17.4)	96 (16.5)	0.78
Uveitis	62 (34.8)	198 (34.1)	0.53
Colitis	11 (6)	59 (10.2)	0.21
NSAIDs	88 (49.4)	301 (51.8)	0.59
csDMARDs	45 (25.2)	128 (22)	0.39
bDMARDs	133 (74.7)	392 (67.5)	0.14
CRP (mg/L)	7.4 (11.2)	6.9 (13)	0.62
ESR (mm/h)	17.2 (18)	14.8 (17)	0.24

Data are shown as n (%), mean $\pm$ SD

HLA-B27, human leucocyte antigen B27; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; bDMARD, biological disease-modifying anti-rheumatic drug; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

a causal relationship between disease activity and employment exists.

Male gender, limitation of spinal mobility, and worsening HAQ scores were all significantly associated with an

Table 2. Regression model for factors associated with unemployment in axial spondyloarthritis.

	OR	95% CI	p
Male gender	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

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; OR, odds ratio; CI, confidence interval.

increased likelihood of unemployment. As males with axSpA have significantly worse average BASMI scores than females, this could explain the higher levels of unemployment observed in males with axSpA. Both BASMI and HAQ scores are routinely recorded in axSpA patients. Monitoring 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 significantly affect a patient's overall well-being and is important to capture. Tools are being developed to identify axSpA patients at risk of impaired productivity; these aim to improve recognition of at-risk individuals and allow intervention (14). The Work Productivity and Activity Impairment questionnaire in AS (WPAI:SpA) was developed specifically for axSpA patients to capture both employment and productivity (15).

The simplicity of this self-administered questionnaire allows for regular monitoring as part of routine care for axSpA patients. Regular use of such a tool would give valuable insights into participation in the workforce and the impact of disease on functional ability.

The strengths of this study were the large size of the patient population and the detailed characterization to support the analysis. Cohorts were adequately powered to detect differences, without individual results disproportionately skewing overall proportions. Data were collected by trained investigators, ensuring reliability of collection. Data were gathered from multiple centres, allowing accurate representation of the true axSpA patient population of Ireland. The inclusion of a regression model identified risk factors for unemployment, which has significant clinical implications.

The main limitation of this study is the cross-sectional nature of the data from the ASRI, preventing the ability to detect causal relationships. Data were collected over 8 years, during which time national unemployment rates fluctuated but remained significantly lower than the unemployment rates observed from patients in the ASRI. Lack of data on occupation type prevented analysis of the association between employment status and specific occupations. Data on education were not available; however, education in Ireland is state funded, with an average age of 19.9 years at the time of completion of education (16). As Ireland does not have centralized medical records, it is difficult to report the percentage of axSpA patients in Ireland captured within the ASRI. However, patients were recruited from all major geographic regions of Ireland and across the socioeconomic spectrum to reflect the true population as accurately as possible.

Conclusion

The prevalence of unemployment in axSpA remains notably higher than nationally reported averages from the general population. Despite a high uptake of bDMARD use, these patients have higher levels of disease activity, poorer levels of function, and worse quality of life than employed axSpA patients. A large proportion of axSpA patients reported work limitations due to their disease. Factors associated with unemployment were male gender, worse spinal mobility, and greater functional impairment. In males, higher BASMI scores were a significant contributory factor to the higher rates of unemployment observed. Prompt intervention would provide an opportunity for occupational support and prevent progression to unemployment. The increased use of tools to identify at-risk patients will allow for rapid recognition and intervention to allow these patients to remain active members of the workforce.

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References

1. Sieper J, Braun J, Dougados M, Baeten D. Axial spondyloarthritis. *Nat Rev Dis Primers* 2015;1:15013.
2. López-Medina C, Molto A, Claudepierre P, Dougados M. Clinical manifestations, disease activity and disease burden of radiographic versus non-radiographic axial spondyloarthritis over 5 years of follow-up in the DESIR cohort. *Ann Rheum Dis* 2020;79:209–16.
3. Magrey MN, Danve AS, Ermann J, Walsh JA. Recognizing axial spondyloarthritis: a guide for primary care. *Mayo Clin Proc* 2020;95:2499–508.
4. Calin A. The individual with ankylosing spondylitis: defining disease status and the impact of the illness. *Br J Rheumatol* 1995;34:663–72.
5. Central Statistics Office (CSO). Statistical Release of Monthly Unemployment September 2015. Central Statistics Office. <https://www.cso.ie/en/releasesandpublications/er/mue/monthlyunemploymentseptember2015/>
6. Central Statistics Office (CSO). Statistical Release of Monthly Unemployment September 2019. Central Statistics Office. <https://www.cso.ie/en/releasesandpublications/er/mue/monthlyunemploymentseptember2019/>
7. Central Statistics Office (CSO). Statistical Release of Monthly Unemployment September 2017. Central Statistics Office. <https://www.cso.ie/en/releasesandpublications/er/mue/monthlyunemploymentaugust2017/>
8. Garrido-Cumbrera M, Gratacos J, Collantes-Estevez E, Zarco P, Sastre C, Sanz-Gómez S, et al. Similarities and differences between non-radiographic and radiographic axial spondyloarthritis: the patient perspective from the Spanish atlas. *Reumatol Clin* 2020;20:S169–258X.
9. Marengo MF, Schneeberger EE, Citera G, Cocco JA. Work status among patients with ankylosing spondylitis in Argentina. *J Clin Rheumatol* 2008;14:273–7.
10. Healey EL, Haywood KL, Jordan KP, Garratt A, Packham JC. Impact of ankylosing spondylitis on work in patients across the UK. *Scand J Rheumatol* 2011;40:34–40.
11. Ramonda R, Marchesoni A, Carletto A, Bianchi G, Cutolo M, Ferraccioli G, et al. Patient-reported impact of spondyloarthritis on work disability and working life: the ATLANTIS survey. *Arthritis Res Ther* 2016;18:78.
12. Min HK, Lee J, Ju JH, Park SH, Kwok SK. Predictors of Assessment of Spondyloarthritis International Society (ASAS) health index in axial spondyloarthritis and comparison of ASAS health index between ankylosing spondylitis and non-radiographic axial spondyloarthritis: data from the Catholic Axial Spondyloarthritis COhort (CASCO). *J Clin Med* 2019;8:4.
13. Redeker I, Hoffmann F, Callhoff J, Haibel H, Sieper J, Zink A, et al. Determinants of psychological well-being in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. *Ann Rheum Dis* 2018;77:1017–24.
14. Martindale J, Shukla R, Goodacre J. The impact of ankylosing spondylitis/axial spondyloarthritis on work productivity. *Best Pract Res Clin Rheumatol* 2015;29:512–23.
15. Reilly MC, Gooch KL, Wong RL, Kupper H, van der Heijde D. Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis. *Rheumatology (Oxford)* 2010;49:812–9.
16. Central Statistics Office (CSO). Census of population 2016 - profile 10 education, skills and the Irish language. Census of Population 2016. Cork: Central Statistics Office, 2016.

The Same But Different? An Analysis of Late-Onset Axial Spondyloarthritis

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Axial spondyloarthritis (axSpA) is an inflammatory arthritis characterized by involvement of the axial skeleton causing symptoms of inflammatory back pain.¹ Axial spondyloarthritis has long been described as presenting in the third decade of life, with the onset rarely occurring at older than 45 years.² Previous research^{3–7} has shown there is a cohort of patients developing axSpA beyond this age. Publications have been limited to small numbers of axSpA patients as part of a larger SpA cohort or small numbers of participants in dedicated axSpA studies.

First described in a case series of 10 patients in 1989,⁸ late onset (LO) axSpA has been slow to inspire further research. Calin et al.⁷ published a letter to the editor in 1991 discussing a cohort of axSpA patients who developed symptoms after the age of 35 years, highlighting the need for further research. This study had a mean age of 38.7 years for LO axSpA, which would meet the current Assessment of SpondyloArthritis international Society (ASAS) classification criteria for inflammatory back pain⁹ and is not typical of patients with LO axSpA in the current literature. However, this article highlighted that axSpA can develop later in life and the need to better identify and understand this subset of patients.

Low back pain in an older adult, regardless of the underlying cause, can cause considerable impairment in quality of life.¹⁰ Older adults have been shown to have a higher sensitivity to pain due to alterations in pain modulation pathways.¹¹ In addition, the increased frequency of other comorbidities including osteoarthritis and degenerative disc disease can cause multisource pain generation.¹² For this reason, it is essential to identify and treat inflammatory pain promptly in this population.

The Ankylosing Spondylitis Registry of Ireland (ASRI) is an epidemiological data source on patients with axSpA in Ireland. Large national registries such as this are an opportunity to further study LO axSpA in large numbers.

METHODS

Patient Population

Participants were recruited from 12 rheumatology departments across Ireland. Eligibility for participation required a diagnosis of axSpA made by a rheumatologist. This captured both radiographic axSpA or ankylosing spondylitis and nonradiographic axSpA. All participants were required to fulfill the ASAS criteria for axSpA to be included in the ASRI. All enrolled patients were

older than 18 years, were fluent in English, and had full capacity at time of enrolment.

Data Collection

Written informed consent was obtained prior to participation. A trained investigator conducted patient visits to capture required data points. This included review of medical records to confirm diagnosis, patient-reported outcomes via validated questionnaires, and focused history and examination. Focused clinical examination captured metrics for calculation of the Bath Ankylosing Spondylitis Metrology Index (BASMI). Data were collected and recorded into an electronic database using pseudo-anonymization of identifying patient information to preserve patient confidentiality. This study was reviewed by the ethics boards of all participating centers and given full approval prior to commencement of data collection.

Statistical Analysis

Patient registered in ASRI were analyzed on the basis of age at symptom onset using IBM SPSS version 26 (IBM Corp., Armonk, NY). Patients were divided into 2 groups with age older than 45 years at symptom onset categorized as LO and age younger than 45 years as typical-onset axSpA. Mean BASMI, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Health Assessment Questionnaire (HAQ), and Ankylosing Spondylitis Quality of Life Scale (ASQoL) scores were compared between the 2 groups and tested for statistical significance using an independent 2-tailed *t* test. Further analysis of categorical variables was performed using a χ^2 test for independence. A *p* value of <0.05 was deemed significant.

RESULTS

A total of 851 patients with axSpA were included in the analysis, composed of 77.4% (659) males, 22.6% (192) females, with mean age of 45.8 years and mean disease duration of 19.4 years (means: ASQoL, 6.52; HAQ, 0.54; BASDAI, 4.03; BASFI, 3.7; BASMI, 4.03). Patient population was 93.7% (797) patients categorized as typical onset and 6.3% (54) patients categorized as LO (Table).

There was a significant difference in age at symptom onset between LO and typical onset (52.8 vs. 24.5 years, *p* < 0.01). Patients with LO axSpA had significantly higher mean BASFI (5.53 vs. 3.58, *p* < 0.01), HAQ (0.75 vs. 0.53, *p* < 0.01), and ASQoL scores (7.68 vs. 6.44, *p* < 0.01) (Figure). Patients with LO axSpA also had higher mean BASDAI (4.19 vs. 4.02, *p* = 0.6) and BASMI (4.97 vs. 3.96, *p* = 0.12), which did not reach significance. Patients with LO axSpA had lower rates of human leukocyte antigen B27 (HLA-B27) positivity (76.5% vs. 91.2%, *p* < 0.01).

No difference was detected between groups regarding gender distribution, ethnicity, patterns of disease, or rates of extra-articular manifestations (EAMs). Prevalence of radiographic axSpA was

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TABLE. Summary of Demographics and Clinical Features Between the Typical Onset axSpA (<45 Years) and LO axSpA (>45 Years)

	Onset <45 y (n = 797)	LO (n = 54)	p value
Males (n = 659)	77% (614)	83% (45)	0.19
Females (n = 192)	23% (183)	16.6% (9)	
Age, y	44.6	62.9	<0.01
Age at symptom onset, y	24.5	52.8	<0.01
Delay to diagnosis	8.35	3.81	<0.01
Disease duration	20.1	10.2	<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
Magnetic resonance imaging sacroiliitis (n = 384)	45.3% (361)	42.6% (23)	0.69
Extra-articular manifestations			
Uveitis	28.5% (227)	24.1% (13)	0.07
Colitis	9.9% (79)	14.8% (8)	0.32
Psoriasis	16.4% (131)	18.5% (10)	0.54
Treatment			
Biologics	69.1% (551)	48.1% (26)	<0.01
Nonsteroidal anti-inflammatory drugs	54.2% (432)	61.1% (33)	0.2

similar between groups (74% vs. 79%, $p = 0.07$). Patients with LO axSpA had lower rates of biologic therapy use (50% vs. 72%, $p < 0.01$) but similar rates of NSAID usage (61.1% vs. 54.2%, $p = 0.2$).

DISCUSSION

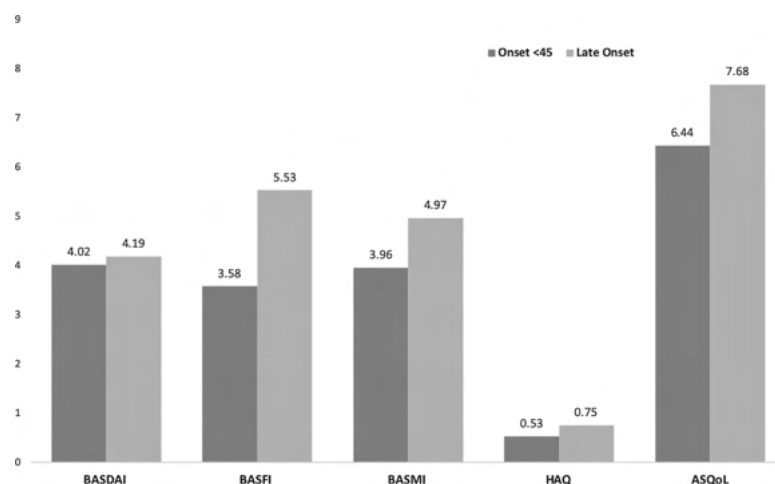
This analysis demonstrates that differences in age at symptom onset between typical and LO axSpA are significant. Patients

with LO axSpA had similar patterns of disease, EAMs, and radiological findings consistent with current classification criteria for axSpA. Patients with LO axSpA had worse mean functional outcomes, which could reflect the older age at symptom onset. In addition, the LO group was older at time of inclusion in the registry.

This study represents one of the largest cohorts of LO axSpA published to date with 52 patients. Data have been previously presented on larger cohorts of up to 227 patients,¹³ but no full text is currently published. The incidence of LO axSpA of 6.3% in our axSpA cohort is lower than that found in 2 Turkish studies, 7.9% and 8.9%,^{5,13} and in 1 Brazilian study, 9.7%.³ Lower rates of 3.5% were reported in cohorts in Spain⁶ and Taiwan.⁴

Geographic variation should be considered when discussing these studies, given the known variation in HLA-B27 prevalence. Both Turkish studies found lower prevalence of HLA-B27 in LO axSpA compared with typical onset, similar to the findings of this study. Chen et al.⁴ examined this in more detail, comparing rates of HLA-B27 positivity in juvenile, adolescent, and LO axSpA and found higher rates of HLA-B27 to be associated with younger age at onset. The role of HLA-B27 in LO axSpA has received limited attention. Certain subtypes of HLA-B27 have been shown to be associated with older age at symptom¹⁴; however, the reason for this is unknown. Another possible genetic link was proposed by Brophy and Calin,¹⁵ who hypothesized age at onset is unrelated to genetic susceptibility load as juvenile-onset axSpA does not lead to worse outcomes. They suggested instead 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. Two articles^{4,6} reported no difference in clinical or functional outcomes, whereas another³ reported higher disease activity and worse functional outcomes. There are a number of possible contributing factors for these outcome variances. There is currently no clear definition of LO axSpA, with studies independently defining what age qualifies as LO. Of the studies discussed, criteria for LO ranges from older than 40 to older than 55 years at symptom onset, which could also contribute to the variation in incidence of LO axSpA recorded. Establishment of criteria to define LO would lead to more uniform comparisons. Limited cohort size is another issue, as this study is the first full publication with more than 50 patients. Large registries from multiple countries would offer the opportunity to pool data to properly analyze LO axSpA.

**FIGURE.** Outcomes based on age at symptom onset.

It is notable LO axSpA was treated significantly less often with biologic agents. The European League Against Rheumatism guidelines on treatment of axSpA from 2016 recommend that biologic therapy be considered in patients with active disease despite treatment.¹⁶ Patients with LO axSpA have worse functional outcomes with a trend toward increased disease activity, so why are they using biologic treatments less? Are they less likely to be offered this treatment? Are they less suitable for such treatment? These questions are just a start to what needs to be examined to better understand variation in medication use in LO axSpA.

The ASAS criteria for axial SpA are currently validated only in patients with an onset of symptoms before the age of 45 years.¹⁷ These criteria are unique in its age limitations to previous criteria used in classification of axSpA. While the causes for low back pain in an older adult are less likely to be inflammatory in nature, axSpA should be considered in patients with symptoms of inflammatory back pain. This analysis demonstrates that LO axSpA fulfills other criteria for classification of axSpA and has similar patterns of disease as typical-onset axSpA.

In conclusion, LO 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 LO axSpA would lead to improved identification of these patients and allow for pooling of data.

REFERENCES

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet*. 2017;390:73–84.
2. Olivieri I, D'Angelo S, Padula A, et al. Spondyloarthritis with onset after age 45. *Curr Rheumatol Rep*. 2013;15:374.
3. Bendahan LT, Machado NP, Mendes JG, et al. Performance of the classification criteria in patients with late-onset axial spondyloarthritis. *Mod Rheumatol*. 2018;28:174–181.
4. Chen HA, Chen CH, Liao HT, et al. Clinical, functional, and radiographic differences among juvenile-onset, adult-onset, and late-onset ankylosing spondylitis. *J Rheumatol*. 2012;39:1013–1018.
5. Karaarslan A, Yilmaz H, Aycan H, et al. Demographic, clinical, and laboratory features of Turkish patients with late onset ankylosing spondylitis. *Bosn J Basic Med Sci*. 2015;15:64–67.
6. Montilla C, Del Pino-Montes J, Collantes-Estevez E, et al. Clinical features of late-onset ankylosing spondylitis: comparison with early-onset disease. *J Rheumatol*. 2012;39:1008–1012.
7. Calin A, Elwood J, Edmunds L. Late onset ankylosing spondylitis—a distinct disorder? *Br J Rheumatol*. 1991;30:69–70.
8. Dubost JJ, Sauvezie B. Late onset peripheral spondyloarthritis. *J Rheumatol*. 1989;16:1214–1217.
9. Sieper J, van der Heijde D, Landewe R, et al. New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis*. 2009;68:784–788.
10. Wong AYL, Forss KS, Jakobsson J, et al. Older adult's experience of chronic low back pain and its implications on their daily life: study protocol of a systematic review of qualitative research. *Syst Rev*. 2018;7:81.
11. Lautenbacher S, Kunz M, Strate P, et al. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain*. 2005;115:410–418.
12. Weiner DK, Sakamoto S, Perera S, et al. Chronic low back pain in older adults: prevalence, reliability, and validity of physical examination findings. *J Am Geriatr Soc*. 2006;54:11–20.
13. Uslu SCG, Cefle A, Yilmaz S, et al. The efficacy and safety of anti-TNF α treatment in ankylosing spondylitis patients with late onset compared to those with adult onset; the data from TURKBIO registry. *Arthritis Rheumatol*. 2019;71.
14. Ma HJ, Yin QF, Liu Y, et al. Polymorphisms of human leukocyte antigen B*27 on clinical phenotype of spondyloarthritis in Chinese. *J Clin Lab Anal*. 2018;32:e22275.
15. Brophy S, Calin A. Ankylosing spondylitis: interaction between genes, joints, age at onset, and disease expression. *J Rheumatol*. 2001;28:2283–2288.
16. van der Heijde D, Ramiro S, Landewe R, et al. 2016 Update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017;76:978–991.
17. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis*. 2009;68:777–783.



Worse scores but similar patterns of disease activity: interpreting outcomes in women with axial spondyloarthritis

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Worse scores but similar patterns of disease activity: interpreting outcomes in women with axial spondyloarthritis

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Objective: The aim of this study was to evaluate the impact of sex on disease activity in axial spondylitis (axSpA).

Method: Data were extracted from the Ankylosing Spondylitis Registry of Ireland (ASRI). In this cross-sectional study, patients were analysed on the basis of sex, with a series of comparison analyses performed.

Results: Overall, 886 participants were enrolled in the ASRI [232 (26.2%) women, 644 (72.6%) men]. Females recorded significantly worse Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (4.57 vs 3.83, $p < 0.01$) and Ankylosing Spondylitis Quality of Life questionnaire (ASQoL) (7.51 vs 6.12, $p < 0.01$) scores than males. There was a stronger correlation in the Bath Ankylosing Spondylitis Functional and Metrology Indices (BASFI and BASMI) in females ($r_s = 0.619$, $p < 0.01$) than in males ($r_s = 0.572$, $p < 0.01$). Analysis of factors in BASDAI revealed that the higher total scores in females compared to males were due not to any single component, but to worse scores in all six components of the BASDAI combined. Ranking of components by severity between sexes revealed identical ranking in four of the six components of the BASDAI.

Conclusions: Women with axSpA reported significantly worse disease activity, quality of life, and functional ability than men. However, the BASDAI captured similar patterns of disease activity. Limitation of spinal mobility in women with axSpA corresponded to greater impairment in functional ability. Further evaluation of disease monitoring tools is required to ensure that disease activity is accurately captured in men and women with axSpA.

Axial spondyloarthritis (axSpA) is an autoinflammatory arthritis predominantly involving the axial spine (1). The defining feature is inflammatory sacroiliitis, which can be detected on X-ray in radiographic axial spondyloarthritis (r-axSpA), or on magnetic resonance imaging (MRI) in non-radiographic axial spondyloarthritis (nr-axSpA) (2). This causes symptoms of inflammatory back pain such as nocturnal pain and prolonged early morning stiffness (EMS). Several articular and extra-articular manifestations (psoriasis, inflammatory colitis, and uveitis) are recognized, which can aid in clinical identification of axSpA. Onset is typically in the third decade, with a higher incidence in Caucasians and an association with human leucocyte antigen (HLA)-B27 (3).

There has been a considerable shift in the 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 (4), more recent

studies have reported ratios closer to 2–3:1 (5). One of the major factors contributing to this dramatic shift is the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA, which recognized not only r-axSpA, also called ankylosing spondylitis (AS), but also nr-axSpA (6). 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 (7). As women with axSpA are more likely to have non-radiographic disease (8), the formal recognition of nr-axSpA allowed these women not only to have a diagnosis of their condition but also to be eligible for treatment previously reserved for r-axSpA only.

Despite the evolution of classification and epidemiology of axSpA, much of what is known about axSpA is based on research into men with AS (9). As a result, there remains a considerable underrepresentation of axSpA in women in published research. Combined with the underrecognition of the disease in women (10), there is a significant need for increased awareness and focused research on the sex-specific impact and disease manifestations of axSpA (11). Previous research into women with axSpA has demonstrated significantly worse quality of life, functional ability, and disease activity, as well as a poorer response to treatment

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compared to men (9). Detailed analysis and characterization of axSpA in women is the first step in optimizing 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 highlight directions for future research.

Method

Study population

The Ankylosing Spondylitis Registry of Ireland (ASRI) is a large, observational, national registry of patients with axSpA in Ireland. Currently, the ASRI contains data on 887 patients recruited from 12 rheumatology centres nationally, representing all geographic regions of Ireland. This study includes data on all axSpA patients captured within the ASRI since enrolment began in 2013. To be considered for enrolment in the ASRI, participants must have been diagnosed with axSpA by a rheumatologist and must meet the 2009 ASAS classification criteria for axSpA. This enabled capture of both radiographic and non-radiographic disease. Additional eligibility criteria included: age over 18 years, fluency in English, and presence of full capacity to consent to participation.

Once identified, eligible patients were invited to participate in the ASRI. To limit the possibility of selection bias, investigators recruited as many patients as possible from each centre, including participants across the spectrum of disease severity, socioeconomic status, and geographic regions in the country. Prior to enrolment, trained investigators discussed what participation in the ASRI would involve, the purpose of the ASRI, and how the collected information would be used and protected. Participants were encouraged to ask questions of the investigator prior to signing a written consent form. Ethical approval for the ASRI was obtained from local hospital ethics committees from all participating centres, including the Joint Research Ethics Committee for St James' and Tallaght University Hospital. Trained investigators at each centre were responsible for local oversight of data collection. All data were collected and stored in compliance with national data protection legislation.

Outcomes and assessment

Enrolment consisted of a single clinical visit involving a structured interview, a series of questionnaires to capture patient-reported outcomes (PROs), a focused clinical examination, and chart review. This captured information on baseline demographics (age, sex, ethnicity), details of

disease history (age at symptom onset, delay to diagnosis, disease duration), pattern of disease (articular and extra-articular manifestations), and treatments [non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and biological agents]. Information on imaging (conventional radiographs, MRI) and serology (inflammatory markers, HLA-B27) was also captured via a medical records review.

Multiple PROs were recorded for each participant. These outcome measures are validated for use in axSpA and capture information on numerous aspects of participants' daily living (12). PROs captured via self-administered questionnaires were the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (13), Bath Ankylosing Spondylitis Function Index (BASFI) (14), Health Assessment Questionnaire (HAQ) (15), and Ankylosing Spondylitis Quality of Life questionnaire (ASQoL) (16). Focused clinical examination to assess spinal mobility allowed for calculation of the Bath Ankylosing Spondylitis Metrology Index (BASMI) (17). Responses were recorded along a numerical rating system of a visual analogue score. For all outcome measures, higher scores indicated a greater level of impairment or severity.

Statistical analysis

Data were extracted from the ASRI and cleaned for analysis. A series of descriptive comparison analyses was carried out on all participants captured in the ASRI, stratified on the basis of sex. Participants who did not have sex recorded were excluded from the analysis. A Shapiro–Wilk test was used to assess normality of distribution for all included variables. Differences between continuous variables in the two groups were tested for significance using an independent two-tailed t-test or a Mann–Whitney U-test. A chi-squared test for independence was used to assess statistical significance in differences in 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 test for normal distribution, in addition to visual inspection of a scatterplot to determine the 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 the strength of correlation of scores within each sex. An alpha level of $p < 0.05$ was deemed significant. SPSS version 26 (IBM Corp., Armonk, NY, USA) was used to carry out all statistical analyses in this study.

Results

At the time of data extraction, 886 participants were enrolled in the ASRI. The patient population comprised 232 females (26.2%) and 644 males (72.6%), with a mean $\pm$ sd age of 45.9 ± 12.6 years (range 18–85 years), mean disease duration of 19.4 ± 12.3 years, and mean delay to diagnosis of 8 ± 8.5 years. Mean scores for the ASRI population were: ASQoL 6.47 [95% confidence interval (CI) 6.07, 6.95], HAQ 0.53 (95% CI 0.55, 0.6), BASDAI 4.02 (95% CI 3.81, 4.19), BASFI 3.67 (95% CI 3.47, 3.89), and BASMI 4 (3.85, 4.17). The majority of the population was Caucasian (90.2%), with a high prevalence of HLA-B27 positivity (88.7%).

No significant differences between sexes were noted in delay to diagnosis (females vs males: 7.42 vs 8.18; 95% CI -2.03 , 0.52 ; $p = 0.24$) or age at symptom onset (25.9 vs 26.6; 95% CI -2.49 , 1.02 ; $p = 0.41$) (Table 1). r-axSpA was more commonly encountered in males than females (78.1% vs 70.7%, $p = 0.02$), while nr-axSpA was significantly more prevalent in females (21.9% vs 29.3%, $p = 0.02$).

In terms of articular manifestations, females had 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 a 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.

Females with axSpA recorded significantly higher ASQoL (7.51 vs 6.12; 95% CI 0.56, 2.22; $p < 0.01$) and BASDAI (4.57 vs 3.83; 95% CI 0.37, 1.10; $p < 0.01$) scores compared to males (Table 2). They also recorded trends towards worse mean HAQ (0.59 vs 0.51; 95% CI -0.002 , 0.16 ; $p = 0.05$) and BASFI scores (3.85 vs 3.63; 95% CI -0.22 , 0.66 ; $p = 0.32$), but these differences were not significant. Spinal mobility, as captured in the BASMI, was significantly less impaired in females than in males (3.58 vs 4.16; 95% CI -0.94 , -0.22 ; $p < 0.01$).

BASDAI analysis

Females with axSpA reported worse mean total BASDAI (4.6 vs 3.83; 95% CI 0.37, 1.10; $p < 0.01$), compared to males. Within the BASDAI, females scored significantly worse than males across all components (Fatigue: 5.56 vs 4.51, $p < 0.01$; Spinal pain: 5.51 vs 4.63, $p < 0.01$; Other pain: 3.82 vs 3.19, $p = 0.01$; Discomfort: 4.05 vs 3.29, $p < 0.01$; EMS: 4.55 vs 3.94, $p = 0.01$), with the exception of duration of EMS, which demonstrated a non-significant trend towards higher average scores in females (3.54 vs 3.12, $p = 0.07$) (Table 2). 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

Table 1. Analysis of patient characteristics on the basis of sex.

	Females	Males	p
Number of patients	232 (26.2)	644 (72.6)	
Age (years)	43.8	46.5	0.01*
Delay to diagnosis (years)	7.42	8.18	0.24
Age at symptom onset (years)	25.9	26.6	0.41
Disease duration (years)	17.9	19.8	0.06
Caucasian	181 (78)	618 (96)	< 0.01*
HLA-B27 ⁺	164/227 (72.2)	438/487 (89.9)	0.68
r-axSpA	164 (70.7)	503 (78.1)	0.02*
nr-axSpA	68 (29.3)	141 (21.9)	0.02*
Pattern of disease			
Peripheral arthritis	84 (36.2)	182 (28.3)	0.08
Enthesitis	43 (18.5)	109 (16.9)	0.56
Dactylitis	23 (9.9)	32 (5)	0.01*
EAMs			
Psoriasis	40 (17.2)	104 (16.1)	0.21
Uveitis	94 (40.5)	203 (35.7)	0.01*
Colitis	40 (17.2)	51 (7.9)	< 0.01*
Medication			
NSAIDs	129 (55.6)	318 (49.4)	0.2
DMARDs	52 (22.4)	154 (23.9)	0.29
Biologics	155 (66.8)	439 (68.2)	0.81
Current ESR (mm/h)	17.9	14.8	0.04*
Current CRP (mg/L)	6.6	7.3	0.46
Patient outcomes			
BASDAI	4.57	3.83	< 0.01*
BASFI	3.85	3.63	0.32
BASMI	3.58	4.16	< 0.01*
HAQ	0.59	0.51	0.05
ASQoL	7.51	6.12	< 0.01*

Data are shown as n (%) or mean values.

HLA-B27, human leucocyte antigen B27; r-axSpA, radiographic ankylosing spondylitis; nr-axSpA, non-radiographic ankylosing spondylitis; EAM, extra-articular manifestation; NSAID, non-steroidal anti-inflammatory drug; DMARD, disease-modifying anti-rheumatic drug; 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 Metrology Index; HAQ, Hospital Assessment Questionnaire; ASQoL, Ankylosing Spondylitis Quality of Life questionnaire.

*Significant difference between sexes ($p < 0.05$).

observed in the component ranked as the most severe. For 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 1).

Spinal mobility and function

Data on both BASMI and BASFI scores were available for 680 patients, and were included in the analysis. Variables were not normally distributed, as assessed by the Shapiro–Wilk 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.

Table 2. Breakdown of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) total and component scores by sex, with ranking of average component scores by severity within each sex.

	Females	Males	p
Mean scores			
BASDAI total	4.57	3.83	< 0.01*
1 – Fatigue	5.56	4.51	< 0.01
2 – Spinal pain	5.51	4.63	< 0.01
3 – Other pain	3.82	3.19	0.01
4 – Discomfort	4.05	3.29	< 0.01
5 – EMS	4.55	3.94	0.01
6 – EMS duration	3.54	3.12	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	

EMS, early morning stiffness.

*Indicates statistically significant difference between sexes ($p < 0.05$)

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 a Spearman's rank-order correlation.

A Spearman's rank-order correlation analysis following splitting of records by sex showed that the correlation became stronger when assessed within each sex [females $r_s(144) = 0.619$, $p < 0.01$; males $r_s(509) = 0.572$, $p < 0.01$] and had a slightly stronger association with in females (Figure 2).

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 PROs, with a higher prevalence of articular and extra-articular manifestations noted in women compared to men with axSpA. The analysis contained within this study provides valuable insight into the impact of axSpA and how this varies between men and women.

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 towards worse HAQ and BASFI, representing greater impairment of function. However, women recorded significantly better spinal mobility, captured via the BASMI, with a lower proportion

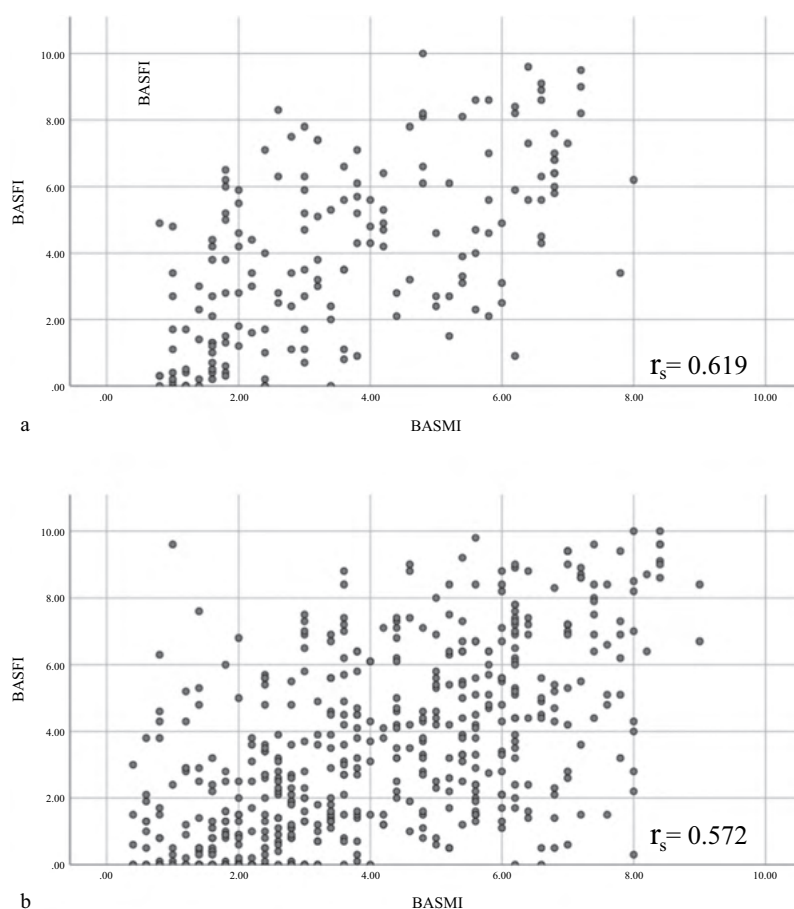


Figure 1. Mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) component scores plotted by sex. EMS, early morning stiffness.

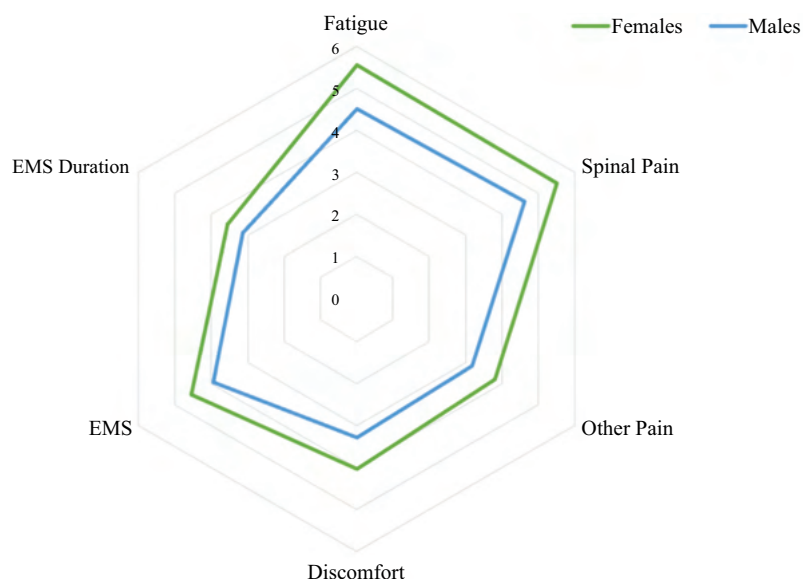


Figure 2. Correlation between Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) in (A) females and (B) males.

classified as r-axSpA than males with axSpA, although the majority of the ASRI population had radiographic disease. These findings are supported by studies in other large international axSpA cohorts, which reported similar differences between sexes (8, 18–21).

Women with axSpA recorded significantly worse total BASDAI scores compared to men, consistent with results from other large axSpA cohorts (8, 19, 20). 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 was noted. This suggests that despite differences in total scores, the overall pattern of disease activity, as captured by the BASDAI, is strikingly similar in men and women.

The question of why women record worse PROs, including the BASDAI, still remains. The findings of our analysis demonstrated that women with axSpA had a significantly higher burden of a number of both articular and extra-articular manifestations. 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 the increased severity of fatigue observed in women with axSpA. Of interest, a previous study examined the topography of pain reporting in axSpA and reporting of symptoms in the BASDAI (22). This revealed that the level of pain corresponded to BASDAI total scores in men, while in women the level of pain was linked to assessment of peripheral and axial symptoms when considered separately. These findings

led to the recommendation of sex-specific approaches when considering the 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 that the wealth of information captured by this tool is interpreted in a way that adequately reflects the clinical picture in both men and women with axSpA.

It has been well established that men with axSpA tend to have greater limitation of spinal mobility, as captured in the BASMI (23, 24), 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; in clinical terms, patients with greater limitation of spinal mobility tend to have an increased level of functional impairment and vice versa. The results of this analysis by sex indicate that this correlation is more significant if compared separately within each sex, and is notably stronger in females.

Men with axSpA have previously been shown to have a higher prevalence of radiographic disease and a worse severity of radiographic disease over time (21, 25, 26). 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. The stronger correlation noted in women with axSpA 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 men compared to women with axSpA. Why this variation occurs is not immediately

apparent; however, research and advances in motion capture technology may offer further insights (27).

Previous studies have proposed that the higher prevalence of centralized sensitization (20) and fibromyalgia (28) in women could be significant contributors to the differences detected in patient outcomes, as both can lead to chronic widespread pain (CWP) (29, 30). Although these issues are more common in women in the general population, they are clinical diagnoses of exclusion (31, 32). The importance of thorough investigation of CWP was highlighted in an Israeli study of known fibromyalgia patients, which found that 10.2% met ASAS criteria for axSpA while up to 25% had imaging findings suggestive of inflammatory disease (33). In patients with a known underlying axSpA, distinguishing between disease activity and CWP can be quite difficult (34, 35). 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 (36). 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 (37, 38) when assessing disease activity in axSpA. A meta-analysis examining the performance of the ASDAS and BASDAI concluded that the ASDAS may not be sensitive enough in the detection of active peripheral disease (39). As peripheral involvement is more common in females with axSpA (5), 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 biological therapies in males with axSpA (40). However, given the known variation in patterns of disease activity between axSpA in women and men, it may be 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 AS in predominantly male cohorts (13, 41). The development of sex-specific scores indicative of active disease could help to better compare scores between men and women. In addition, evaluation of outcome measures regarding their ability to capture the burden of articular and extra-articular manifestations in both sexes may provide further insights into the variation in outcomes observed between sexes.

Despite the higher prevalence of several disease manifestations and worse PROs in women with axSpA, medication use was statistically similar between the sexes. This pattern of medication use is not unique to the ASRI, with similarities in the frequency of use of DMARDs and biological therapy in men and women observed in other large cohort studies (8, 18). A 2020 publication examining medication use before and after

the recognition of nr-axSpA found no change in use of DMARDs or biologics between males and females (42). 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?

The most obvious but least understood cause for variations between men and women is hormonal differences (43). Oestrogens have been shown to inhibit production of tumour necrosis factor- α and decrease differentiation of Th17 cells (44), which has 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 (45). In addition, we must consider the significant hormonal shifts that the female body undergoes over the course of a lifetime and how they affect disease activity. These include menstruation, pregnancy, and menopause, as data suggest that the overall effects of hormones are concentration dependent (46). Studies on pregnancy in axSpA vary widely, but a high prevalence of active disease during pregnancy, peaking in the second trimester, has been reported (47). Research on menstrual variation in disease activity is incredibly limited; however, one study reported an inverse relationship between oestrogen level and erythrocyte sedimentation rate (48). 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.

This study has several potential limitations. Data for the analysis contained within this study were cross-sectional in nature owing 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. At the time of analysis, ASDAS results were not available for a large proportion of the ASRI population, preventing comparative analysis of the performance of the ASDAS and the BASDAI in our population. This has been studied in detail in numerous axSpA populations previously, and thus sex-specific patterns in reporting of the ASDAS are well established. As fluency in English was required for participation, it is possible that this resulted in exclusion of certain smaller populations from enrolment in the ASRI; however, English fluency in Ireland is 97.5% so this is unlikely (49). Ireland does not have centralized medical records, so it was not feasible to report the percentage of axSpA patients in Ireland captured within the ASRI. However, recruitment was from all major geographic regions of the country and included all levels of the socioeconomic spectrum to reflect the

true population as accurately as possible and limit selection bias.

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. They also reported significantly worse disease activity and quality of life. However, the overall pattern of symptom severity as captured by the BASDAI was similar in men and women. Despite better mean spinal mobility overall compared to men with axSpA, limitation of spinal mobility in women with axSpA corresponded to a greater impairment in functional ability. These results suggest that 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. In addition, further studies are required to examine the impact of significant hormonal changes on disease activity and disease progression in women with axSpA.

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References

- Robinson PC, van der Linden S, Khan MA, Taylor WJ. Axial spondyloarthritis: concept, construct, classification and implications for therapy. *Nat Rev Rheumatol* 2021;17:109–18.
- Braun J, Baraliakos X, Buehring B, Kiltz U, Fruth M. Imaging of axial spondyloarthritis. New aspects and differential diagnoses. *Clin Exp Rheumatol* 2018;36 Suppl 114:35–42.
- Marzo-Ortega H. Axial spondyloarthritis: coming of age. *Rheumatology (Oxford)* 2020;59:iv1–iv5.
- Gran JT, Husby G. Ankylosing spondylitis in women. *Semin Arthritis Rheum* 1990;19:303–12.
- Rusman T, van Bentum RE, van der Horst-bruinsma IE. Sex and gender differences in axial spondyloarthritis: myths and truths. *Rheumatology (Oxford)* 2020;59:iv38–iv46.
- Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777–83.
- Protopopov M, Poddubnyy D. Radiographic progression in non-radiographic axial spondyloarthritis. *Expert Rev Clin Immunol* 2018;14:525–33.
- de Jong H, Paramarta JE, de Winter J, Baeten D, van de Sande M. Differences between females and males in axial spondyloarthritis: data from a real-life cross-sectional cohort. *Scand J Rheumatol* 2020;49:28–32.
- Rusman T, van Vollenhoven RF, van der Horst-bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. *Curr Rheumatol Rep* 2018;20:35.
- Garrido-Cumbrera M, Poddubnyy D, Gossec L, Mahapatra R, Bundy C, Makri S, et al. Gender differences in patient journey to diagnosis and disease outcomes: results from the European Map of Axial Spondyloarthritis (EMAS). *Clin Rheumatol* 2021;40:2753–61.
- Ruiz-Cantero MT, Blasco-Blasco M. Perspectiva de género en epidemiología clínica. Aprendiendo con el caso de las espondilodiartritis [Gender perspective in clinical epidemiology. Learning from spondyloarthritis]. *Gac Sanit* 2020;34:83–6.
- Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), and Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S). *Arthritis Care Res (Hoboken)* 2011;63 Suppl 11:S47–58.
- Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21:2286–91.
- Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21:2281–5.
- Kwan YH, Fong W, Lui NL, Yong ST, Cheung YB, Malhotra R, et al. Validity and reliability of the Health Assessment Questionnaire among patients with spondyloarthritis in Singapore. *Int J Rheum Dis* 2018;21:699–704.
- Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Ann Rheum Dis* 2003;62:20–6.
- Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol* 1994;21:1694–8.
- Andreasen RA, Kristensen LE, Egstrup K, Baraliakos X, Strand V, Horn HC, et al. The impact of sex and disease classification on patient-reported outcome measures in axial spondyloarthritis: a descriptive prospective cross-sectional study. *Arthritis Res Ther* 2019;21:221.
- Tournadre A, Pereira B, Lhoste A, Dubost JJ, Ristori JM, Claudepierre P, et al. Differences between women and men with recent-onset axial spondyloarthritis: results from a prospective multicenter French cohort. *Arthritis Care Res (Hoboken)* 2013;65:1482–9.
- Mease PJ, McLean RR, Dube B, Liu M, Rebello S, Glynn M, et al. Comparison of men and women with axial spondyloarthritis in the US-based corona psoriatic arthritis/spondyloarthritis registry. *J Rheumatol* 2021;48:1528–36.
- Wallman JK, Kapetanovic MC, Petersson IF, Geborek P, Kristensen LE. Comparison of non-radiographic axial spondyloarthritis and ankylosing spondylitis patients—baseline characteristics, treatment adherence, and development of clinical variables during

- three years of anti-TNF therapy in clinical practice. *Arthritis Res Ther* 2015;17:378.
22. Swinnen TW, Westhovens R, Dankaerts W, de Vlam K. Widespread pain in axial spondyloarthritis: clinical importance and gender differences. *Arthritis Res Ther* 2018;20:156.
 23. Webers C, Essers I, Ramiro S, Stolwijk C, Landewé R, van der Heijde D, et al. Gender-attributable differences in outcome of ankylosing spondylitis: long-term results from the Outcome in Ankylosing Spondylitis International Study. *Rheumatology (Oxford)* 2016;55:419–28.
 24. Biallas RL, Dean LE, Davidson L, Hollick R, Pathan E, Robertson L, et al. The role of metrology in axSpA: does it provide unique information in assessing patients and predicting outcome? Results from the BSRBR-AS registry. *Arthritis Care Res (Hoboken)* 2020.
 25. Huang JX, Chung HY, Chui ETF, Lee KH, Chan SCW, Tsang HHL, et al. Intensity of spinal inflammation is associated with radiological structural damage in patients with active axial spondyloarthritis. *Rheumatol Adv Pract* 2020;4:rkz049.
 26. Baraliakos X, Braun J. Non-radiographic axial spondyloarthritis and ankylosing spondylitis: what are the similarities and differences? *RMD Open* 2015;1:e000053.
 27. Gardiner PV, Small D, Muñoz-Esquivel K, Condell J, Cuesta-Vargas A, Williams J, et al. Validity and reliability of a sensor-based electronic spinal mobility index for axial spondyloarthritis. *Rheumatology (Oxford)* 2020;59:3415–23.
 28. Rencber N, Saglam G, Huner B, Kuru O. Presence of fibromyalgia syndrome and its relationship with clinical parameters in patients with axial spondyloarthritis. *Pain Physician* 2019;22:E579–e85.
 29. Lubrano E, Perrotta FM, Manara M, D'Angelo S, Addimanda O, Ramonda R, et al. The sex influence on response to tumor necrosis factor- α inhibitors and remission in axial spondyloarthritis. *J Rheumatol* 2018;45:195–201.
 30. Lorenzin M, Ortolan A, Frallonardo P, Oliviero F, Punzi L, Ramonda R. Predictors of response and drug survival in ankylosing spondylitis patients treated with infliximab. *BMC Musculoskelet Disord* 2015;16:166.
 31. Marques AP, Santo A, Berssaneti AA, Matsutani LA, Yuan SLK. Prevalence of fibromyalgia: literature review update. *Rev Bras Reumatol Engl Ed* 2017;57:356–63.
 32. Smith MT Jr., Remeniuk B, Finan PH, Speed TJ, Tompkins DA, Robinson M, et al. Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: implications for sex differences in chronic pain. *Sleep* 2019;42:1–15.
 33. Ablin JN, Eshed I, Berman M, Aloush V, Wigler I, Caspi D, et al. Prevalence of axial spondyloarthritis among patients with fibromyalgia: a magnetic resonance imaging study with application of the assessment of spondyloarthritis international society classification criteria. *Arthritis Care Res (Hoboken)* 2017;69:724–9.
 34. López-Medina C, Moltó A. Comorbid pain in axial spondyloarthritis, including fibromyalgia. *Ther Adv Musculoskelet Dis* 2020;12:1759720x20966123.
 35. Dougados M, Perrot S. Fibromyalgia and central sensitization in chronic inflammatory joint diseases. *Joint Bone Spine* 2017;84:511–3.
 36. Slobodin G, Reyhan I, Avshovich N, Balbir-Gurman A, Boulman N, Elias M, et al. Recently diagnosed axial spondyloarthritis: gender differences and factors related to delay in diagnosis. *Clin Rheumatol* 2011;30:1075–80.
 37. Salaffi F, De Angelis R, Carotti M, Gutierrez M, Sarzi-Putini P, Atzeni F. Fibromyalgia in patients with axial spondyloarthritis: epidemiological profile and effect on measures of disease activity. *Rheumatol Int* 2014;34:1103–10.
 38. van der Horst-bruinsma IE, Zack DJ, Szumski A, Koenig AS. Female patients with ankylosing spondylitis: analysis of the impact of gender across treatment studies. *Ann Rheum Dis* 2013;72:1221–4.
 39. Blasco-Blasco M, Castrejón I, Jovaní V, Pascual E, Ruiz-Cantero MT. Reviewing disease activity indices in spondyloarthritis from the gender perspective: a systematic review and meta-analysis. *J Rheumatol* 2021;48:1395–404.
 40. Marona J, Sepriano A, Rodrigues-Manica S, Pimentel-Santos F, Mourão AF, Gouveia N, et al. Eligibility criteria for biologic disease-modifying antirheumatic drugs in axial spondyloarthritis: going beyond BASDAI. *RMD Open* 2020;6:e001145.
 41. Calin A, Nakache JP, Gueguen A, Zeidler H, Mielants H, Dougados M. Defining disease activity in ankylosing spondylitis: is a combination of variables (Bath Ankylosing Spondylitis Disease Activity Index) an appropriate instrument? *Rheumatology (Oxford)* 1999;38:878–82.
 42. Nieto RE, Plasencia Rodriguez C, Peiteado López D, Villalba Yllán A, Balsa Criado A, Navarro-Compán V. Are we treating women patients with real axial spondyloarthritis? *Semin Arthritis Rheum* 2020;50:432–5.
 43. Wright GC, Kaine J, Deodhar A. Understanding differences between men and women with axial spondyloarthritis. *Semin Arthritis Rheum* 2020;50:687–94.
 44. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nat Rev Immunol* 2008;8:737–44.
 45. Mahendira D, Thavaneswaran A, Carty A, Haroon N, Anton A, Passalent L, et al. Analysis of the effect of the oral contraceptive pill on clinical outcomes in women with ankylosing spondylitis. *J Rheumatol* 2014;41:1344–8.
 46. Shepherd R, Cheung AS, Pang K, Saffery R, Novakovic B. Sexual dimorphism in innate immunity: the role of sex hormones and epigenetics. *Front Immunol* 2020;11:604000.
 47. Maguire S, O'Dwyer T, Mockler D, O'Shea F, Wilson F. Pregnancy in axial spondyloarthropathy: a systematic review & meta-analysis. *Semin Arthritis Rheum* 2020;50:1269–79.
 48. Jimenez-Balderas FJ, Tapia-Serrano R, Madero-Cervera JJ, Murrieta S, Mintz G. Ovarian function studies in active ankylosing spondylitis in women. Clinical response to estrogen therapy. *J Rheumatol* 1990;17:497–502.
 49. Central Statistics Office (CSO). Census 2016 published reports [Website]. Cork, Ireland 2016 [cited 2021]. Available from: <https://www.cso.ie/en/census/census2016reports/>.

Supplementary material

Supplemental data for this article can be accessed [here](#).

The negative impact of undiagnosed depression in axial spondyloarthritis

Sirs,

The true prevalence of depression is suspected to be underestimated as the diagnosis can persist undetected in a significant proportion of the population (1). The reasons for this are multifactorial but include under recognition of symptoms, difficulty accessing appropriate services, and societal stigma (2). Depression in axial spondyloarthritis (axSpA) is known to be more prevalent than in the general population (3-5) and is associated with younger age, increased disease activity and lower levels of exercise (6, 7). Early identification of depression in the general population can result in improved quality of life and higher rates of clinical remission following treatment (8).

The aim of this analysis was to screen for undiagnosed depression in a cohort of patients with known axSpA. AxSpA patients attending the Rheumatology department in St James' Hospital between February and October 2020 were invited to complete the Patient Health Questionnaire 9 (PHQ-9) and the Hospital Anxiety and Depression Scale for Depression (HADS-D). Those with known depression were excluded from participation.

These validated Psychiatry tools to screen for undiagnosed depression (9) have previously functioned well in studies on mental health in rheumatic disease (10). Abnormal HADS-D scores (>11) or moderate PHQ-9 scores (>10) are considered clinically significant and suggestive of underlying depression.

The data were analysed for statistical significance using independent t-tests for continuous variables and a chi² test for independence or Fisher's exact test for categorical variables. A one-way analysis of variance analysis (ANOVA) determined significance of variation in outcomes between classification of HADS-D and PHQ-9 results. All necessary assumptions were met for each statistical test. A *p*-value of <0.05 was considered significant. Informed consent was obtained from all participants prior to participation. This study was approved by the St James'/Tallaght Hospital Joint Ethics Committee. Seventy-one axSpA patients were included, consisting of 70.4% (50) males and 29.5% (21) females, with mean age 47.9 years (SD 15.4, range 20–78) and mean disease duration 19.7 years (SD 14.3). 9.9% (7) of participants recorded abnormal HADS-D scores, while 23.9% (17) recorded moderate to severe PHQ-9 scores indicative of underlying depression. AxSpA females averaged 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 sexes.

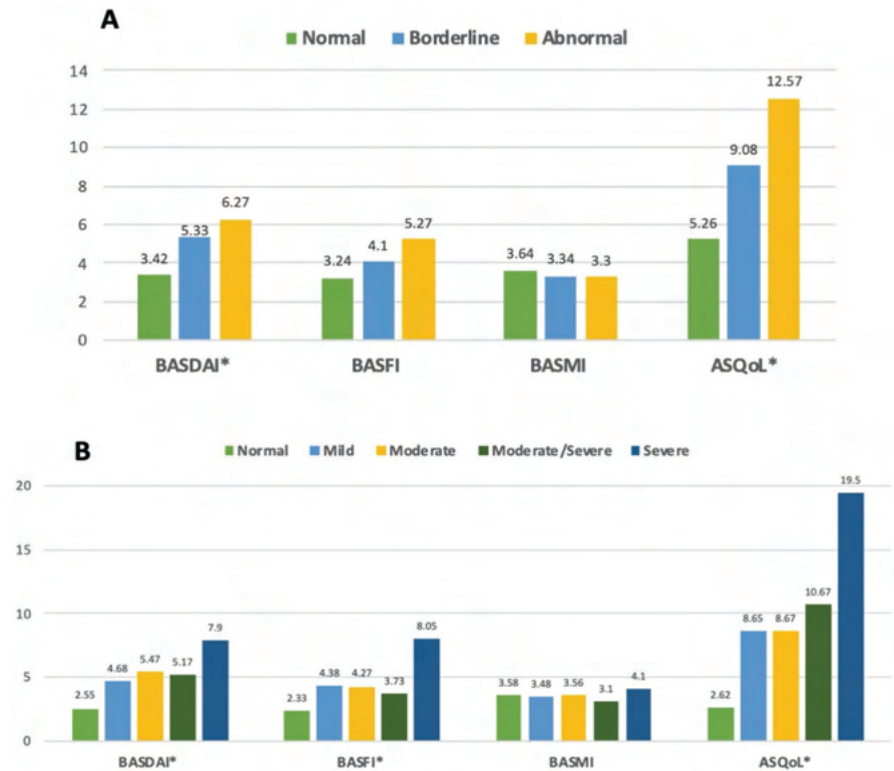


Fig. 1. Patient outcomes by classification with (A) HADS-D score and (B) PHQ-9 score, *indicates statistically significant differences between classification categories at the *p*<0.05 level.

Analysis revealed significantly worse BASDAI (6.27 vs. 3.42, *p*<0.01) and ASQoL scores (12.57 vs. 5.26, *p*<0.01) in patients with abnormal compared to normal HADS-D scores (Fig. 1). In PHQ-9 scores, significantly worse BASDAI (7.9 vs. 2.55, *p*<0.01), BASFI (8.05 vs. 2.33, *p*<0.01) and ASQoL (19.5 vs. 2.62, *p*<0.01) was noted in patients classified as severe compared to normal.

Elevated PHQ-9 and HADS-D scores concerning for undiagnosed depression, were frequently encountered in axSpA patients and were associated with higher disease activity and worse quality of life. Abnormal scores were more common in women with axSpA compared to men, which raises concerns around the high prevalence of undiagnosed depression and the impact on disease control in this population. The findings of this study would suggest that clinicians treating axSpA should consider mental health and potentially consider screening for depression in this population.

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. During 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.

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References

- MALHI GS, MANN JJ: Depression. *Lancet* 2018; 392: 2299-312.
- KOHN R, SAXENA S, LEVAV I, SARACENO B: The treatment gap in mental health care. *Bull World Health Organ* 2004; 82: 858-66.
- SHEN CC, HU LY, YANG AC, KUO BI, CHIANG YY, TSAI SJ: Risk of psychiatric disorders following ankylosing spondylitis: a nationwide population-based retrospective cohort study. *J Rheumatol* 2016; 43: 625-31.
- MEESTERS JJ, BREMANDER A, BERGMAN S, PETERSSON IF, TURKIEWICZ A, ENGLUND M: The risk for depression in patients with ankylosing spondylitis: a population-based cohort study. *Arthritis Res Ther* 2014; 16: 418.
- PARK JY, HOWREN AM, ZUSMAN EZ, ESDAILE JM, DE VERA MA: The incidence of depression and anxiety in patients with ankylosing spondylitis: a

Letters to the Editors

- systematic review and meta-analysis. *BMC Rheumatol* 2020; 4: 12.
6. REDEKER I, HOFFMANN F, CALLHOFF J *et al.*: Determinants of psychological well-being in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. *Ann Rheum Dis* 2018; 77: 1017-24.
7. HWANG MC, LEE MJ, GENSLER LS *et al.*: Longitudinal associations between depressive symptoms and clinical factors in ankylosing spondylitis patients: analysis from an observational cohort. *Rheumatol Int* 2020; 40: 1053-61.
8. SIU AL, BIBBINS-DOMINGO K, GROSSMAN DC *et al.*: Screening for Depression in Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* 2016; 315: 380-7.
9. ALI GC, RYAN G, DE SILVA MJ: Validated screening tools for common mental disorders in low and middle income countries: a systematic review. *PLoS One* 2016; 11: e0156939.
10. INGEGNOLI F, SCHIOPPO T, UBIALI T *et al.*: Patient perception of depressive symptoms in rheumatic diseases: a cross-sectional survey. *J Clin Rheumatol* 2022; 28: e18-22.

Central Obesity in Axial Spondyloarthritis: The Missing Link to Understanding Worse Outcomes in Women?

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ABSTRACT. *Objective.* To determine (1) the prevalence of central obesity in axial spondyloarthritis (axSpA) and its effect on disease-related outcomes and (2) how this differs between sexes.

Methods. Data were extracted from the Ankylosing Spondylitis Registry of Ireland. Patients with physical measurements for the calculation of anthropometric measures were included. BMI and waist-to-hip ratio (WHR) were used to compare classifications of obesity. Comparison analyses based on sex and central obesity were carried out. Multivariate analysis examined the effects of these factors on the following patient-reported outcomes: the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire, and the Health Assessment Questionnaire (HAQ).

Results. In total, 753 patients were included in the analysis. Of these patients, 29.6% (n = 223) were classified as obese based on their BMI, and 41.3% (n = 311) were classified as centrally obese according to the WHR. The prevalence of central obesity was significantly higher among women with axSpA compared to men (71.6% vs 29.9%, $P < 0.01$). Central obesity had a clear effect on patient outcomes, regardless of sex. Presence of central obesity was associated with significantly worse BASFI scores ($P < 0.01$), HAQ scores ($P < 0.01$), and ASQoL questionnaire scores ($P = 0.01$), with a nonsignificant trend toward worse BASDAI scores ($P = 0.07$).

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

Key Indexing Terms: abdominal obesity, ankylosing spondylitis, arthritis, obesity, spondyloarthropathies, women's health

Worldwide prevalence of obesity has been steadily increasing^{1,2} despite numerous public health campaigns to increase public awareness. Obesity is known to be associated with an increased risk of all-cause mortality³ and is the second most common preventable cause of death in the United States.⁴ As the prevalence of this health issue surges, so too do the frequencies of associated complications, such as type 2 diabetes and cardiovascular disease, which have a significant effect on patients' overall quality of life (QOL) and place significant demands on the healthcare system.⁵

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This rising prevalence is especially concerning in axial spondyloarthritis (axSpA), an inflammatory arthritis predominantly involving the axial spine.⁶ Obesity in axSpA has previously been associated with higher levels of disease activity^{7,8} and decreased response to treatment.⁹ The presence of obesity has even been linked to new syndesmophyte formation and enthesitis.¹⁰ This is related to adipose tissue secretion of proinflammatory cytokines, called adipocytokines, which in high concentrations can promote a persistent systemic inflammatory state.¹¹ 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.¹² Despite the established negative effect of obesity in axSpA, it remains a frequently encountered comorbidity with a reported prevalence of 14% to 27%.^{13,14}

The presence of obesity is commonly determined by calculation of BMI. However, additional anthropometric scores have been developed to move beyond weight excess and focus on determining the prevalence of abdominal or central obesity. The waist-to-hip ratio (WHR) is a validated measure that is used to screen for central obesity in the general population.¹⁵ Central deposition of adipose tissue is associated with increased risk of cardiovascular disease, type 2 diabetes, and premature

death.^{16,17,18,19} Typically, central obesity is more often found among males because of deposition of visceral fat, whereas females are more prone to gluteal-femoral subcutaneous fat deposition.²⁰ During menopause, there is a shift toward more central fat deposition, which increases further in the postmenopausal period.^{21,22}

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 also examined how this differs between men and women with axSpA.

METHODS

Patient population. Data for the analysis were extracted from 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 centers, representing all major geographic regions of the country. Since being launched in 2013, 892 patients have been enrolled in the ASRI, with recruitment ongoing in multiple centers. This analysis included all participants with anthropometric data recorded who were enrolled in the ASRI since the time of its inception.

All participants were required to meet several inclusion criteria in order to be considered for enrollment: diagnosed with axSpA by a rheumatologist; met the Assessment of SpondyloArthritis international Society (ASAS) criteria for axSpA at the time of enrollment, which allowed for data collection on both radiographic axSpA (r-axSpA) and nonradiographic axSpA (nr-axSpA); aged > 18 years; had full capacity; and fluent in English. All eligibility criteria were required at the time of enrollment in order to be included in the ASRI.

Written informed consent was obtained from each patient prior to enrollment. 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 at any time and encouraged to discuss questions with investigators prior to signing the consent declaration. Ethical approval was received from local hospital ethics boards at each site that contributed patients to the ASRI. For the main center, St James’s Hospital, the study was approved by the St James’s Hospital/Tallaght University Hospital Joint Research Ethics Committee (approval no. 2019-07[27]; Supplementary Table 1, available with the online version of this article).

Outcome definitions and assessment. Each participant attended a single clinical visit conducted by a trained investigator, allowing all data to be collected at a single timepoint. Medical records were reviewed for radiology results, patterns of disease, and medication usage. Data were collected on participant demographics; disease duration; delay to diagnosis; patterns of disease, including both articular and extraarticular manifestations; and presence of comorbidities.

Participants completed self-administered questionnaires to provide information on patient outcomes; responses were recorded on a numerical scale, with higher scores indicating greater severity. Specific outcomes that were investigated include those measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), the Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Disease Activity Score (ASDAS), the Health Assessment Questionnaire (HAQ), and the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire. A focused clinical examination measured spinal mobility to allow for calculation of the Bath Ankylosing Spondylitis Metrology Index (BASMI). Physical measurements were also recorded: waist circumference measured halfway between the lowest rib and the iliac crest, and hip circumference measured at the widest part of the hips and buttocks region.²³ All outcome measures in this analysis were validated for use in axSpA.

Participants were analyzed on the basis of sex and the presence of obesity. Obesity was defined by BMI, calculated as weight in kilograms divided by height in meters squared; a participant with a result > 30 was categorized as obese, as per the Centers for Disease Control and Prevention definition.²⁴ Central obesity was assessed by the WHR and defined according to the World Health Organization guidelines²⁵ (Table 1).

Statistical analysis: IBM SPSS Statistics for Windows (version 26; IBM Corp) was used for statistical analysis and data processing. Comparison analyses determined variation in the prevalence of obesity and variation between sexes. Categorical variables were recorded as frequencies with percentages, with a chi-square test for independence or a Fisher exact test for statistical significance. Means and SDs were calculated for numerical variables within each group, with an independent *t* test or Mann-Whitney *U* test to assess the significance of differences between groups. A Shapiro-Wilk test was carried out on all included variables to determine normality of the distribution. To assess the relationship between the WHR and BMI, a Spearman rank-order correlation was run because variables were not normally distributed. Scatterplots were constructed to visualize the presence of a monotonic relationship for each analysis.

A 2-way multivariate ANOVA assessed the effects of sex (ie, male vs female) and central obesity, as measured by the WHR, on patient-reported outcomes (PROs; ie, BASDAI, BASFI, ASQoL, and HAQ). An α level of < 0.05 was deemed significant. A binary logistic regression model examined the effects of age, sex (ie, male vs female), axSpA classification (ie, radiographic vs nonradiographic), BASDAI score, BASFI score, and BASMI score on the likelihood of central obesity. A Bonferroni correction was applied to determine *P* values for levels of statistical significance of linearity. All necessary assumptions for each statistical test were met.

RESULTS

At data extraction, physical measurements were available for 753 participants enrolled in the ASRI; of these participants, 88.4% (n = 666) were White, 27.6% (n = 208) were female, and 71.4% (n = 538) were male (Table 2). The mean age of the participants was 45.6 (SD 12.6, range 18–85) years; the mean disease duration was 18.8 years (SD 12.3). Out of all the participants, 75.2% (n = 566) were classified as having r-axSpA, whereas 24.8% (n = 187) were classified as having nr-axSpA. Mean scores for the self-administered questionnaires were as follows: BASDAI, mean 4.11 (95% CI 3.91–4.26); BASFI, mean 3.68 (95% CI 3.46–3.84); BASMI, mean 4.0 (95% CI 3.37–4.45); HAQ, mean 0.527 (95% CI 0.49–0.57); ASQoL, mean 6.72 (95% CI 6.31–7.12); and ASDAS, mean 2.4 (95% CI 1.99–2.65). In terms of anthropometric measurements, the mean BMI was 28.2 (SD 6.3) and the mean WHR was 0.941 (SD 0.104).

In total, 29.6% (n = 223) of the patients were considered obese based on BMI results, whereas 41.2% (n = 310) were considered centrally obese according to the WHR. Comparison

Table 1. WHR definitions for classification of central obesity as per the WHO²⁵.

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

Data are WHR values. WHO: World Health Organization; WHR: waist-to-hip ratio.

Table 2. Characteristics of participants, including comparison by sex and presence of central obesity as measured by the WHR.

	Total	Women	Men	<i>P</i>	No Central Obesity	Central Obesity	<i>P</i>
Participants, n	753	208	538	–	442	311	–
Age, yrs	45.6 (12.6)	43.6 (12.0)	46.1 (12.7)	0.03	43.7 (12.3)	48.6 (12.6)	< 0.01
Age of onset, yrs	26.8 (10.9)	25.9 (9.8)	27.1 (11.2)	0.22	25.7 (9.9)	28.7 (12.1)	< 0.01
Disease duration, yrs	18.8 (12.3)	17.8 (12.1)	19.0 (12.3)	0.25	18.1 (11.6)	19.9 (13.2)	0.06
Delay to diagnosis, yrs	7.8 (8.5)	7.34 (7.9)	8.0 (8.7)	0.35	7.7 (8.0)	7.9 (9.0)	0.73
HLA-B27+ ^a	88.6 (530/598)	89.3 (150/168)	89.8 (380/423)	0.80	87.6 (324/370)	90.4 (206/228)	< 0.01
White	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
NSAIDs	51.7 (389)	53.8 (112)	50.2 (270)	0.47	20.1 (89)	21.2 (66)	0.72
csDMARDs	18.7 (141)	20.7 (43)	18.0 (97)	0.42	20.8 (92)	23.2 (72)	0.24
bDMARDs	68.0 (512)	65.9 (137)	68.8 (370)	0.70	67.4 (298)	68.8 (214)	0.85

Continuous variables are expressed as mean (SD) and categorical variables are expressed as % (n) unless otherwise indicated. ^a Values in parentheses are n/N. Values in bold are statistically significant. bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; nr-axSpA: nonradiographic axial spondyloarthritis; NSAID: nonsteroidal antiinflammatory drug; r-axSpA: radiographic axial spondyloarthritis; WHR: waist-to-hip ratio.

analysis based on sex revealed no significant variation in mean BMI (27.9 vs 28.3, $P = 0.44$) or prevalence of obesity based on BMI (29.8% vs 29.9%, $P = 0.21$) between women and men (Table 3). Normal weight was the most common classification for women, based on BMI, whereas overweight was the most common classification for men.

WHR analysis revealed higher mean WHRs among men compared to women (0.956 vs 0.897, $P < 0.01$). However, the prevalence of central obesity was significantly higher among women than men (71.6% vs 29.9%, $P < 0.01$; Figure 1). Obesity was the most common classification among women, affecting 71.6% (149/208) of them, whereas overweight was the most common classification among men, affecting 46.1% (248/538) of them. Further, only 12.0% (25/208) of women

were classified as normal weight according to the WHR (Table 3).

Analysis of average PROs revealed significantly worse ASQoL scores (7.66 vs 6.05, $P < 0.01$), BASFI scores (4.23 vs 3.30, $P < 0.01$), HAQ scores (0.63 vs 0.45, $P < 0.01$), and BASDAI scores (4.37 vs 3.92, $P = 0.01$) among participants with central obesity compared to those without. As there was a higher proportion of women in the central obesity cohort, further analyses were carried out to determine if sex was a contributing factor in the differences observed.

A multivariate analysis was carried out to determine the effects of sex and central obesity on PROs, including the BASDAI, BASFI, ASQoL, and HAQ. A significant interaction effect was not detected between sex and central obesity ($F = 0.5$,

Table 3. Assessment of anthropometric measures by sex.

	Women	Men	<i>P</i>
Participants, n	208	538	–
Weight, kg	75.1 (18.0)	84.9 (15.4)	< 0.01
BMI	27.9 (6.7)	28.3 (6.2)	0.44
Weight classified by BMI			–
Underweight	2.9 (6)	0.9 (5)	0.21
Normal weight	35.6 (74)	28.1 (151)	–
Overweight	31.7 (66)	38.7 (207)	–
Obese ^a	29.8 (62)	29.9 (161)	–
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
WHR	0.897 (0.1)	0.956 (0.09)	< 0.01
Weight classified by WHR			–
Normal weight	12.0 (25)	24.0 (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 are expressed as mean (SD) and categorical variables are expressed as % (n). ^a Compared to the overall prevalence of obesity in Ireland of 27%. Values in bold are statistically significant. WHR: waist-to-hip ratio.

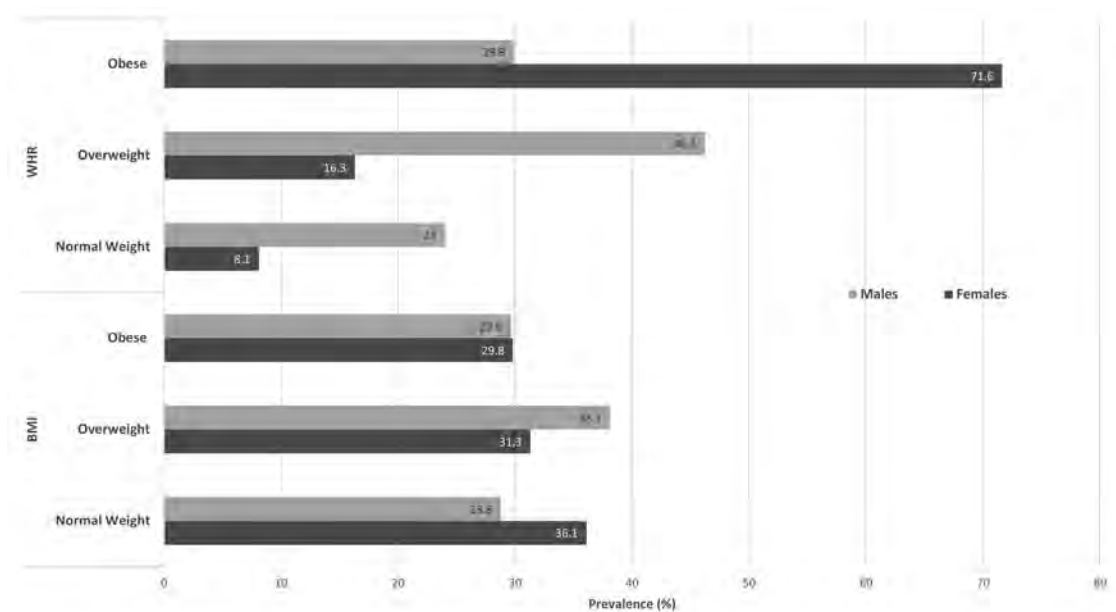


Figure 1. Weight classification as determined using the waist-to-hip ratio (WHR) and BMI by sex.

Wilks $\lambda = 0.997$, $P = 0.74$). However, there was a significant main effect of both sex ($F = 3.99$, $P < 0.01$) and central obesity ($F = 5.68$, $P < 0.01$) on PROs when assessed individually.

A follow-up univariate 2-way ANOVA found a significant main effect of central obesity on several PROs. Specifically, effects were found on ASQoL scores ($F = 7.87$, $P = 0.01$), BASFI scores ($F = 19.45$, $P < 0.01$), and HAQ scores ($F = 12.25$, $P < 0.01$), with a nonsignificant trend detected for BASDAI scores ($F = 3.63$, $P = 0.07$). Follow-up analysis of PROs between centrally obese and normal-weight participants revealed the following average differences: ASQoL, 2.00 (95% CI 3.31–0.70, $P < 0.01$); BASFI, 1.40 (95% CI 2.02–0.80, $P < 0.01$); HAQ, 0.24 (95% CI 0.36–0.12, $P < 0.01$); and BASDAI, 0.65 (95% CI 1.21–0.08, $P = 0.02$). 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 correlation between BMI and the WHR among patients with axSpA ($r_s = 0.456$, $P < 0.01$). When assessed within each sex, the strength of this correlation was found to be stronger among men with axSpA ($r_s = 0.538$, $P < 0.01$) but weaker among women with axSpA ($r_s = 0.349$, $P < 0.01$), although both remained statistically significant.

A binomial regression analysis was performed to identify factors associated with central obesity as determined by the WHR. The logistic regression model was statistically significant ($\chi^2_7 = 96.23$, $P < 0.01$), with an area under the receiver-operating characteristic curve of 0.742 (95% CI 0.699–0.785), indicating an acceptable level of discrimination (Figure 2).

Of the 7 predictor variables assessed (ie, age, female sex, r-axSpA, BASMI, BASDAI, BASFI, and ASQoL), only 2 were statistically significant: age and sex (Table 4). This indicated that both increasing age (odds ratio [OR] 1.03, 95% CI 1.01–1.05)

and female sex (OR 6.76, 95% CI 4.12–11.1) were associated with an increased likelihood of a patient with axSpA having central obesity.

DISCUSSION

This study detailed the high prevalence and detrimental effects of central obesity in axSpA using data from a large, well-characterized national axSpA registry. Obesity, as classified by BMI, has previously been shown to be one of the most prevalent comorbidities in axSpA, with numerous negative implications regarding disease activity and disease progression. 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 effects of this modifiable risk factor on patient outcomes, including disease activity, functional ability, and QOL.

Prevalence of obesity, as classified by BMI, was similar among both sexes (29.8% vs 29.9%, $P = 0.21$). Obesity is one of the most prevalent comorbidities in axSpA, with a recent metaanalysis reporting a pooled prevalence of 14%.¹³ 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.^{26,27} Although it is difficult to determine the true national prevalence of obesity, most recent data report an Irish obesity prevalence of 27%²⁸ compared to 25.2% in the European Union.²⁹ Obesity prevalence in Ireland is currently similar among men and women, although evidence suggests this will soon change.²⁷ Longitudinal data indicate that the European population with the steepest rise in obesity is Irish women.²⁷ Alarming, young women, aged 18–35 years, are driving this rapid increase. This emphasizes the need for early recognition and lifestyle modification from an early age.

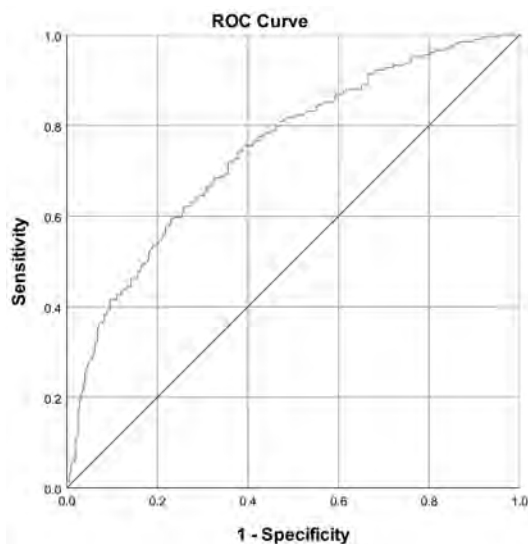


Figure 2. Receiver-operating characteristic (ROC) curve for factors associated with central obesity.

Table 4. Determining the likelihood of central obesity as measured by the WHR.

	OR	95% CI	P
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	0.98–1.10	0.24

Values in bold are statistically significant. ASQoL: Ankylosing Spondylitis Quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; OR: odds ratio; r-axSpA: radiographic axial spondyloarthritis; WHR: waist-to-hip ratio.

The most surprising finding from this current analysis was the significantly higher prevalence of central obesity among women with axSpA compared to men (71.6% vs 29.9%, $P < 0.01$). Previously, central obesity in the general population was perceived as more common among males.²⁰ However, an epidemiological study examining trends in central obesity in the US noted that prevalence was increasing steadily at an annual rate of 0.56% among males and 0.75% among females and that, by 2030, it would affect up to 55.6% of males and 80% of females.³⁰ This finding is cause for alarm, as central obesity is known to be associated with insulin resistance,³¹ renal impairment,³² and higher risk of mortality, even among women with a normal BMI.¹⁶ For women of childbearing age, central obesity is associated with an increased risk of gestational diabetes, preeclampsia, and the need for cesarean sections.^{33,34} Unfortunately, there is scant literature examining this issue specifically in axSpA. Research in obesity has demonstrated that excess adipose tissue creates a persistent low-grade inflammatory

state driven by proinflammatory adipocytokines.³⁵ This is especially concerning in patients with inflammatory arthritis, such as axSpA, as persistent inflammation could drive worsening of disease activity. As the concentration of adipocytokines is directly related to body fat mass, reduction of excess adipose tissue has the potential to correct this systemic inflammatory reaction. 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. This analysis highlighted disparities in obesity detection using 2 anthropometric tools (ie, BMI and WHR) among women with axSpA. For men with axSpA, the prevalence of obesity was similar regardless of the tool used (BMI, 29.6% vs WHR, 29.9%). However, for women, there was a stark change in prevalence of obesity when comparing BMI (29.8%) and the WHR (71.6%). This difference in classification between sexes was quantified in a correlation analysis, which found the relationship between BMI and the WHR to be stronger among men than women with axSpA. This suggests that although BMI is a quick tool to screen for obesity, it underestimates obesity in women. This difference in the strength of association between sexes may reflect the fact that BMI was a tool developed and validated for use in males.³⁶ Since its development in the 1830s by a Belgian statistician to describe the average man, BMI has become one of the most commonly used tools to quantify physical size and general health.³⁷ However, studies in postmenopausal women indicate that BMI is not a reliable indicator of obesity status among women.³⁸ In addition, universal BMI cut-offs for obesity have been found to perform poorly among women of differing ethnic backgrounds.³⁹ This clearly demonstrates that it is time to reconsider the use of BMI to screen for obesity in females, especially those with axSpA.

The prevalence of central obesity was similar among those with r-axSpA and nr-axSpA (42.6% vs 37.4%, $P = 0.21$). However, the prevalence of HLA-B27 was higher in patients with central obesity compared to those with no central obesity (90.4% vs 87.6%, $P < 0.01$; Table 2). There is limited knowledge of central obesity in axSpA; however, an ankylosing spondylitis study did note that central obesity was associated with radiographic progression over time.⁴⁰ The ASAS COMOrbidities in SPondyloArthritis (COMOSPA) study also demonstrated that mean waist circumference was significantly lower in patients with axSpA who were positive for HLA-B27 compared to those who were negative for HLA-B27.⁴¹ Additional longitudinal data are required to investigate the relationship between radiographic disease, presence of HLA-B27, and central obesity in axSpA.

Assessment of baseline demographics of patients with central obesity and those without revealed that those with central obesity were older (mean 48.6 vs 43.7 years, $P < 0.01$) and had a later age of onset (mean 28.7 vs 25.7 years, $P < 0.01$; Table 2). Risk of central obesity in the general population is recognized to increase with age,⁴² with men and postmenopausal women

having up to twice as much visceral adipose tissue (VAT) compared to premenopausal females.⁴³ In women, these changes are mediated by increased androgen secretion and a decline in estrogen concentration associated with reduction in ovarian function during menopause.²¹ While women from the general population report an increase in myalgia and arthralgia during the onset of menopause,⁴⁴ there are limited and conflicting data on the effects of changes in estrogen concentration on disease activity among women with axSpA.⁴⁵

To examine this further, a model was constructed to determine the factors that are associated with the presence of central obesity in axSpA. 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 among women with axSpA, who averaged 6.76 times higher odds of central obesity compared to men with axSpA, highlighting the dramatically higher prevalence of central obesity among women with axSpA.

Women with axSpA have previously demonstrated worse PROs compared to men, despite a lower prevalence of radiographic disease and better spinal mobility.⁴⁵ This disconnect between radiographic burden and outcome scores has perplexed axSpA researchers for some time. Obesity in axSpA is known to contribute to worse patient outcomes regardless of sex.^{7,46} Given the unexpectedly high prevalence of central obesity detected among women in this study, a follow-up analysis examined the interaction between female sex and central obesity to determine if there was a synergistic effect on PROs. Although the interaction did not reach statistical significance, the effects of both female sex and central obesity remained significant when considered individually. Central obesity was found to be significantly associated with all PROs, with the exception of the BASDAI outcome, which demonstrated a nonsignificant trend toward worse scores in central obesity ($P = 0.07$). Differences in BASDAI scores between the 2 cohorts were more subtle than for the other PROs, which is likely the reason that the association between central obesity and this outcome did not reach significance. However, if tested on a larger scale, it is suspected that the effect of central obesity on BASDAI scores would be significant. This suggests that central obesity could play a key role in explaining the sex differences observed in PROs in axSpA. Further studies are needed to corroborate these findings in other axSpA cohorts; development of longitudinal data is also needed to determine if there is a causal relationship between central obesity and worse PROs.

The health risks associated with central obesity are attributable to the presence of VAT, which can be directly measured by various imaging modalities, including dual-energy x-ray absorptiometry (DXA) and magnetic resonance imaging.⁴⁷ Studies using DXA suggest that persistent disease activity in axSpA is associated with increased free fat mass in women,⁴⁸ with higher body fat content associated with a worse response to anti-tumor necrosis factor- α therapies.⁴⁹ In clinical practice, it is not practical or economical to repeatedly image patients to screen for central obesity. During an axSpA consultation, physical measurements are routinely recorded for calculation of the BASMI. In this

setting, calculation of the WHR 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. Prompt identification creates a window of opportunity for multidisciplinary intervention, including education on lifestyle modification, dietary management with dietitians, and exercise therapy with physiotherapists. Obesity research has proven that early intervention and comprehensive structured programs are the most effective strategies for weight reduction and long-term maintenance.⁵⁰ Thus, incorporation of the WHR is essential for improving identification of central obesity in axSpA.

Our study has some 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 for further analysis of these relationships. Not all patients within the ASRI had physical measurements recorded; as such, they were excluded from the analysis where such measurements were not available.

In conclusion, there is a high prevalence of central obesity in axSpA, as classified by the WHR, most notably among women with axSpA. This modifiable comorbidity was significantly associated with worse functional ability, poorer QOL, and a trend toward 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 the use of the WHR when screening for obesity in this population. Central obesity is a potentially modifiable state that, if identified, may be a key target for intervention among patients with axSpA. Further public health campaigns are needed to raise awareness and improve recognition of this issue in axSpA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* 2016;387:1377-96.
2. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. *JAMA* 2018;319:1723-5.
3. Global BMI Mortality Collaboration; Di Angelantonio E, Bhupathiraju Sh N, et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388:776-86.
4. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA* 2004;291:1238-45.
5. Kinlen D, Cody D, O'Shea D. Complications of obesity. *QJM* 2018;111:437-43.
6. Sieper J, Braun J, Dougados M, Baeten D. Axial spondyloarthritis. *Nat Rev Dis Primers* 2015;1:15013.
7. Liew JW, Huang IJ, Loudon DN, Singh N, Gensler LS. Association of body mass index on disease activity in axial spondyloarthritis: systematic review and meta-analysis. *RMD Open* 2020;6:e001225.

8. Bindesbøll C, Garrido-Cumbrera M, Bakland G, Dagfinrud H. Obesity increases disease activity of Norwegian patients with axial spondyloarthritis: results from the European Map of Axial Spondyloarthritis Survey. *Curr Rheumatol Rep* 2020;22:43.
9. Zurita Prada PA, Urrego Laurín CL, Guillén Astete CA, Kanaffo Caltelblanco S, Navarro-Compán V. Influence of smoking and obesity on treatment response in patients with axial spondyloarthritis: a systematic literature review. *Clin Rheumatol* 2021;40:1673-86.
10. Bakirci S, Dabague J, Eder L, McGonagle D, Aydin SZ. The role of obesity on inflammation and damage in spondyloarthritis: a systematic literature review on body mass index and imaging. *Clin Exp Rheumatol* 2020;38:144-8.
11. Unamuno X, Gómez-Ambrosi J, Rodríguez A, Becerril S, Frühbeck G, Catalán V. Adipokine dysregulation and adipose tissue inflammation in human obesity. *Eur J Clin Invest* 2018;48:e12997.
12. Zorena K, Jachimowicz-Duda O, Ślęzak D, Robakowska M, Mrugacz M. Adipokines and obesity. Potential link to metabolic disorders and chronic complications. *Int J Mol Sci* 2020;21:3570.
13. Zhao SS, Robertson S, Reich T, Harrison NL, Moorts RJ, Goodson NJ. Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis. *Rheumatology* 2020;59:iv47-57.
14. Fitzgerald G, Gallagher P, O'Shea FD. Multimorbidity in axial spondyloarthropathy and its association with disease outcomes: results from the Ankylosing Spondylitis Registry of Ireland cohort. *J Rheumatol* 2020;47:218-26.
15. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist:hip ratio as predictors of cardiovascular risk--a review of the literature. *Eur J Clin Nutr* 2010;64:16-22.
16. Sun Y, Liu B, Snetselaar LG, et al. Association of normal-weight central obesity with all-cause and cause-specific mortality among postmenopausal women. *JAMA Netw Open* 2019;2:e197337.
17. Anderson CAM, Mongraw-Chaffin M. Central obesity in older adults: what should be the priority? *J Am Heart Assoc* 2018;7:e010119.
18. Wan J, Zhou P, Wang D, et al. Impact of normal weight central obesity on clinical outcomes in male patients with premature acute coronary syndrome. *Angiology* 2019;70:960-8.
19. Vazquez G, Duval S, Jacobs DR, Jr., Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 2007;29:115-28.
20. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. *Mol Cell Endocrinol* 2015;402:113-9.
21. Dmitruk A, Czezelewski J, Czezelewska E, Golach J, Parnicka U. Body composition and fatty tissue distribution in women with various menstrual status. *Rocz Panstw Zakl Hig* 2018;69:95-101.
22. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: a metaanalysis. *Am J Obstet Gynecol* 2019;221:393-409.e50.
23. World Health Organization. Waist circumference and waist to hip ratio: report of a WHO expert consultation. Geneva, Switzerland: WHO; 2008.
24. Centers for Disease Control and Prevention. Defining adult overweight & obesity. [Internet. Accessed June 15, 2021.] Available from: <https://www.cdc.gov/obesity/adult/defining.html>
25. Nishida C, Ko GT, Kumanyika S. Body fat distribution and noncommunicable diseases in populations: overview of the 2008 WHO Expert Consultation on Waist Circumference and Waist-Hip Ratio. *Eur J Clin Nutr* 2010;64:2-5.
26. McCarthy SN, Gibney MJ, Flynn A, Irish Universities Nutrition Alliance. Overweight, obesity and physical activity levels in Irish adults: evidence from the North/South Ireland food consumption survey. *Proc Nutr Soc* 2002;61:3-7.
27. Boylan EA, McNulty BA, Walton J, Flynn A, Nugent AP, Gibney MJ. The prevalence and trends in overweight and obesity in Irish adults between 1990 and 2011. *Public Health Nutr* 2014;17:2389-97.
28. Altobelli E, Angeletti PM, Profeta VF, Petrocelli R. Lifestyle risk factors for type 2 diabetes mellitus and national diabetes care systems in European countries. *Nutrients* 2020;12:2806.
29. Krzysztozek J, Laudańska-Krzemińska I, Bronikowski M. Assessment of epidemiological obesity among adults in EU countries. *Ann Agric Environ Med* 2019;26:341-9.
30. Wang Y, Beydoun MA, Min J, Xue H, Kaminsky LA, Cheskin LJ. Has the prevalence of overweight, obesity and central obesity levelled off in the United States? Trends, patterns, disparities, and future projections for the obesity epidemic. *Int J Epidemiol* 2020;49:810-23.
31. Liu MM, Liu QJ, Wen J, et al. Waist-to-hip ratio is the most relevant obesity index at each phase of insulin secretion among obese patients. *J Diabetes Complications* 2018;32:670-6.
32. Tsao YC, Chen JY, Yeh WC, Li WC. Gender- and age-specific associations between visceral obesity and renal function impairment. *Obes Facts* 2019;12:67-77.
33. Yao D, Chang Q, Wu QJ, et al. Relationship between maternal central obesity and the risk of gestational diabetes mellitus: a systematic review and meta-analysis of cohort studies. *J Diabetes Res* 2020;2020:6303820.
34. Lim J, Han K, Kim SY, et al. Effects of central obesity on maternal complications in Korean women of reproductive age. *Obes Res Clin Pract* 2019;13:156-63.
35. Chimenti MS, Perricone C, D'Antonio A, et al. Genetics, epigenetics, and gender impact in axial-spondyloarthritis susceptibility: an update on genetic polymorphisms and their sex related associations. *Front Genet* 2021;12:671976.
36. Blackburn H, Jacobs D Jr. Commentary: origins and evolution of body mass index (BMI): continuing saga. *Int J Epidemiol* 2014;43:665-9.
37. Gutin I. In BMI we trust: reframing the body mass index as a measure of health. *Soc Theory Health* 2018;16:256-71.
38. Banack HR, Wactawski-Wende J, Hovey KM, Stokes A. Is BMI a valid measure of obesity in postmenopausal women? *Menopause* 2018;25:307-13.
39. Rush EC, Goedecke JH, Jennings C, et al. BMI, fat and muscle differences in urban women of five ethnicities from two countries. *Int J Obes* 2007;31:1232-9.
40. Chen CH, Chen HA, Liu CH, Liao HT, Chou CT, Chen CH. Association of obesity with inflammation, disease severity and cardiovascular risk factors among patients with ankylosing spondylitis. *Int J Rheum Dis* 2020;23:1165-74.
41. Arévalo M, López-Medina C, Moreno Martínez-Losa M, et al. Role of HLA-B27 in the comorbidities observed in axial spondyloarthritis: data from COMOSPA. *Joint Bone Spine* 2020;87:445-8.
42. Tchernof A, Després JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev* 2013;93:359-404.
43. Kotani K, Tokunaga K, Fujioka S, et al. Sexual dimorphism of age-related changes in whole-body fat distribution in the obese. *Int J Obes Relat Metab Disord* 1994;18:207-2.
44. Watt FE. Musculoskeletal pain and menopause. *Post Reprod Health* 2018;24:34-43.
45. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. *Curr Rheumatol Rep* 2018;20:35.

46. Maas F, Arends S, van der Veer E, et al. Obesity is common in axial spondyloarthritis and is associated with poor clinical outcome. *J Rheumatol* 2016;43:383-7.
47. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur Heart J* 2007;28:850-6.
48. Ibáñez Vodnizza S, Visman IM, van Denderen C, et al. Muscle wasting in male TNF- α blocker naïve ankylosing spondylitis patients: a comparison of gender differences in body composition. *Rheumatology* 2017;56:1566-72.
49. Ibáñez Vodnizza SE, Nurmohamed MT, Visman IM, et al. Fat mass lowers the response to tumor necrosis factor- α blockers in patients with ankylosing spondylitis. *J Rheumatol* 2017;44:1355-61.
50. Ramage S, Farmer A, Eccles KA, McCargar L. Healthy strategies for successful weight loss and weight maintenance: a systematic review. *Appl Physiol Nutr Metab* 2014;39:1-20.



What to expect when women with axial spondyloarthritis are expecting: Prevalence of complications of pregnancies in women with axial spondyloarthritis

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ABSTRACT

Background: 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 cross-sectional information on demographics, imaging, treatment, and patient outcomes. A dedicated section collects data on pregnancy, fertility and breastfeeding. For each axSpA woman, data on all pregnancies was recorded. 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 preeclampsia (6.8 % vs 2.8%, $p < 0.01$) were more prevalent in axSpA pregnancies than GRN. Low birth weight was more prevalent in axSpA pregnancies (8.2 % vs 2.9%, $p < 0.01$), however small for gestational age was less prevalent (5.4 % vs 11%, $p < 0.01$).

Conclusions: Preterm birth, preeclampsia and low birth weight 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.

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Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory arthritis affecting the axial spine and sacroiliac joints [1]. This term refers to both radiographic axSpA (r-axSpA), also called ankylosing spondylitis, as well as non-radiographic axSpA (nr-axSpA) [2]. Symptoms include early morning stiffness, back pain which improves with exercise and restricted range of motion which are characteristic of

inflammatory back pain. Previously believed to affect mostly men, more recent epidemiological studies have demonstrated this male predominance is not as high as originally believed [3]. The age of onset is typically in the second to third decade, which for women is a key period of their childbearing years [1].

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 [4]. Improved data collection via national registries have been key to recent advances in the understanding of the impact of rheumatic

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disease on pregnancy [5–7]. Research focus on pregnancy in rheumatic diseases has been biased towards systemic lupus erythematosus (SLE) [8,9] and rheumatoid arthritis (RA) [10,11] 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 [12–14]. Recent studies have demonstrated that axSpA pregnancies have higher rates of certain pregnancy and fetal complications compared to pregnancies in the general population [15,16]. This was supported by findings from a 2020 systematic review and meta-analysis [17]. Certain pregnancy outcomes including breastfeeding and cesarian sections vary globally due to differences in practice, social preferences and cultural influences [18–20]. 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.

Methods

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 across the country representing all major geographical regions and sociodemographic backgrounds. Since time of inception, 886 patients have been enrolled in the ASRI with recruitment ongoing. Our study included all female participants with a history of pregnancy.

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) classification criteria for axSpA, allowing data collection on both radiographic and non-radiographic disease. 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 to be included in the ASRI.

Written informed consent was obtained from each patient prior to enrolment. This process included discussion of purpose of data collection, data protection and publication of studies using data from the ASRI. Ethical approval was received from local hospital ethic boards at each participating center.

Participation in the ASRI involved a single clinical visit conducted by a trained investigator, which allowed for data to be captured at a single time point. Medical records were reviewed for radiology results, patterns of disease and medication usage. Data was collected on participant demographics, duration of disease, delay to diagnosis, patterns of disease and presence of comorbidities. A series of self-administered questionnaires were also completed as part of this visit to capture patient reported outcomes. A focused clinical examination captured measurements of spinal mobility for calculation of the Bath Ankylosing Spondylitis Spinal Mobility Index (BASMI).

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.

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. Due to the known prolonged delay in diagnosis and onset in the childbearing years, collection of pregnancy data was not limited to pregnancies which took place after axSpA diagnosis. Hence data on all pregnancies was recorded for each participating woman. Pregnancy complications captured included miscarriage, preeclampsia, gestational diabetes, pre-term delivery and cesarian section. Fetal complications captured were low birth weight (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 (supplemental Table 1).

Data on these outcomes was recorded retrospectively for women with axSpA enrolled in the ASRI with a history of pregnancy. The prevalence of each recorded outcome was compared to weighted pooled prevalence from a recent meta-analysis on this topic [17]. 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 invitro fertilization (IVF).

Participants with a history of pregnancy were directly questioned about severity of axSpA symptoms or disease activity at 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.

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 [17] 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 1224,348 pregnancies (Table 1). Results were also discussed in the context of the latest Irish national data to provide normative context.

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 χ^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.

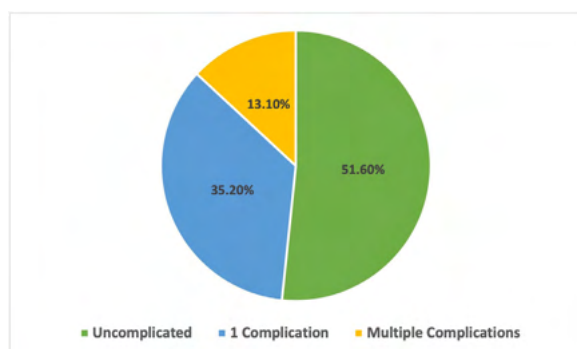
Results

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 at enrolment was 43.9 years, with a mean disease duration of 18 years and mean delay to diagnosis 7.9 years. 70.7% (164) had radiographic axSpA, while 29.3% (68) had non-radiographic disease.

Table 1

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 center	77
Jakobsson et al.	2016	2001–2009	Sweden	Cross-sectional	National Register	1082
Timur et al.	2016	2007–2015	Turkey	Case control	Single center	40
Kristjandottir et al.	2019	1981–2017	Iceland	Cross-sectional	National Register	3214
Park et al.	2019	1994–2017	Korea	Cross-sectional	Multi-center	12,926
Strouse et al.	2019	2007–2012	USA	Case control	Multi-center	10,244
Mork et al.	2019	1997–2016	Denmark	Cross-sectional	National Register	1195,882
Prospective Studies						
Ostensen et al.	1983	1979–1982	Norway	Case control	Single center	31
Zbinden et al.	2018	2000–2016	Switzerland	Case control	Single center	70
Smith et al.	2019	2004–2018	USA	Case control	Multi-center	717

**Fig. 1.** Prevalence of complications per pregnancy in pregnancies of women with axSpA.

Mean scores for females in the ASRI were: BASDAI 4.57, BASFI 3.85, BASMI 3.58, HAQ 0.59, and ASQoL 7.51.

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 livebirths. Of these pregnancies 51.6% (173) were uncomplicated and 48.5% (162) were complicated, with 13.1% (44) encountering multiple complications (Fig. 1). An additional 20 women denied any previous history of pregnancy or attempting to conceive.

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 cesarian section in 13.3% (37) followed by preterm birth in 12.5% (35) (table 2). Infection requiring hospitalization 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: preeclampsia (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 preeclampsia 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 2). 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.

Miscarriage prevalence was also significantly higher in axSpA pregnancies compared to GRN (16.7 % vs 3.2%, $p = 0.04$). However, there was limited data available on this outcome in the GRN to allow for comparison.

Prevalence of cesarian 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.

Fetal complications

The most common fetal complication was NICU admission in 12.2% (34) (table 2), however no significant difference was noted between axSpA and GRN (12.2 % vs 11.9%, $p = 0.47$). Low birth weight (LBW) was significantly more prevalent in axSpA pregnancies (8.2 %

Table 2

Prevalence of pregnancy and fetal complications between women with axSpA compared to GRN.

	AxSpAWomen	GRN*	p value	OR	95% CI
n	279	1224,348			
Pregnancy complications					
preeclampsia	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
cesarian section	13.3% (37)	18.6% (225,359)	0.27	0.85	0.63, 1.14
Miscarriage	16.7% (56)	3.2% (1)	0.04	5.35	0.77, 37.36
Infection	2.9% (8)				
Fetal Complications					
Low Birth Weight	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).

Table 3
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)

vs 2.9%, $p < 0.01$), with the odds of low birth weight 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.

Breastfeeding

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

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.

Disease activity & 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 3). 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).

Discussion

This study of pregnancy data from the ASRI, demonstrates a 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 optimizing 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 preeclampsia were significantly more prevalent in axSpA pregnancies compared to GRN. The findings regarding preterm birth are similar to studies in Denmark [16] and the United States [21]. Although individual studies failed to detect a difference in prevalence of preeclampsia, pooling of data via meta-analyses demonstrated an increased risk of this complication in axSpA pregnancies [17,22]. Many pregnancy complications, including

preeclampsia, can increase the risk of preterm birth [23]. In Ireland, the increasing average maternal age at delivery has been identified as one of the key contributors to the rising rates of preeclampsia nationally [24]. However, increasing maternal age is not a challenge unique to Ireland with similar trends noted in many developed countries [25,26]. Advanced maternal age is a risk factor for preterm birth in the general population, although there are numerous additional risk factors to also consider [27]. This includes systemic inflammation [23], with a previous study in axSpA demonstrating preterm birth risk to be increased in mothers with increased disease activity during pregnancy [28]. 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 [29]. Recognition of the higher prevalence of preterm birth in axSpA pregnancies is crucial to advancing monitoring of these patients to minimize 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 cesarian 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 cesarian 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 [17,22]. 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 gynecological complications [30]. Alarmed at this trend, the World Health organisation (WHO) issued a consensus statement encouraging cesarian sections to be performed only when medically indicated and encouraged use of the Robinson system to standardize data collection to further study this phenomenon [31]. This was supported by the lack of evidence for non-medically indicated CS as detailed by a 2012 Cochrane review [32]. Although rates of CS are currently on the rise in Ireland [33,34], older comparative research indicates CS rates in Ireland were previously significantly lower than those reported in the United States [35]. This emphasizes 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. Of the available data on miscarriage, the prevalence in Ireland has been noted to decrease over time from 7.1% in 2005 to 5.2% in 2016 [36]. This is dramatically lower than the 16.7% noted in axSpA pregnancies within the ASRI, however data from a prospective French axSpA cohort reported a prevalence of 7.5% [37]. This higher prevalence may reflect the prolonged period over which pregnancy data from the ASRI was collected. A controlled prospective study is needed to determine if there truly is an increased risk of miscarriage in axSpA pregnancies. Until that time, pregnancy planning and optimization 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 birth weight (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 [38]. 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 [39,40]. This is mediated by adaptive changes in utero to optimize nutritional extraction resulting in permanent changes in metabolism and fat storage after delivery [41]. 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 10th centile for the corresponding gestational age [42]. 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. As such, in a retrospective study there is a risk this outcome may have been under reported. 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 [43]. Results from individual studies are divergent, with pooled results suggesting a non-significant trend towards increased prevalence in axSpA pregnancies [17]. 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 [44]. 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 [45]. Public health initiatives have continued to campaign to raise public awareness of breastfeeding however, rates globally remain below 50% [46]. Within the ASRI the prevalence of breastfeeding was notably lower at 33.7% compared to the national Irish prevalence of 59.9% [47]. Although there is scant published data on this issue in axSpA, a similar trend has also been reported in rheumatoid arthritis [48]. A major contributing factor to this issue may be related to medication use. Fortunately, recent guidelines have been published for by the American College of Rheumatology clearly outlining medication safety at each stage of pregnancy including lactation [49]. 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 [50]. It is important to note that in the general population this has not been proven to result in reduced fertility [51]. 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) [52]. Infertility in the general population is estimated to affect 8–12% of couples worldwide [53], in line with results of this study. Pregnancy planning in axSpA women is key to optimizing 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. Firstly, pregnancy can mimic common axSpA symptoms, which complicates monitoring of disease activity due to difficulty differentiating between pregnancy and inflammatory symptoms [54,55]. Development of tools adapted for use in pregnancy is urgently needed to reliably capture axSpA activity throughout pregnancy. Another issue encountered was the lack of standard outcome measures used to quantify disease activity prior to the development of the BASDAI in 1994 [56]. 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 [28]. However, larger prospective studies are needed to capture changes in disease activity in more detail throughout pregnancy and corroborate these findings. Data from rheumatoid arthritis pregnancy cohorts indicate advances in treatment options and use have resulted in improved disease control in pregnancy, however similar studies in axSpA are needed [57].

Limitations

Data collection on pregnancy in the ASRI was limited to the results reported within this study. Information was not available on maternal age at delivery or treatment during pregnancy. As the collection of pregnancy data was retrospective, there was the potential for recall bias. However, for all recorded complications if a patient was unsure no answer was recorded. Additionally, the nature of the data collection within the ASRI resulted in cross-sectional study design. For this reason, it was not possible to assess for a causal relationship between disease activity and prevalence of pregnancy outcomes currently. Information on treatment during pregnancy would aid in interpretation of disease activity during 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.

Conclusion

This study details pregnancy outcomes of women with axSpA from a large, well characterised national registry. Within the ASRI, pregnant women with axSpA faced a high prevalence of complications overall. Specifically preterm birth, preeclampsia and low birth weight 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 optimize 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.

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Declaration of Competing Interests

The authors have no competing interests to declare.

CRediT Author statement

Sinead Maguire: conceptualization, formal analysis, investigation, data curation, writing – original draft, writing – reviews & edits, visualisation, project administration; **Fiona Wilson:** writing – review & editing, supervision; **Phil Gallagher:** data curation, investigation, project administration; **Muhanad MS Mohamed:** investigation, **Senan Maher:** investigation, **Finbar O'Shea:** conceptualization, methodology, supervision, writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.semarthrit.2022.151993](https://doi.org/10.1016/j.semarthrit.2022.151993).

References

- [1] Sieper J, Braun J, Dougados M, Baeten D. Axial spondyloarthritis. *Nat Rev Dis Primers* 2015;1:15013. doi: [10.1038/nrdp.2015.13](https://doi.org/10.1038/nrdp.2015.13).
- [2] Taurog JD, Chhabra A, Colbert RA. Ankylosing Spondylitis and Axial Spondyloarthritis. *N Engl J Med* 2016;374(26):2563–74. doi: [10.1056/NEJMra1406182](https://doi.org/10.1056/NEJMra1406182).
- [3] Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis—Women are not so lucky. *Curr Rheumatol Rep* 2018;20(6):35. doi: [10.1007/s11926-018-0744-2](https://doi.org/10.1007/s11926-018-0744-2).
- [4] Meissner Y, Fischer-Betz R, Andreoli L, Costedoat-Chalumeau N, De Cock D, Dolhain R, Forger F, Goll D, Molto A, Nelson-Piercy C, Özdemir R, Raio L, Rodríguez-García SC, Sciascia S, Wallenius M, Zbinden A, Zink A, Strangfeld A. EULAR recommendations for a core data set for pregnancy registries in rheumatology. *Ann Rheum Dis* 2021;80(1):49–56. doi: [10.1136/annrheumdis-2020-218356](https://doi.org/10.1136/annrheumdis-2020-218356).
- [5] Wallenius M, Salvesen K, Daltveit AK, Skomsvoll JF. Rheumatoid arthritis and outcomes in first and subsequent births based on data from a national birth registry. *Acta Obstet Gynecol Scand* 2014;93(3):302–7. doi: [10.1111/aogs.12324](https://doi.org/10.1111/aogs.12324).
- [6] Simard JF, Chaichian Y, Rossides M, Wikstrom AK, Shaw GM, Druzin ML. Preterm delivery phenotypes in systemic lupus erythematosus pregnancies. *Am J Perinatol* 2019;36(9):964–8. doi: [10.1055/s-0038-1675648](https://doi.org/10.1055/s-0038-1675648).
- [7] Meissner Y, Strangfeld A, Costedoat-Chalumeau N, Förger F, Goll D, Molto A, Özdemir R, Wallenius M, Fischer-Betz R. European Network of Pregnancy Registers in Rheumatology (EuNeP)—An overview of procedures and data collection. *Arthritis Res Ther* 2019;21(1):241. doi: [10.1186/s13075-019-2019-3](https://doi.org/10.1186/s13075-019-2019-3).
- [8] Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010;5(11):2060–8. doi: [10.2215/cjn.00240110](https://doi.org/10.2215/cjn.00240110).
- [9] Andreoli L, Bertias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, Doria A, Fischer-Betz R, Forger F, Moraes-Fontes MF, Khamashta M, King J, Lojaco A, Marchiori F, Meroni PL, Mosca M, Motta M, Ostensen M, Pamfil C, Raio L, Schneider M, Svenungsson E, Tektonidou M, Yavuz S, Boumpas D, Tincani A. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis* 2017;76(3):476–85. doi: [10.1136/annrheumdis-2016-209770](https://doi.org/10.1136/annrheumdis-2016-209770).
- [10] Raine C, Austin K, Giles I. Mechanisms determining the amelioration of rheumatoid arthritis in pregnancy—A systematic review. *Semin Arthritis Rheum* 2020;50(6):1357–69. doi: [10.1016/j.semarthrit.2020.03.006](https://doi.org/10.1016/j.semarthrit.2020.03.006).
- [11] Jethwa H, Lam S, Smith C, Giles I. Does rheumatoid arthritis really improve during pregnancy? A systematic review and meta-analysis. *J Rheumatol* 2019;46(3):245–50. doi: [10.3899/jrheum.180226](https://doi.org/10.3899/jrheum.180226).
- [12] Ostensen M, Ostensen H. Ankylosing spondylitis—the female aspect. *J Rheumatol* 1998;25(1):120–4.
- [13] Jakobsson GL, Stephansson O, Asklund J, Jacobsson LT. Pregnancy outcomes in patients with ankylosing spondylitis—A nationwide register study. *Ann Rheum Dis* 2016;75(10):1838–42. doi: [10.1136/annrheumdis-2015-207992](https://doi.org/10.1136/annrheumdis-2015-207992).
- [14] Lui NL, Haroon N, Carty A, Shen H, Cook RJ, Shanmugarajah S, Gladman DD, Inman RD. Effect of pregnancy on ankylosing spondylitis—A case-control study. *J Rheumatol* 2011;38(11):2442–4. doi: [10.3899/jrheum.101174](https://doi.org/10.3899/jrheum.101174).
- [15] Smith CJF, Bandoli G, Kavanagh A, Chambers CD. Birth outcomes and disease activity during pregnancy in a prospective cohort of women with psoriatic arthritis and ankylosing spondylitis. *Arthritis Care Res* 2020;72(7):1029–37. doi: [10.1002/acr.23924](https://doi.org/10.1002/acr.23924).
- [16] Mørk S, Voss A, Möller S, Bliddal M. Spondyloarthritis and outcomes in pregnancy and labor—A nationwide register-based cohort study. *Arthritis Care Res* 2021;73(2):282–8. doi: [10.1002/acr.24111](https://doi.org/10.1002/acr.24111).
- [17] Maguire S, O'Dwyer T, Mockler D, O'Shea F, Wilson F. Pregnancy in axial spondyloarthritis—A systematic review & meta-analysis. *Semin Arthritis Rheum* 2020;50(6):1269–79. doi: [10.1016/j.semarthrit.2020.08.011](https://doi.org/10.1016/j.semarthrit.2020.08.011).
- [18] Boerma T, Ronsmans C, Melesse DY, Barros AJD, Barros FC, Juan L, Moller AB, Say L, Hosseinpoor AR, Yi M, de Lyra Rabello Neto D, Temmerman M. Global epidemiology of use of and disparities in caesarean sections. *Lancet* 2018;392(10155):1341–8. doi: [10.1016/s0140-6736\(18\)31928-7](https://doi.org/10.1016/s0140-6736(18)31928-7).
- [19] Rito AI, Buoncristiano M, Spinelli A, Salanave B, Kunešová M, Hejgaard T, García Solano M, Fijałkowska A, Sturua L, Hyska J, Kelleher C, Duleva V, Musić Milanović S, Farrugia Sant'Angelo V, Abdrakhmanova S, Kujundzić E, Peterkova V, Gualtieri A, Pudule I, Petrauskienė A, Tanrygulyeva M, Sherali R, Huidumac-Petrescu C, Williams J, Ahrens W, Breda J. Association between characteristics at birth, breastfeeding and obesity in 22 countries—The WHO European childhood obesity surveillance initiative - COSI 2015/2017. *Obes Facts* 2019;12(2):226–43. doi: [10.1159/000500425](https://doi.org/10.1159/000500425).
- [20] Ibanez G, Martin N, Denantes M, Saurel-Cubizolles MJ, Ringa V, Magnier AM. Prevalence of breastfeeding in industrialized countries. *Rev Epidemiol Sante Publique* 2012;60(4):305–20. doi: [10.1016/j.respe.2012.02.008](https://doi.org/10.1016/j.respe.2012.02.008).
- [21] Strouse J, Donovan BM, Fatima M, Fernandez-Ruiz R, Baer RJ, Nidey N, Forbess C, Bandoli G, Paynter R, Parikh N, Jelliffe-Pawłowski L, Ryckman KK, Singh N. Impact of autoimmune rheumatic diseases on birth outcomes—A population-based study. *RMD Open* 2019;5(1):e000878. doi: [10.1136/rmdopen-2018-000878](https://doi.org/10.1136/rmdopen-2018-000878).
- [22] Hamroun S, Hamroun A, Bigna JJ, Allado E, Förger F, Molto A. Fertility and pregnancy outcomes in women with spondyloarthritis—A systematic review and meta-analysis. *Rheumatology (Oxford)* 2021. doi: [10.1093/rheumatology/keab589](https://doi.org/10.1093/rheumatology/keab589).
- [23] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371(9606):75–84. doi: [10.1016/s0140-6736\(08\)60074-4](https://doi.org/10.1016/s0140-6736(08)60074-4).
- [24] Corrigan L, O'Farrell A, Moran P, Daly D. Hypertension in pregnancy—Prevalence, risk factors and outcomes for women birthing in Ireland. *Pregnancy Hypertens* 2021;24:1–6. doi: [10.1016/j.preghy.2021.02.005](https://doi.org/10.1016/j.preghy.2021.02.005).
- [25] Sheen JJ, Huang Y, Andrikopoulou M, Wright JD, Goffman D, D'Alton ME, Friedman AM. Maternal age and preeclampsia outcomes during delivery hospitalizations. *Am J Perinatol* 2020;37(1):44–52. doi: [10.1055/s-0039-1694794](https://doi.org/10.1055/s-0039-1694794).
- [26] Yang Q, Greenland S, Flanders WD. Associations of maternal age- and parity-related factors with trends in low-birthweight rates—United States, 1980 through 2000. *Am J Public Health* 2006;96(5):856–61. doi: [10.2105/ajph.2004.049312](https://doi.org/10.2105/ajph.2004.049312).
- [27] Fuchs F, Monet B, Ducruet T, Chaillet N, Audibert F. Effect of maternal age on the risk of preterm birth—A large cohort study. *PLoS One* 2018;13(1):e0191002. doi: [10.1371/journal.pone.0191002](https://doi.org/10.1371/journal.pone.0191002).
- [28] Zbinden A, van den Brandt S, Ostensen M, Villiger PM, Förger F. Risk for adverse pregnancy outcome in axial spondyloarthritis and rheumatoid arthritis—Disease activity matters. *Rheumatology (Oxford)* 2018;57(7):1235–42. doi: [10.1093/rheumatology/key053](https://doi.org/10.1093/rheumatology/key053).
- [29] Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. *Best Pract Res Clin Obstet Gynaecol* 2018;52:3–12. doi: [10.1016/j.bpobgyn.2018.04.003](https://doi.org/10.1016/j.bpobgyn.2018.04.003).
- [30] Antoine C, Young BK. Caesarean section one hundred years 1920–2020—The good, the bad and the ugly. *J Perinat Med* 2020;49(1):5–16. doi: [10.1515/jpm-2020-0305](https://doi.org/10.1515/jpm-2020-0305).
- [31] Betran AP, Torloni MR, Zhang JJ, Gülmezoglu AM. WHO statement on caesarean section rates. *BJOG* 2016;123(5):667–70. doi: [10.1111/1471-0528.13526](https://doi.org/10.1111/1471-0528.13526).
- [32] Lavender T, Hofmeyr GJ, Neilson JP, Kingdon C, Gyte GM. Caesarean section for non-medical reasons at term. *Cochrane Database Syst Rev* 2012;2012(3):Cd004660. doi: [10.1002/14651858.CD004660.pub3](https://doi.org/10.1002/14651858.CD004660.pub3).
- [33] Hospital C.W.I.U. (2019) Annual Clinical Collection (trans: Gynaecology O). 1 edn.,
- [34] Sinnott SJ, Brick A, Layte R, Cunningham N, Turner MJ. National variation in caesarean section rates—A cross sectional study in Ireland. *PLoS One* 2016;11(6):e0156172. doi: [10.1371/journal.pone.0156172](https://doi.org/10.1371/journal.pone.0156172).
- [35] Leveno KJ, Cunningham FG, Pritchard JA. Caesarean section—An answer to the House of Horne. *Am J Obstet Gynecol* 1985;153(8):838–44. doi: [10.1016/0002-9378\(85\)90686-6](https://doi.org/10.1016/0002-9378(85)90686-6).
- [36] San Lazaro Campillo I, Meaney S, O'Donoghue K, Corcoran P. Miscarriage hospitalisations—A national population-based study of incidence and outcomes, 2005–2016. *Reprod Health* 2019;16(1):51. doi: [10.1186/s12978-019-0720-y](https://doi.org/10.1186/s12978-019-0720-y).
- [37] Pons M, Dougados M, Costedoat-Chalumeau N, Briot K, Goupille P, Roux C, Molto A. Pregnancy rates and outcomes in early axial spondyloarthritis—An analysis of the DESIR cohort. *Jt. Bone Spine* 2021;88(2):105075. doi: [10.1016/j.jbspin.2020.09.007](https://doi.org/10.1016/j.jbspin.2020.09.007).
- [38] McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *N Engl J Med* 1985;312(2):82–90. doi: [10.1056/nejm198501103120204](https://doi.org/10.1056/nejm198501103120204).
- [39] Nakano Y. Adult-onset diseases in low birth weight infants—Association with adipose tissue maldevelopment. *J Atheroscler Thromb* 2020;27(5):397–405. doi: [10.5551/jat.RV17039](https://doi.org/10.5551/jat.RV17039).
- [40] Feng C, Osgood ND, Dyck RF. Low birth weight, cumulative obesity dose, and the risk of incident type 2 diabetes. *J Diabetes Res* 2018;8435762 2018. doi: [10.1155/2018/8435762](https://doi.org/10.1155/2018/8435762).
- [41] Barker DJ. The origins of the developmental origins theory. *J Intern Med* 2007;261(5):412–7. doi: [10.1111/j.1365-2796.2007.01809.x](https://doi.org/10.1111/j.1365-2796.2007.01809.x).
- [42] Pásztor N, Kozinszky Z, Pál A. [Fetus, small for gestational age]. *Orv Hetil* 2014;155(33):1301–5. doi: [10.1556/oh.2014.29982](https://doi.org/10.1556/oh.2014.29982).
- [43] Wilcox AJ, Cortese M, McConaughy DR, Moster D, Basso O. The limits of small-for-gestational-age as a high-risk category. *Eur J Epidemiol* 2021;36(10):985–91. doi: [10.1007/s10654-021-00810-z](https://doi.org/10.1007/s10654-021-00810-z).

- [44] Bellù R, Condò M. Breastfeeding promotion—Evidence and problems. *Pediatr Med Chir* 2017;39(2):156. doi: [10.4081/pmc.2017.156](https://doi.org/10.4081/pmc.2017.156).
- [45] Binns C, Lee M, Low WY. The long-term public health benefits of breastfeeding. *Asia Pac J Public Health* 2016;28(1):7–14. doi: [10.1177/1010539515624964](https://doi.org/10.1177/1010539515624964).
- [46] Rollins NC, Bhandari N, Hajeebhoy N, Horton S, Lutter CK, Martines JC, Piwoz EG, Richter LM, Victora CG. Why invest, and what it will take to improve breastfeeding practices? *Lancet* 2016;387(10017):491–504. doi: [10.1016/s0140-6736\(15\)01044-2](https://doi.org/10.1016/s0140-6736(15)01044-2).
- [47] Executive HPOwHS (2018) Perinatal Statistics Report. Health Service Executive
- [48] Ince-Askan H, Hazes JMW, Dolhain R. Breastfeeding among women with rheumatoid arthritis compared with the general population—Results from a nationwide prospective cohort study. *J Rheumatol* 2019;46(9):1067–74. doi: [10.3899/jrheum.180805](https://doi.org/10.3899/jrheum.180805).
- [49] Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, Marder W, Guyatt G, Branch DW, Buyon J, Christopher-Stine L, Crow-Hercher R, Cush J, Druzin M, Kavanaugh A, Laskin CA, Plante L, Salmon J, Simard J, Somers EC, Steen V, Tedeschi SK, Vinet E, White CW, Yazdany J, Barbhaiya M, Bettendorf B, Eudy A, Jayatilake A, Shah AA, Sullivan N, Tarter LL, Birru Talabi M, Turgunbaev M, Turner A, D'Anci KE. 2020 American college of rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol* 2020;72(4):529–56. doi: [10.1002/art.41191](https://doi.org/10.1002/art.41191).
- [50] Yalçın Bahat P, Kadiroğulları P, Topbas Selcuki NF, Yücel B, Çakmak K, Üreyen Özdemir E. Ovarian reserve in patients with ankylosing spondylitis. *Arch Gynecol Obstet* 2021;303(1):189–93. doi: [10.1007/s00404-020-05824-8](https://doi.org/10.1007/s00404-020-05824-8).
- [51] Steiner AZ, Pritchard D, Stanczyk FZ, Kesner JS, Meadows JW, Herring AH, Baird DD. Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. *JAMA* 2017;318(14):1367–76. doi: [10.1001/jama.2017.14588](https://doi.org/10.1001/jama.2017.14588).
- [52] Ursin K, Lydersen S, Skomsvoll JF, Salvesen K, SSK H, Jakobsen B, Wallenius M. Factors associated with time to pregnancy in women with axial spondyloarthritis—A registry-based multicenter study. *Arthritis Care Res* 2021;73(8):1201–9. doi: [10.1002/acr.24233](https://doi.org/10.1002/acr.24233).
- [53] Vander Borgh M, Wyns C. Fertility and infertility—Definition and epidemiology. *Clin Biochem* 2018;62:2–10. doi: [10.1016/j.clinbiochem.2018.03.012](https://doi.org/10.1016/j.clinbiochem.2018.03.012).
- [54] Maguire SOS. Management of pregnancy in rheumatic disease. *EMJ Rheumatol* 2021;8(1):83–93.
- [55] Østensen M, Fuhrer L, Mathieu R, Seitz M, Villiger PM. A prospective study of pregnant patients with rheumatoid arthritis and ankylosing spondylitis using validated clinical instruments. *Ann Rheum Dis* 2004;63(10):1212–7. doi: [10.1136/ard.2003.016881](https://doi.org/10.1136/ard.2003.016881).
- [56] Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis—The bath ankylosing spondylitis disease activity index. *J Rheumatol* 1994;21(12):2286–91.
- [57] Smeele HT, Röder E, Wintjes HM, Kranenburg-van Koppen LJ, Hazes JM, Dolhain RJ. Modern treatment approach results in low disease activity in 90% of pregnant rheumatoid arthritis patients—The PreCARE study. *Ann Rheum Dis* 2021;80(7):859–64. doi: [10.1136/annrheumdis-2020-219547](https://doi.org/10.1136/annrheumdis-2020-219547).



OBSERVATIONAL RESEARCH

Advances in treatment of axial spondyloarthritis are associated with improved patient outcomes: data from the Ankylosing Spondylitis Registry of Ireland (ASRI)

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Abstract

The Ankylosing Spondylitis Registry of Ireland (ASRI) captures both radiographic and non-radiographic axial spondyloarthritis (axSpA) in a large, well characterised cohort. This is a valuable resource for studies in therapeutics and burden of disease, following a period of rapid change in the field of axSpA. This study aims to perform a focused analysis on patient outcomes and pattern of medication usage in axSpA. 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. Currently 885 patients are enrolled in the ASRI, made up of 72.5% (642) males and 26.9% (238) females. The majority 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. 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.

Keywords Axial spondyloarthritis · Epidemiology · Outcomes · Registry · Autoinflammatory diseases

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 purpose of a registry is to capture a large patient population over

a pre-determined geographic area to assess outcomes [1]. National registries have been developed for numerous rheumatic diseases around the world leading to improved understanding of disease progression [2], patterns of disease [3], comorbidities [4] and medication response [5].

The ASRI was developed primarily to characterise axial spondyloarthritis (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-musculoskeletal manifestations (EMMs), 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 [6]. The expansion of classification

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criteria to recognise both nr-axSpA and radiographic axSpA (r-axSpA), also called ankylosing spondylitis (AS), marked a considerable shift from more traditional phenotypes as captured by the modified New York criteria [7]. This triggered a period of re-evaluation of axSpA as a whole, as well as numerous comparative analyses of r-axSpA and nr-axSpA [8].

Another major area of change in axSpA is treatment, which is an area of significant advancement over the past two decades [9]. Previously limited to non-steroidal anti-inflammatories (NSAIDs) and corticosteroids, therapeutic options now include synthetic disease modifying anti-rheumatic drugs (sDMARDs) and biologics [10]. Biologic agents in particular have revolutionized management of axSpA since their introduction to Ireland in 2003 leading to dramatic improvements of patient outcomes, quality of life and level of functional ability when commenced in the early stages of disease [11].

The data collected in the ASRI over the past 8 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 prevalence of comorbidities in axSpA.

Methods

Patient population

Participants were recruited from 12 centres across Ireland. All enrolled patients were over the age of 18, had full mental capacity and were fluent in English. To be considered for ASRI patients must have been diagnosed with r-axSpA or AS, or nr-axSpA by a rheumatologist. All patients fulfilled the Assessment of Spondyloarthritis International Society (ASAS) criteria for axSpA at the time of enrolment. Written informed consent was obtained from each participant prior to enrolment. Ethical approval was received from local hospital ethic boards at each site which contributed patients to the ASRI.

Data collection

A trained investigator conducted patient visits which included patient-reported outcome (PRO) questionnaires, review of medical records, focused history and examination. 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 inter-malleolar distance.

Data was collected and recorded into an electronic database using pseudoanonymisation of patient information. Data collection included baseline demographics, pattern of disease, background history, family history, radiology, spinal measurements and disease activity measures. All data was stored in compliance with national GDPR legislation.

Outcome measures

The following validated outcome measures were collected:

- Bath AS Disease Activity Index (BASDAI) [12]—PRO assessing disease activity on a scale of 0–10
- Bath AS Functional Index (BASFI) [13]—PRO assessing functional status on a scale of 0–10
- Bath AS Metrology Index (BASMI) [14]—assesses spinal mobility on a scale of 0–10
- AS Quality of Life (ASQoL) score [15]—PRO on a scale of 0–18
- Health Assessment Questionnaire (HAQ) [16]—PRO assessing disability on a scale of 0–3.

Statistical analysis

Patient population was analysed using IBM SPSS version 26. Categorical variables were documented as percentages with associated frequency counts. Continuous variables were expressed as means with standard deviations (SD). 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 χ^2 test for independence test for significance in categorical variables. A *p* value of <0.05 was deemed significant.

Results

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 mean disease duration of 19.4 years (SD 12.3) (Table 1). The majority of the population enrolled in the ASRI was Caucasian (92.4%). Mean scores at time of entry were: BASDAI

Table 1 Baseline characteristics of the ASRI population

	<i>n</i> = 885	%
Age*	45.8 (12.6)	
Disease duration	19.4 (12.3)	
Age at symptom onset	26.4 (10.7)	
Delay to diagnosis	7.98 (8.2)	
Caucasian	19	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-musculoskeletal manifestations		
Uveitis	302	34.1
Psoriasis	146	16.5
Colitis	92	10.4
Co-morbidities		
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

HLA B27 human leukocyte antigen B27, MRI magnetic resonance imaging

*Means expressed in years (standard deviation)

4.02 (SD 2.4), BASFI 3.70 (SD 2.9), HAQ 0.53 (SD 0.52), ASQoL 6.53 (SD 5.5) and BASMI 4.02 (SD 2.1).

The majority (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 (EMMs) was recorded in this population with psoriasis in 16.5% (146), inflammatory bowel disease in 10.4% (92) and uveitis in 34.1% (302).

There was a high prevalence of co-morbidities with 40.6% (359) recorded as having at least one comorbidity. Hypertension, hyperlipidemia and depression were the most commonly reported comorbidities in this cohort (Table 1).

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).

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. Patients without exposure to any specific medication for axSpA 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 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).

Difference in BASDAI scores between groups 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 (4.79 vs 3.37, *p* = 0.01) (Table 3). However, patients on no medication recorded significantly worse mean BASMI scores compared to those on NSAIDs (4.5 vs 3.65, *p* < 0.01). Patients on biologics alone reported significantly better BASFI (3.15 vs 4.34, *p* < 0.01), HAQ (0.42 vs 0.66, *p* < 0.01) and ASQoL (5.17 vs 8.34, *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 (3.42 vs 4.23, *p* = 0.01), HAQ (0.42 vs 0.54, *p* < 0.01) and ASQoL scores (5.17 vs 6.61, *p* < 0.01).

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 EMM noted in 34.1%, while

Table 2 Baseline demographics by treatment categories

	No medication	NSAIDs only	Biologics only	Combination therapy	<i>p</i> value
<i>n</i>	94	187	334	272	
Age*	50.3	46	45	45.9	0.01
Symptom onset	28.6	28.1	25.9	25.4	0.01
Disease duration	21.7	17.9	19.1	20	0.10
Delay to dx	9.49	8.72	7.34	7.65	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
BMI	28.5	28.2	27.7	29.4	0.26
r-axSpA	80.0% (75)	68.0% (127)	73.1% (244)	81.6% (222)	< 0.01

NSAIDs nonsteroidal anti-inflammatory drugs, Dx diagnosis, HLA-B27 human leukocyte antigen B27, BMI body mass index, r-axSpA radiographic axial spondyloarthritis

*Continuous variables expressed as means (standard deviation). Categorical variables expressed as %(n)

All *p* values are italicized, all *p* values less than 0.05 are bolded to indicate significance.

Table 3 Breakdown of analysis of variance (ANOVA) on outcome measures

	No medication	NSAIDs only	Biologics only	Combination therapy	<i>p</i> value
BASDAI	3.37 3.37 3.37	4.23 4.23 4.23	3.42 3.42 3.42	4.79 4.79 4.79	0.01
BASFI	3.31 3.31	3.78	3.15 3.15	4.34 4.34	< 0.01
HAQ	0.47 0.47	0.54	0.42 0.42	0.66 0.66	< 0.01
ASQoL	5.57 5.57	6.61 6.61 6.61	5.17 5.17 5.17	8.34 8.34 8.34	< 0.01
BASMI	4.5 4.5	3.65 3.65	3.86	4.25	< 0.01

Treatment categories with statistically significant variation listed below each heading

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

All *p* values are italicized, all *p* values less than 0.05 are bolded to indicate significance.

peripheral arthritis the most common articular manifestation reported in 30.3%. These findings are consistent with data from other national axSpA registries [17–19]. 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 [20]. AxSpA was previously thought to be a predominantly male disease with historical male to female ratios as high as 10:1 [21]

with more recent studies reporting this ratio to be close to 2–3:1 [22]. 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 8.53 years in the United Kingdom [23], 4.9 years in France [24] and a mean time of 6.7 years from a systematic review on 64 axSpA studies [25]. This delay remains a particularly concerning result given the advancements in diagnostic imaging and recognition of the impact of early treatment initiation [26]. 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 [27]. 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 hyperlipidemia (15.8%) with ischemic heart disease reported in only 3.7% of the cohort. The low prevalence of ischemic heart disease may reflect the relatively young mean age of the ASRI, but the high frequency of hypertension and hyperlipidemia 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 [28]. Presence of comorbidities in axSpA has been associated with worse patient outcomes [29] and poorer response to treatment [30]. 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 [31].

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 [32, 33]. 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 [30]. Further research in this area has discovered that smokers are more likely to be employed in manual labor

suggesting that mechanical strain could also be a factor in the observed outcomes [34]. Finally, 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 mobility as reflected by BASMI. Delay in diagnosis and lack of treatment have previously been shown to be associated with worse outcomes in axSpA [35], thus the emphasis on prompt recognition of symptoms in current guidelines and public health campaigns to improve time to diagnosis in axSpA [10, 36]. 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 [37]. During this time the Assessment of Spondyloarthritis International Society (ASAS) released new classification criteria which introduced the concept of axSpA [6]. 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 [10]. Treatment in combination with physiotherapy and exercise can provide significant improvement in disease activity, quality of life and functional ability [38]. 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 [39, 40]. 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.

Finally, 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

The ASRI is currently cross-sectional in design with patient data captured from a single clinical visit and chart review at the time. In the discussion of treatment and patient outcomes, confounding by indication bias must be considered. As such, the current design of the ASRI does not allow for establishment of a causal relationship between these two variables. Plans are in place for development of longitudinal data in the form of structured clinical visits. This will allow further analyses to further understand the impact of treatment on patient outcomes, as well as capture the full effect of recent changes in classification and management of axSpA.

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.

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Declarations

Conflict of interest The authors have no conflict of interests to report.

References

1. Gliklich REDNLM (2014) AHRQ Methods for effective health care. In: Gliklich RE, Dreyer NA, Leavy MB (eds) Registries for evaluating patient outcomes: a user's guide. Agency for Healthcare Research and Quality (US), Rockville (MD)
2. Zhao SS, Yoshida K, Jones GT, Hughes DM, Tedeschi SK, Lyu H, Moots RJ, Solomon DH, Goodson NJ (2020) Impact of smoking in response to tumor necrosis factor inhibitors in axial spondyloarthritis: methodologic considerations for longitudinal observational studies. *Arthritis Care Res* 72(4):591–599. <https://doi.org/10.1002/acr.23851>
3. Love TJ, Gudbjornsson B, Gudjonsson JE, Valdimarsson H (2007) Psoriatic arthritis in Reykjavik, Iceland: prevalence, demographics, and disease course. *J Rheumatol* 34(10):2082–2088
4. Jin S, Li M, Fang Y, Li Q, Liu J, Duan X, Liu Y, Wu R, Shi X, Wang Y, Jiang Z, Wang Y, Yu C, Wang Q, Tian X, Zhao Y, Zeng X (2017) Chinese Registry of rheumatoid arthritis (CREDIT): II. Prevalence and risk factors of major comorbidities in Chinese patients with rheumatoid arthritis. *Arthritis Res Ther* 19(1):251. <https://doi.org/10.1186/s13075-017-1457-z>
5. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, Kollerup G, Linde L, Lindegaard HM, Poulsen UE, Schlemmer A, Jensen DV, Jensen S, Hostenkamp G, Østergaard M (2010) Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of

- surveillance of clinical practice in the nationwide Danish DAN-BIO registry. *Arthritis Rheum* 62(1):22–32. <https://doi.org/10.1002/art.27227>
6. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, Braun J, Chou CT, Collantes-Estevez E, Dougados M, Huang F, Gu J, Khan MA, Kirazli Y, Maksymowych WP, Mielants H, Sørensen IJ, Ozgocmen S, Roussou E, Valle-Oñate R, Weber U, Wei J, Sieper J (2009) The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 68(6):777–783. <https://doi.org/10.1136/ard.2009.108233>
 7. Poddubnyy D (2020) Classification vs diagnostic criteria: the challenge of diagnosing axial spondyloarthritis. *Rheumatology* 59(4):iv6–iv17. <https://doi.org/10.1093/rheumatology/keaa250>
 8. López-Medina C, Ramiro S, van der Heijde D, Sieper J, Dougados M, Molto A (2019) Characteristics and burden of disease in patients with radiographic and non-radiographic axial Spondyloarthritis: a comparison by systematic literature review and meta-analysis. *RMD Open* 5(2):e001108. <https://doi.org/10.1136/rmdopen-2019-001108>
 9. Torgutalp M, Poddubnyy D (2018) Emerging treatment options for spondyloarthritis. *Best Pract Res Clin Rheumatol* 32(3):472–484. <https://doi.org/10.1016/j.berh.2019.01.014>
 10. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, Haroon N, Borenstein D, Wang R, Biehl A, Fang MA, Louie G, Majithia V, Ng B, Bigham R, Pianin M, Shah AA, Sullivan N, Turgunbaev M, Oristaglio J, Turner A, Maksymowych WP, Caplan L (2019) 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. *Arthritis Rheumatol* 71(10):1599–1613. <https://doi.org/10.1002/art.41042>
 11. Jones A, Ciurtin C, Ismajli M, Leandro M, Sengupta R, Machado PM (2018) Biologics for treating axial spondyloarthritis. *Expert Opin Biol Ther* 18(6):641–652. <https://doi.org/10.1080/14712598.2018.1468884>
 12. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A (1994) A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 21(12):2286–2291
 13. Calin A, Garrett S, Whitelock H, Kennedy LG, O’Hea J, Mallorie P, Jenkinson T (1994) A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 21(12):2281–2285
 14. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A (1994) Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. *J Rheumatol* 21(9):1694–1698
 15. Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, McKenna SP, Tennant A, van der Heijde D, Chamberlain MA (2003) Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. *Ann Rheum Dis* 62(1):20–26. <https://doi.org/10.1136/ard.62.1.20>
 16. Daltroy LH, Larson MG, Roberts NW, Liang MH (1990) A modification of the Health Assessment Questionnaire for the spondyloarthropathies. *J Rheumatol* 17(7):946–950
 17. Mease PJ, Heijde DV, Karki C, Palmer JB, Liu M, Pandurengan R, Park Y, Greenberg JD (2018) Characterization of patients with ankylosing spondylitis and nonradiographic axial spondyloarthritis in the US-based corona registry. *Arthritis Care Res* 70(11):1661–1670. <https://doi.org/10.1002/acr.23534>
 18. van Lunteren M, Sepriano A, Landewé R, Sieper J, Rudwaleit M, van der Heijde D, van Gaalen F (2018) Do ethnicity, degree of family relationship, and the spondyloarthritis subtype in affected relatives influence the association between a positive family history for spondyloarthritis and HLA-B27 carriership? Results from the worldwide ASAS cohort. *Arthritis Res Ther* 20(1):166. <https://doi.org/10.1186/s13075-018-1672-2>
 19. de Winter JJ, van Mens LJ, van der Heijde D, Landewé R, Baeten DL (2016) Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. *Arthritis Res Ther* 18(1):196. <https://doi.org/10.1186/s13075-016-1093-z>
 20. Boonen A, Sieper J, van der Heijde D, Dougados M, Bukowski JF, Valluri S, Vlahos B, Kotak S (2015) The burden of non-radiographic axial spondyloarthritis. *Semin Arthritis Rheum* 44(5):556–562. <https://doi.org/10.1016/j.semarthrit.2014.10.009>
 21. Rusman T, van Bentum RE, van der Horst-Bruinsma IE (2020) Sex and gender differences in axial spondyloarthritis: myths and truths. *Rheumatology* 59(4):iv38–iv46. <https://doi.org/10.1093/rheumatology/keaa543>
 22. Wright GC, Kaine J, Deodhar A (2020) Understanding differences between men and women with axial spondyloarthritis. *Semin Arthritis Rheum* 50(4):687–694. <https://doi.org/10.1016/j.semarthrit.2020.05.005>
 23. Sykes MP, Doll H, Sengupta R, Gaffney K (2015) Delay to diagnosis in axial spondyloarthritis: are we improving in the UK? *Rheumatology* 54(12):2283–2284. <https://doi.org/10.1093/rheumatology/kev288>
 24. Masson Behar V, Dougados M, Etcheto A, Kreis S, Fabre S, Hudry C, Dadoun S, Rein C, Pertuiset E, Fautrel B, Gossec L (2017) Diagnostic delay in axial spondyloarthritis: a cross-sectional study of 432 patients. *Joint Bone Spine* 84(4):467–471. <https://doi.org/10.1016/j.jbspin.2016.06.005>
 25. Zhao SS, Pittam B, Harrison NL, Ahmed AE, Goodson NJ, Hughes DM (2021) Diagnostic delay in axial spondyloarthritis: a systematic review and meta-analysis. *Rheumatology*. <https://doi.org/10.1093/rheumatology/keaa807>
 26. Barnett R, Ingram T, Sengupta R (2020) Axial spondyloarthritis 10 years on: still looking for the lost tribe. *Rheumatology* 59(4):iv25–iv37. <https://doi.org/10.1093/rheumatology/keaa472>
 27. Redeker I, Callhoff J, Hoffmann F, Haibel H, Sieper J, Zink A, Poddubnyy D (2019) Determinants of diagnostic delay in axial spondyloarthritis: an analysis based on linked claims and patient-reported survey data. *Rheumatology* 58(9):1634–1638. <https://doi.org/10.1093/rheumatology/kez090>
 28. Derakhshan MH, Goodson NJ, Packham JC, Sengupta R, Molto A, Marzo-Ortega H, Siebert S (2019) Increased risk of hypertension associated with spondyloarthritis disease duration: results from the ASAS-COMOSPA study. *J Rheumatol* 46(7):701–709. <https://doi.org/10.3899/jrheum.180538>
 29. Fitzgerald G, Gallagher P, O’Shea FD (2020) Multimorbidity in axial spondyloarthropathy and its association with disease outcomes: results from the Ankylosing Spondylitis Registry of Ireland cohort. *J Rheumatol* 47(2):218–226. <https://doi.org/10.3899/jrheum.181415>
 30. Zhao SS, Robertson S, Reich T, Harrison NL, Moots RJ, Goodson NJ (2020) Prevalence and impact of comorbidities in axial spondyloarthritis: systematic review and meta-analysis. *Rheumatology* 59(4):iv47–iv57. <https://doi.org/10.1093/rheumatology/keaa246>
 31. Redeker I, Callhoff J, Hoffmann F, Marschall U, Haibel H, Sieper J, Zink A, Poddubnyy D (2020) The prevalence and impact of comorbidities on patients with axial spondyloarthritis: results from a nationwide population-based study. *Arthritis Res Ther* 22(1):210. <https://doi.org/10.1186/s13075-020-02301-0>
 32. Moltó A, Etcheto A, van der Heijde D, Landewé R, van den Bosch F, Bautista Molano W, Burgos-Vargas R, Cheung PP, Collantes-Estevez E, Deodhar A, El-Zorkany B, Erdes S, Gu J, Hajjaj-Hasouni N, Kiltz U, Kim TH, Kishimoto M, Luo SF, Machado PM,

- Maksymowych WP, Maldonado-Cocco J, Marzo-Ortega H, Montecucco CM, Ozgoçmen S, van Gaalen F, Dougados M (2016) Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. *Ann Rheum Dis* 75(6):1016–1023. <https://doi.org/10.1136/annrheumdis-2015-208174>
33. Zhao S, Jones GT, Macfarlane GJ, Hughes DM, Dean LE, Moots RJ, Goodson NJ (2019) Associations between smoking and extra-axial manifestations and disease severity in axial spondyloarthritis: results from the BSR Biologics Register for Ankylosing Spondylitis (BSRBR-AS). *Rheumatology* 58(5):811–819. <https://doi.org/10.1093/rheumatology/key371>
 34. Nikiphorou E, Ramiro S, Sepriano A, Ruysen-Witrand A, Landewé RBM, van der Heijde D (2020) Do smoking and socio-economic factors influence imaging outcomes in axial spondyloarthritis? Five-year data from the DESIR Cohort. *Arthritis Rheumatol* 72(11):1855–1862. <https://doi.org/10.1002/art.41408>
 35. Seo MR, Baek HL, Yoon HH, Ryu HJ, Choi HJ, Baek HJ, Ko KP (2015) Delayed diagnosis is linked to worse outcomes and unfavourable treatment responses in patients with axial spondyloarthritis. *Clin Rheumatol* 34(8):1397–1405. <https://doi.org/10.1007/s10067-014-2768-y>
 36. Adshead R, Donnelly S, Knight P, Tahir H (2020) Axial spondyloarthritis: overcoming the barriers to early diagnosis-an early inflammatory back pain service. *Curr Rheumatol Rep* 22(10):59. <https://doi.org/10.1007/s11926-020-00923-6>
 37. Fragoulis GE, Siebert S (2020) Treatment strategies in axial spondyloarthritis: what, when and how? *Rheumatology* 59(4):iv79–iv89. <https://doi.org/10.1093/rheumatology/keaa435>
 38. Ritchlin C, Adamopoulos IE (2021) Axial spondyloarthritis: new advances in diagnosis and management. *BMJ* 372:m4447. <https://doi.org/10.1136/bmj.m4447>
 39. Schjerning AM, McGettigan P, Gislason G (2020) Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol* 17(9):574–584. <https://doi.org/10.1038/s41569-020-0366-z>
 40. Lucas GNC, Leitão ACC, Alencar RL, Xavier RMF, Daher EF, Silva Junior GBD (2019) Pathophysiological aspects of nephropathy caused by non-steroidal anti-inflammatory drugs. *J Bras Nefrol* 41(1):124–130. <https://doi.org/10.1590/2175-8239-jbn-2018-0107>

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247 HIGH UNEMPLOYMENT RATES IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: Previous registry studies have noted increased rates of unemployment in patients with ankylosing spondylitis (AS). With improved treatment options and earlier detection of AS, it was anticipated that this would no longer be true. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data on AS patients in Ireland. The aim of this study was to examine unemployment rates in this population and possible links with disease activity, function and quality of life.

Methods: An analysis of the current patient population of the ASRI was performed using IBM SPSS Statistics version 25. Comparison of the mean ASQoL, HAQ, BASDAI, BASFI and BASMI scores were carried out between those employed versus those unemployed. An independent two tailed T test and a Mann Whitney U test was then carried out to determine significance. Further analysis was then performed using patient age and disease duration.

Results: At the time of analysis 734 patients were enrolled in the registry. The mean age was 45 years, with 77% males and 23% female, mean duration of disease 18 years (means: ASQoL 6.6, HAQ 0.5, BASDAI 4.0, BASFI 3.6, BASMI 3.6). Unemployment rate in the ASRI population was 23%, which is noticeably higher than the national unemployment of 6%. Those patients were also noted to have higher ASQoL (9.7 versus 5.6), HAQ (0.85 versus 0.45), BASDAI (5.3 versus 3.7), and BASFI scores (5.2 versus 3.2). The difference between the means was statistically significant ($p < 0.05$) across all 4 measures. However, BASMI scores were significantly lower in the unemployed (3.8 versus 3.0). No statistically significant difference was detected between genders. The distribution of age and disease duration was determined to be equal between the groups.

Conclusion: There is a higher prevalence of unemployment in the AS population as compared to the general population. Unemployed AS patients tend to have decreased quality of life, poorer levels of function, and higher levels of disease activity. Further research is needed to determine causation between level of disease activity and employment.

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¹University Hospital Waterford, Rheumatology, Waterford, Ireland; ²St James' Hospital, Rheumatology, Dublin, Ireland

Background: Previous registry studies have noted increased rates of unemployment in patients with ankylosing spondylitis (AS)(1-2). With improved treatment options and earlier detection of AS, it was anticipated that this would no longer be true.

Objectives: The Ankylosing Spondylitis Registry of Ireland(ASRI) is a source of epidemiological data on AS patient in Ireland. The aim of this study was to examine unemployment rates in this population and possible links with disease activity, function and quality of life.

Methods: An analysis of the patient population of the ASRI with data collected from 2013 to 2017 was performed using IBM SPSS Statistics version 25. Comparison of the mean ASQoL, HAQ, BASDAI, BASFI, and BASMI score were carried out between those employed versus those unemployed. An independent two tailed t test and a Mann Whitney U test was then carried out to determine significance. Further analysis was then performed using patient age and disease duration.

Results: At the time of analysis 734 patient were enrolled in the registry. The mean age was 45 years, with 77% male and 23% female, mean duration of disease was 18 years (means: ASQoL 6.6, HAQ 0.5, BASDAI 4.0, BASFI 3.6, BASMI 3.6). Unemployment rate in the ASRI population was 23%. National unemployment during the same time period was noticeably lower with a range of 6.2% to 13.1% (3). Those patients were also noted to have higher ASQoL (9.7 versus 5.6), HAQ (0.85 versus 0.45), BASDAI (5.3 versus 3.7), and BASFI scores (5.2 versus 3.2). The difference between the means was statistically significant ($p < 0.05$) across all 4 measures. However, BASMI scores were significantly lower in the unemployed (3.8 versus 3.0). No statistically significant difference was detected between genders. The distribution of age and disease duration was determined to be equal between the groups.

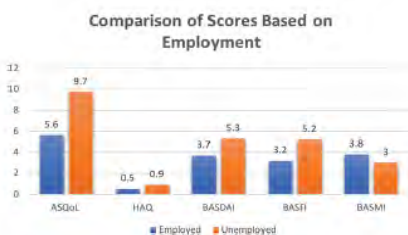


Figure 1

Conclusion: There is a higher prevalence of unemployment in the AS population as compared to the general population. Unemployed AS patients tend to have decreased quality of life, poorer levels of function, and higher levels of disease activity. Further research is needed to determine a causation between level of disease activity and employment.

REFERENCES:

- [1.] Webers C, Vanhoof L, Genderen SV, *et al*; Employment perspectives of patients with ankylosing spondylitis in the biologics era; *Annals of the Rheumatic Diseases* 2017;76:157.
- [2] Webers C, *et al*; Employment and the role of personal factors among patients with ankylosing spondylitis: a Dutch cross-sectional case-control study; *RMD Open* 2018. Jun27;4(1)
- [3] Central Statistics Office Ireland

Worse Outcomes for Female Patients with Axial Spondyloarthritis

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Meeting: 2019 ACR/ARP Annual Meeting

Keywords: Ankylosing spondylitis (AS), axial spondyloarthritis, inflammatory arthritis and women's health, inflammatory back pain

SESSION INFORMATION

Date: Sunday, November 10, 2019

Session Type: Poster Session (Sunday)

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Clinical Poster I: Axial Spondyloarthritis, Clinical Features

Session Time: 9:00AM-11:00AM

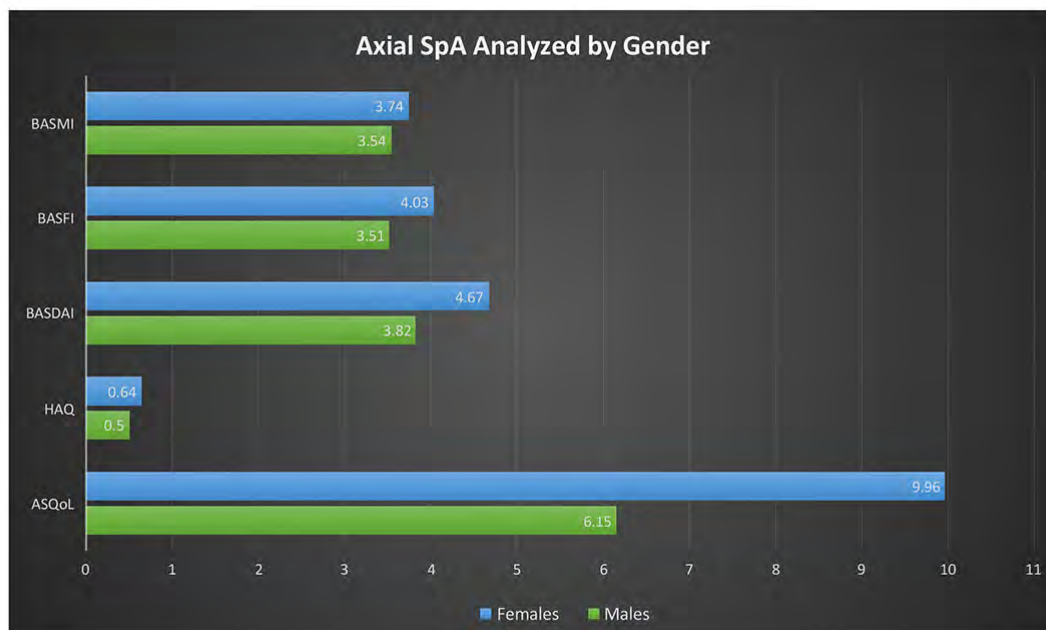
Background/Purpose: Axial Spondyloarthritis(axSpA) is known to have a male predominance. There is little available literature examining affected female patients. Previous studies have included small numbers of females, leading to a lack of detailed analysis of variations between genders. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data on patients with axSpA in Ireland. The purpose of this study was to determine if there is a significant difference in disease activity and patterns of disease between genders.

Methods: Analysis of the patient population registered in the ASRI using IBM SPSS version 25. Patients were analyzed on the basis of gender. Mean ASQoL, HAQ, BASDAI, BASFI and BASMI scores were compared. Difference between the two groups was tested for statistical analysis using an independent two tailed t test and a Mann Whitney U test. Further analysis was performed to determine difference in patterns of disease, extra-articular manifestations, medication usage and co-morbidities using a chi-squared test for independence.

Results: Data for 734 patients were reviewed via the registry. The patient population was 14.6% (171) females, 85.4%(563) males, with mean age of 45 years and a mean disease duration of 18 years (means: ASQoL 6.57, HAQ 0.54, BASDAI 4.02, BASFI 3.63, BASMI 3.58). Female patients had higher ASQoL (7.96 vs. 6.15, $p < 0.01$), HAQ (0.64 vs. 0.50, $p < 0.01$), BASDAI (4.66 vs. 3.82, $p < 0.01$), and BASFI scores (4.03 vs. 3.51, $p=0.03$). No significant difference between BASMI was found between genders (3.74 vs. 3.54, $p=0.83$) (Figure 1). No significant difference was found in delay to diagnosis (7.79 years in females vs. 8.56 years in males, $p=0.05$) or HLA B27 positivity (67% vs. 69%, $p=0.45$). Both genders had comparable incidence of arthritis(39.8% vs. 30.4%, $p=0.07$) and enthesitis (18.8% vs. 16.7, $p=0.74$), however females had higher rates of MRI sacroiliitis(48.5% vs. 42.6%, $p=0.02$) and dactylitis(12.3% vs. 5.2%, $p < 0.01$). Analysis of medication usage showed no significant difference in use of sDMARD (18.7% vs 19.7%, $p=0.7$) or biologic exposure (70% vs. 76.8%, $p=0.96$). A higher proportion of females used NSAIDs (58.5% vs. 48.5%, $p=0.02$) while a lower proportion of women are currently on biologic therapy (77.7% vs. 87.2%, $p=0.01$). Regarding extra-articular manifestations, females had higher rates of both inflammatory bowel disease (15.8% vs. 7.8%, $p < 0.01$) and uveitis (43.9% vs. 32.1%, $p=0.01$). A range of co-morbidities were also analyzed, however no statistically significant difference in incidence was found (table 1).

Conclusion: There are significant differences between genders in patients with axSpA. This analysis demonstrates that females tend to have higher disease activity, worse levels of function leading to greater impact on their quality of life. Perhaps as a reflection of this, female patients have higher rates of NSAID usage. Females also have higher rates of extra-articular manifestations including inflammatory bowel disease and uveitis. Dedicated research into female patient with axSpA is needed to appropriately address and treat their disease.

	Females (n=171)	Males (n=563)	Total (n=734)	p-value
Age	42.73	45.72	45.02	0.01
Disease duration	17.01	19.13	18.64	0.05
Caucasian	22.8% (168)	73.6% (540)	94.5% (708)	0.4
Delay to diagnosis	7.79	8.56	8.39	0.27
HLA B27 +	67% (115)	69% (387)	68% (502)	0.45
Measures of Disease:				
BASDAI	4.66	3.82	4.02	< 0.01
ASQoL	7.96	6.15	6.57	< 0.01
BASFI	4.03	3.51	3.63	0.03
BASMI	3.74	3.54	3.58	0.38
HAQ	0.64	0.5	0.54	< 0.01
Extra-articular Manifestations:				
Uveitis	43.9% (75)	32.1% (181)	34.9% (256)	0.01
Psoriasis	17% (29)	18.1% (102)	17.8% (131)	0.28
IBD	15.8% (27)	7.8% (44)	9.7% (71)	< 0.01
Co-morbidities:				
IHD	4.1% (7)	3% (17)	3.3% (24)	0.47
CVD	0% (0)	2.1% (12)	1.6% (12)	0.08
HTN	18.1% (31)	22% (124)	21.1% (155)	0.29
Hyperlipidaemia	15.2% (26)	16.5% (93)	16.2% (119)	0.72
DM	3.5% (6)	5% (28)	4.6% (34)	0.54
PUD	7% (12)	7.1% (40)	7.1% (52)	0.97
TB	2.9% (5)	3.7% (21)	3.5% (26)	0.62
Osteoporosis	7.6% (13)	4.6% (26)	5.3% (39)	0.13
Depression	13.5% (23)	9.4% (53)	10.4% (76)	0.13
Cancer	4.1% (7)	3% (17)	3.3% (24)	0.49



Disclosure: S. Maguire, AbbVie, 9; G. Fitzgerald, AbbVie, 9, Pfizer, 9, Novartis, 9, UCB, 9; C. Sheehy, None; F. O'Shea, None.

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ACR Meeting Abstracts - <https://acrabstracts.org/abstract/worse-outcomes-for-female-patients-with-axial-spondyloarthritis/>

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Background: Axial spondyloarthritis(axSpA) is a form of inflammatory arthritis that primarily affects the axial skeleton and sacroiliac joint, but can be associated with a peripheral arthritis. Rapid advances in the field of axSpA has led to faster detection, diagnosis and treatment of this disease. This improved management has led to improved level of function and quality of life for patients, despite this a proportion of patients are still requiring joint replacement surgery. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data on patients with axSpA in Ireland. Given the large size of the ASRI to date, this is a prime opportunity to analyze patients with axSpA requiring joint replacement surgery.

Objectives: Detailed analysis of a large cohort of patients with axSpA with a focus on those who underwent joint replacement to determine trends in disease and baseline demographics.

Methods: The patient population registered in the ASRI was analysed using IBM SPSS version 26. Analysis was performed by comparing patients who underwent joint replacement surgery to the rest of the ASRI cohort. Mean age, disease duration, delay to diagnosis and scores of disease activity (BASDAI, BASFI, HAQ, ASQoL and BASMI) were compared between these two groups. Differences between the groups was tested for significance using an independent two tailed t-test. Further analysis on gender, HLA-B27 status, co-morbidities and medication exposure was done using a chi-squared test for independence. A p value of less than 0.05 was deemed significant.

Results: At present 860 patients are currently enrolled in the ASRI with 76.6% (659) males and 23.4% (201) females. Average age of patients is 45.8 years, mean disease duration of 19.4 years with 95.5% (821) of patients listed as Caucasian. Mean scores were BASDAI 4.02, BASFI 3.7, BASMI 4.02, HAQ 0.55, and ASQoL of 6.51. In total 33 (3.8%) of patients underwent joint replacement surgery. These patients were noted to be significantly older than the rest of the cohort (55.3 years old vs 45.1, p<0.01), with a longer disease duration (31.6 years vs 18.3, p<0.01) and higher rates of HLA-B27 positivity (94.7% vs 80.2%, p<0.01). No significant differences were noted between gender (table 1). No significant difference was found between medication exposure rates, although the joint replacement population did have higher rates of NSAID, sDMARD and biologic therapy usage than the rest of the population although this did not reach significance. These patients also scored worse in all measures of disease activity, although this only reached significance in the BASFI (5.67 vs 3.64, p<0.01), HAQ (0.9 vs 0.54, p<0.01) and the BASMI (6.07 vs 3.94, p<0.01).

Table 1.

	Joint replacement (n=33)	No Joint Replacement (n=827)	p value
Age	55.3	45.1	<0.01
Disease duration	31.6	18.31	<0.01
Delay to dx	6.97	7.97	0.51
HLA-B27+	94.7% (18)	71.9% (491)	<0.01
Males	78.8% (26)	84.7% (535)	0.76
Females	21.2% (7)	19.3% (160)	0.76
Mean Scores			
BASDAI	4.91	4.06	0.06
BASFI	5.67	3.64	<0.01
HAQ	0.9	0.54	<0.01
ASQoL	7.42	6.67	0.45
BASMI	6.07	3.94	<0.01
Medications			
NSAIDs	51.5% (17)	47% (389)	0.21
Bio tx	72.7% (24)	57.2% (473)	0.9
DMARDs	33.3% (11)	15.7% (130)	0.1

Conclusion: Patients requiring joint replacement surgery, although few in number, represent a cohort with significantly impaired function and quality of life. This is likely due to the fact that these patients were older with more established disease. It is therefore not surprising that this cohort had significantly worse spinal mobility. As registries continue to develop, it will be interesting to see if rates of joint replacement surgery will decline with increased use of biologic therapy at an earlier stage of disease. This will help to differentiate patients requiring joint replacement surgery due to underlying inflammatory arthritis and those with osteoarthritis.

Disclosure of Interests: Sinead Maguire Grant/research support from: ASRI is supported by funding from Pfizer, AbbVie and UCB, Phil Gallagher: None declared, Finbar Barry O'Shea Grant/research support from: ASRI is supported by funding from Pfizer, AbbVie and UCB

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Background: Ankylosing spondylitis(AS) has long been described as presenting in the third decade of life with the onset rarely occurring over the age of 45 years old. Previous research has shown there are small numbers of patients being diagnosed with AS later in life. These studies have been limited to small numbers limiting the ability to detect patterns in disease. The Ankylosing Spondylitis Registry of Ireland (ASRI) is an epidemiological data source on patients with AS in Ireland. Large registries, such as this, are an opportunity to further study this subtype in large numbers with greater power to detect differences between late and typical onset.

Objectives: The purpose of this study was to examine late onset AS in a large, well characterized cohort.

Methods: Patient registered in ASRI were analysed on the basis of their age of symptom onset using IBM SPSS version 26. Patients were divided into two groups with an age over 45 years old at symptoms onset categorized as 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 looking at differences in gender, HLA B27 status, sacroiliitis on MRI, medication use and extra-articular manifestations(EAMs) was also performed using a chi-squared test for independence.

Results: A total of 851 patients with AS were included in the analysis. Of these patients 659(77.4%) were males, with 192(22.6%) females, mean age of 45.8 years and mean disease duration of 19.4 years (means: ASQoL 6.52, HAQ 0.54, BASDAI 4.03, BASFI 3.7, BASMI 4.03). Patient population was made up of 797 patients(93.7%) categorized as typical onset, 54 patients(6.3%) categorized as late onset(table 1). Males had a higher rate of late onset AS than females, but this did not reach significance (6.8% vs 4.7%, p=0.19). Patients with late onset AS were noted to have higher BASFI (5.53 vs 3.58, p<0.01), HAQ (0.75 vs 0.53, p<0.01) and ASQoL scores (7.68 vs 6.44, p<0.01). Late onset patients also had lower rates of HLA-B27 positivity (76.5% vs 91.2%, p<0.01). No significant difference was detected in BASDAI or BASMI scores. No difference was detected between groups regarding rates EAMs. The late onset AS patients were noted to have lower rates of biologic therapy use (50% vs 72%, p<0.01). No significant difference was detected in rates of NSAID use.

Table 1.

	Onset < 45 years (n=797)	Late Onset (n=54)	p value
Males (n=659)	93.2% (614)	6.8% (83.3)	0.19
Females (n=192)	23% (183)	16.6% (9)	
HLA B27+ (n=580)	90.5% (554)	76.5% (26)	<0.01
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
MRI Sacroiliitis (n=384)	45.3% (361)	42.6% (23)	0.69
Bilateral sacroiliitis (n=668)	79% (628)	74% (40)	0.07
BASDAI	4.02	4.19	0.6
BASFI	3.58	5.53	<0.01
BASMI	3.96	4.97	0.12
HAQ	0.53	0.75	<0.01
ASQoL	6.44	7.68	<0.01
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
Smokers (ever)	57.3% (457)	64.8% (35)	0.01
Alcohol consumption (ever)	82% (654)	75.9% (41)	0.53
Biologic tx	69.1% (551)	48.1% (26)	<0.01
NSAID tx	54.2% (432)	61.1% (33)	0.2

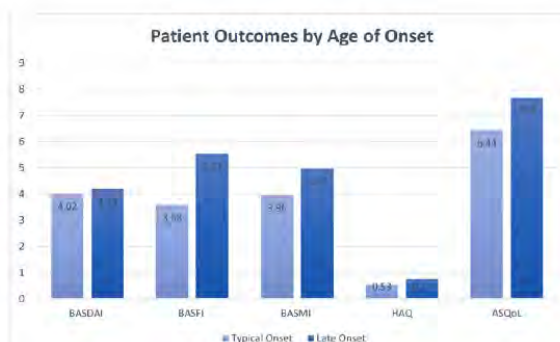


Figure 1.

Conclusion: This analysis shows that late onset AS does occur in up to 6.3% of patients with AS. Patients with late onset disease were noted to have similar patterns of disease, EAMs and radiological findings consistent with current

S. Maguire¹, P. Gallagher², F. B. O'shea¹. ¹St James' Hospital, Rheumatology, Dublin, Ireland; ²St Vincents Hospital, Rheumatology, Dublin, Ireland

Background: Axial spondyloarthritis(axSpA) treatment has undergone a number of significant developments over the past number of decades. Previously

limited to non-steroidal anti-inflammatories (NSAIDs) and corticosteroids, treatment options now include synthetic disease modifying anti-rheumatic drugs(sDMARDs) and biologic agents. The development of national registries for inflammatory arthritis provides an opportunity to study medication usage in a large cohort of patients with axSpA. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data on patients with axSpA in Ireland. The aim of this study was to examine medication exposure and outcomes.

Objectives: To characterize a large cohort of patients with axSpA in terms of medications usage, burden of disease and patient reported outcomes.

Methods: The patient population registered in the ASRI was analysed using IBM SPSS version 26. Patients were analyzed on the basis of medication exposure. The four treatment groups were classified as no treatment, NSAIDs only, biologics only, or biologics and NSAIDs. Mean age, duration of disease and delay to diagnosis was compared between groups. Burden of disease was assessed via mean BASDAI, BASFI, BASMI, HAQ and ASQoL between the four groups. Differences between groups was tested for statistical significance a one-way analysis of variance (ANOVA). A chi-squared test for independence was used to compare differences in rates of HLA-B27 positivity rates and gender. Results were deemed significant where $p < 0.05$.

Results: At present 860 patients are currently enrolled in the ASRI with 76.6% (659) males and 23.4% (201) females. Average age of patients is 45.8 years, mean disease duration of 19.4 years with 95.5% (821) of patients listed as Caucasian. Mean scores were BASDAI 4.02, BASFI 3.7, BASMI 4.02, HAQ 0.55, and ASQoL of 6.51. Treatment groups were made up of 9.9%(85) on no treatment, 22.2%(191) NSAIDs treatment only, 34.8%(299) biologics treatment only and 32.1%(276) treated with both NSAIDs and biologics. Patients only on NSAIDs were noted to be older than patients on biologics, and those on both biologics and NSAIDs ($p=0.02$). Patients on NSAIDs were older at symptom onset than those on both biologic and NSAID treatment ($p=0.02$), however the effect size is small(0.012). No significant difference was noted between groups regarding disease duration, delay to diagnosis or distribution between genders (table 1). Difference in BASDAI scores between groups was significant between all groups, with patients on both biologics and NSAIDs having the highest scores and those on no treatment with the lowest scores(4.74 vs 3.37) possibly a reflection of disease severity(table 2).

Table 1.

	ASRI	No tx	NSAIDs tx	Biologic tx	Biologic & NSAIDsp	value
Number	860	9.9% (85)	22.2% (191)	37.8% (299)	32.1% (276)	
Age	45.8	49.7	46.2	45.3	45.1	0.02
Symptom onset	26.4	27.5	28.2	26.1	25.2	0.02
Disease duration	19.4	22.2	18	19.1	19.8	0.06
Delay to dx	8	9.8	8.1	7.4	8	0.13

Table 2.

	ASRI	No tx	NSAIDs tx	Biologic tx	Biologic & NSAIDs	p value	Effect Size
BASDAI	4.02	3.37	4.21	3.4	4.74		0.06
		3.37	4.21		4.74	0.04	
			4.21	3.4		<0.01	
				3.4	4.74	<0.01	

Conclusion: A large proportion of patients in the ASRI were treated with either biologics only or both biologics and NSAIDs. No treatment was the least common treatment within this cohort. Patients not on treatment tended to be older than those on any type of treatment. Overall patients on biologics alone tended to have better patient reported outcomes as compared to all other treatment groups. The development of longitudinal data for the ASRI will help to further understand the reason behind these differences.

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

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Meeting: **ACR Convergence 2020**

Keywords: **Ankylosing spondylitis (AS), Autoinflammatory diseases, Epidemiology, gender, pregnancy**

SESSION INFORMATION

Date: **Sunday, November 8, 2020**

Session Type: **Poster Session C**

Session Title: **Spondyloarthritis Including Psoriatic Arthritis – Diagnosis, Manifestations, & Outcomes Poster II: Extra-MSK & Comorbidities**

Session Time: **9:00AM-11:00AM**

Background/Purpose: Axial spondyloarthritis (axSpA) is an inflammatory arthritis affecting the sacroiliac joints and the spine. Although this chronic condition affects a wide range of ages, many females affected are of childbearing age. At present it is unclear how axSpA affects pregnancy, in terms of prevalence of pregnancy related complications and foetal 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.

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 September 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 standardized 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, χ^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 an increase in the prevalence of pre-eclampsia (OR 1.3, 95% CI 0.92-1.82) and IUGR (OR 1.17, 95% CI 0.26-5.17) and a statistically significant increase in prevalence of cesarean section (OR 1.85, 95% CI: 1.46-2.30) in axSpA females (table 1). Prevalence of all analyzed fetal complications was higher in axSpA pregnancies (table 2), this did not reach significance. Disease activity during pregnancy varied significantly, but overall 47.8% of patients

assessed by standardized outcomes reported increased disease activity in pregnancy. Few studies examined medication usage in pregnancy.

Conclusion: Females with axSpA overall have significantly higher prevalence of cesarean section then the general population. This analysis suggests a trend towards higher rates 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 varied with time and country. Ongoing development of national registries could help to better understand axSpA in pregnancy.

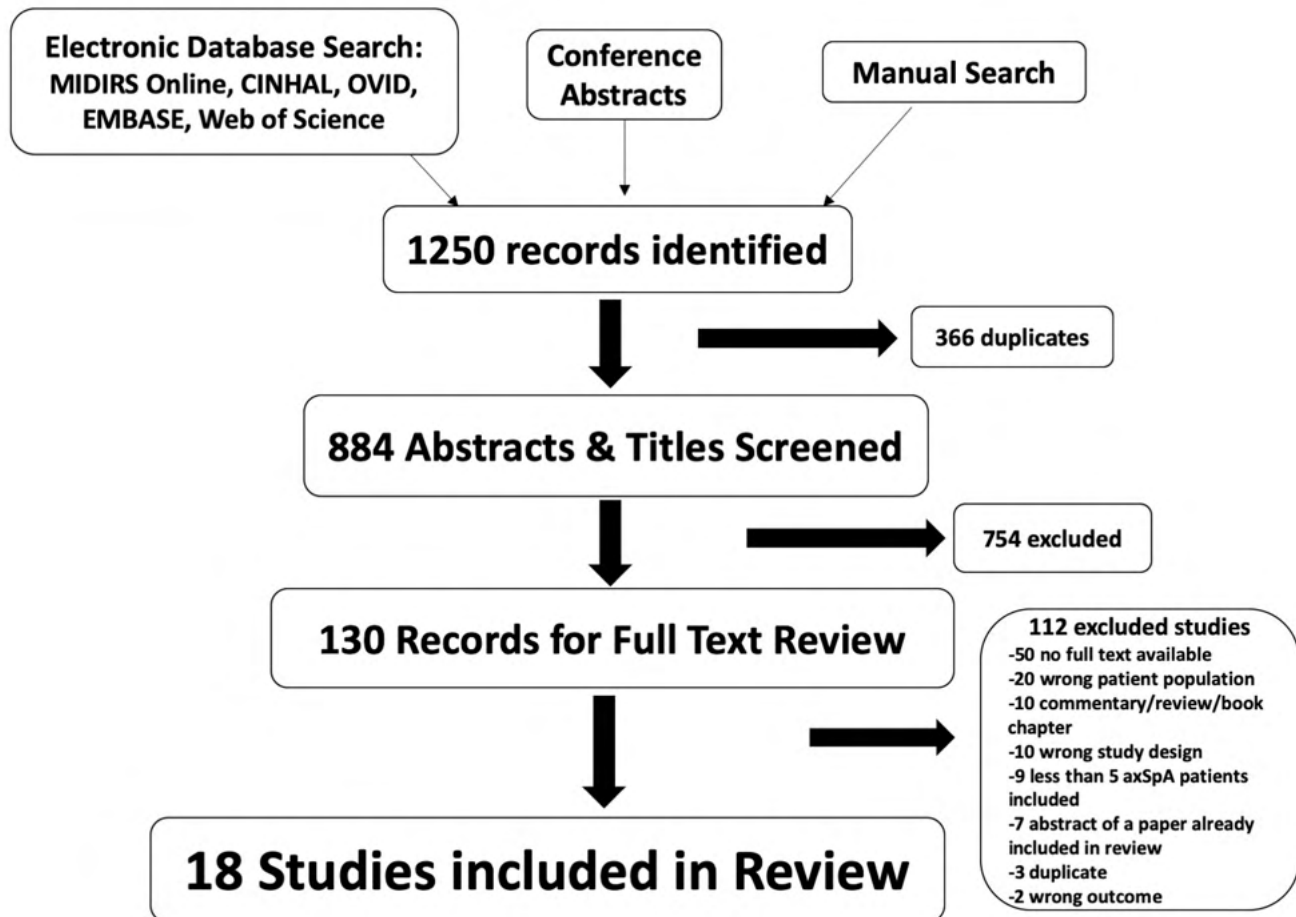


Figure 1: Study Selection

	OR	95% CI	AxSpA Weighted Pooled Mean (%)	Control Weighted Pooled Mean (%)
Cesarean Section	1.85	(1.46, 2.30)	37.3	18.6
Preterm birth	0.84	(0.39, 1.81)	5.5	5.3
<i>Sensitivity Analysis</i>	1.24	(0.94, 1.64)	8	5.3
Miscarriage	0.75	(0.03, 19.7)	3	3.2
Pre-eclampsia	1.74	(0.85, 3.54)	2.8	2.5
<i>Sensitivity Analysis</i>	1.3	(0.92, 1.82)	2.1	2.5
Gestational diabetes	0.88	(0.24, 3.21)	4.3	5.7
IUGR	1.17	(0.26, 5.17)	4.3	4.7
PPROM	0.92	(0.2, 4.24)	6.7	N/A
Stillbirth	0.7	(0.26, 1.85)	0.7	1.1

Table 1: Summary of Pregnancy Complications

	OR	95% CI	axSpA Weighted Pooled Mean (%)	Control Weighted Pooled Mean (%)
LBW	1.47	(0.98, 2.21)	6.3	2.9
SGA	1.66	(0.93, 2.95)	8.7	11
Congenital abnormalities	1.34	(0.63, 2.84)	3.4	3
NICU admissions	1.55	(0.96, 2.51)	17.4	11.9

Table 2: Summary of Fetal Complications

Disclosure: S. Maguire, None; T. O'Dwyer, None; F. Wilson, None; D. Mockler, None; F. O'Shea, None.

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ACR Meeting Abstracts - <https://acrabstracts.org/abstract/pregnancy-in-axial-spondyloarthritis-a-systematic-review-meta-analysis/>

Spinal Mobility and Function: How Closely Do They Associate in Axial Spondyloarthritis?

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Meeting: **ACR Convergence 2020**

Keywords: **autoimmune diseases, Disease Activity, Outcome measures, Spondylarthropathies, spondyloarthritis**

SESSION INFORMATION

Date: Monday, November 9, 2020

Session Type: Poster Session D

Session Title: Spondyloarthritis Including Psoriatic Arthritis – Diagnosis, Manifestations, & Outcomes Poster III: Axial SpA

Session Time: 9:00AM-11:00AM

Background/Purpose: Axial spondyloarthritis (axSpA) is a form of inflammatory arthritis affecting the axial skeleton. Persistent disease activity can result in restricted spinal mobility over time, and is presumed to lead to functional impairment although evidence to date on this subject has been limited. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data on patients with axSpA in Ireland. The aim of this study was to examine the relationship between degree of spinal mobility (as assessed by BASMI score) and effect on functional ability (as assessed by BASFI score).

Methods: IBM SPSS version 24 was used to run the analysis of the patient population registered in the ASRI to date. Patients with both BASFI and BASMI scores were included in the analysis. Both variables were assessed with a Shapiro-Wilk's test for normal distribution. Variables were also assessed for presence of a monotonic relationship by visual inspection of a scatterplot of the two variables. Once a monotonic relationship was established a Spearman's rank-order correlation between BASMI and BASFI was analyzed. Further analysis with a Pearson's partial correlation was preformed to control for gender. Records were then split by gender and a Spearman's rank-order correlation was undertaken to assess strength of correlation of scores within each gender.

Results: In total 847 patients were assessed for inclusion. Data on both BASMI and BASFI scores were available on 647 of these patients, which were included in the analysis. Variables were not normally distributed as assessed by Shapiro-Wilk's test ($p < 0.01$). Preliminary analysis showed the relationship between these measures to be monotonic (as the BASFI score increases, so too does the BASMI score), as determined by visual inspection of the scatterplot. There was a statistically significant, strong positive correlation between BASMI and BASFI scores in axSpA patients, $r_s(645) = 0.509$, $p = 0.001$ (figure 1) based on calculations by Spearman's rank-order correlation. A Pearson's partial correlation showed that the strength of this correlation was stronger when controlled for gender, $r_{\text{partial}}(645) = 0.521$, and remained statistically significant $p < 0.001$. A Spearman's rank-order correlation analysis following splitting of records by gender showed the correlation becomes stronger if assessed within each gender (Females $r_s(144) = 0.577$, $p < 0.01$; Males $r_s(509) = 0.576$, $p < 0.01$) and has a slightly stronger association with in females (figure 2).

Conclusion: BASFI scores have a strong positive correlation with BASMI scores in patients with axSpA. In clinical terms, patients with worse limitation of spinal mobility are likely to have greater level of functional impairment and vice versa. Analysis by gender shows this correlation is more significant if compared within each gender, and is slightly stronger in females with axSpA.

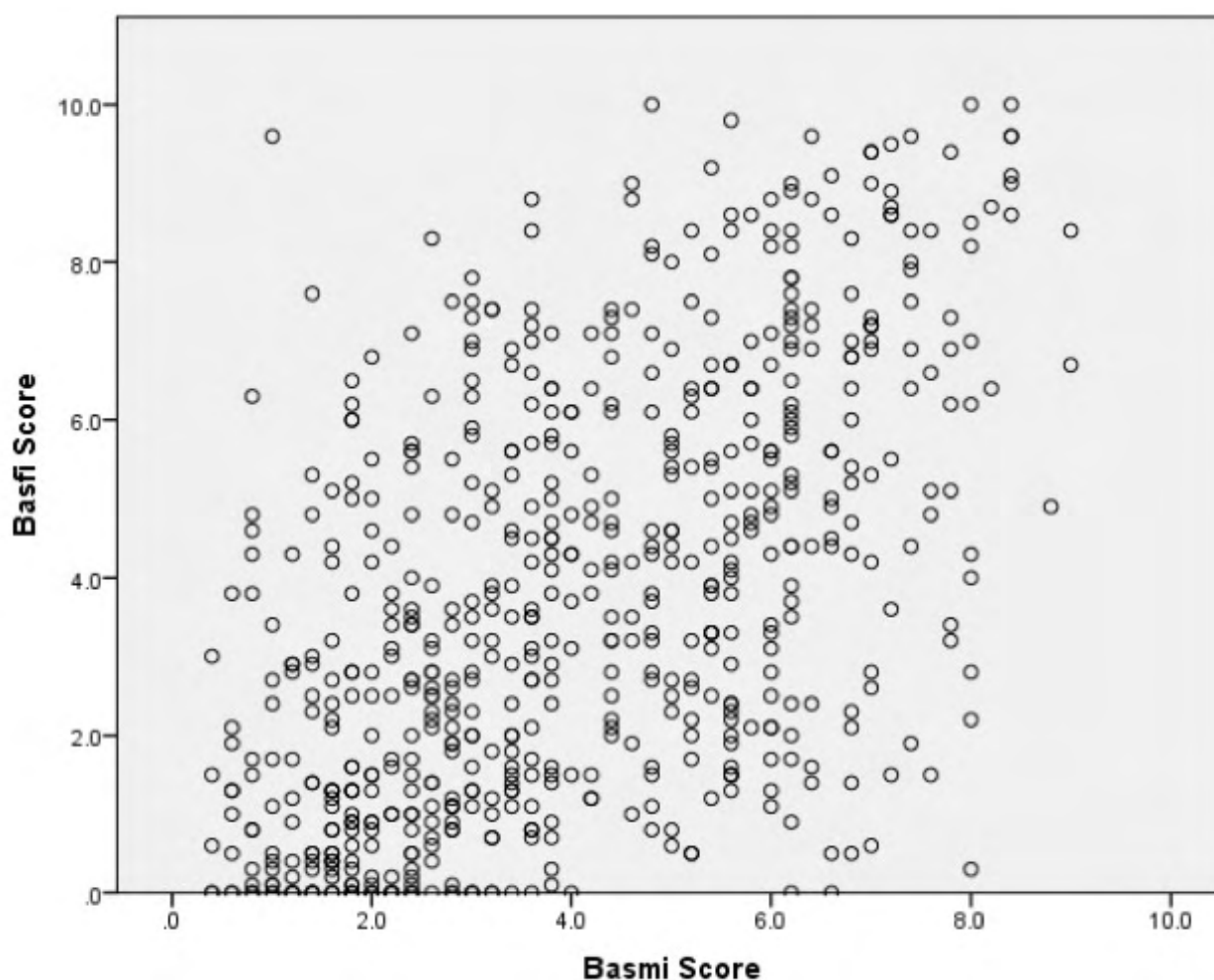


Figure 1: Correlation between BASFI and BASMI in the ASRI population

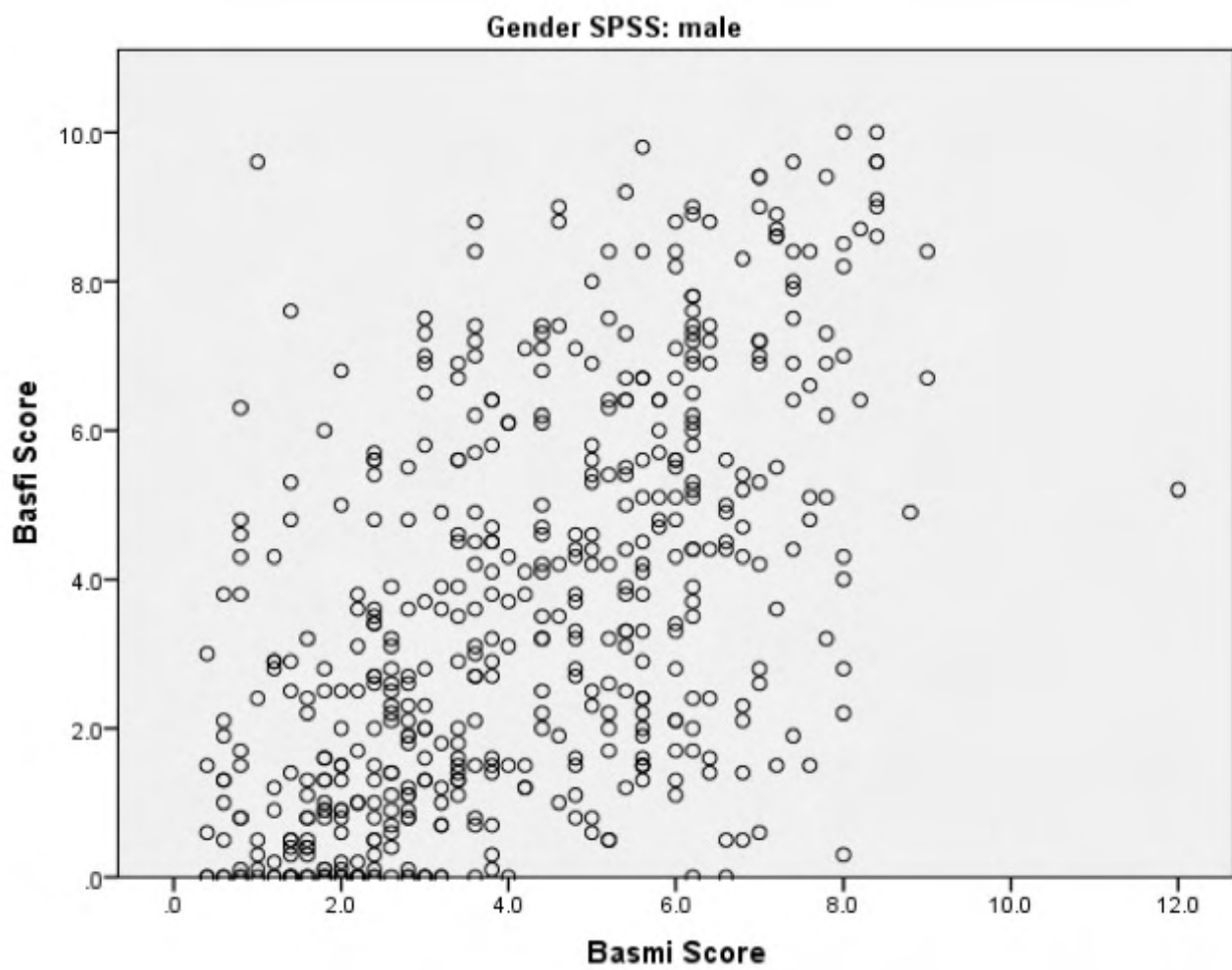


Figure 2a: Correlation between BASMI and BASFI in Males

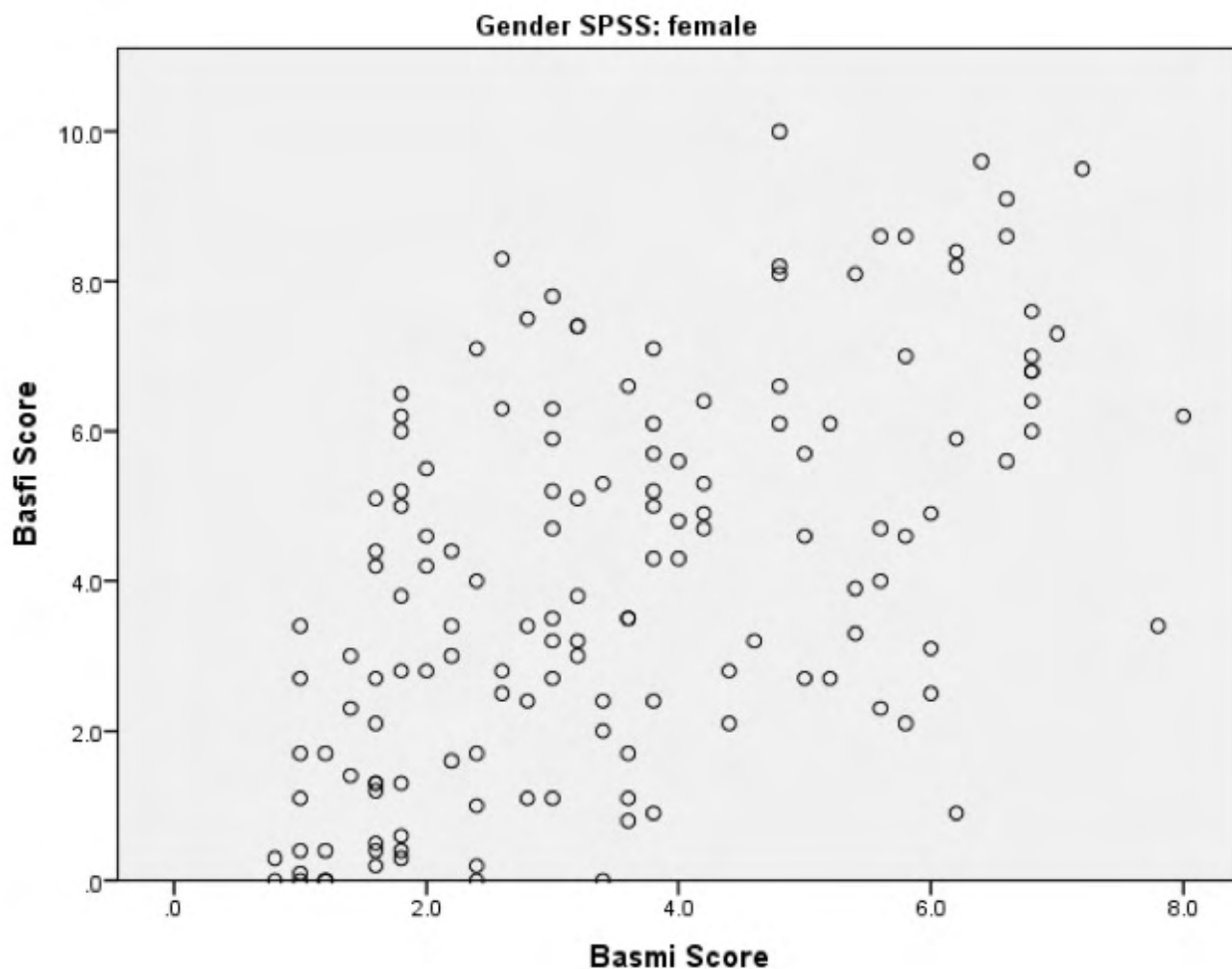


Figure 2b: Correlation between BASMI and BASFI in Females

Disclosure: S. Maguire, None; P. Gallagher, None; F. O'Shea, None.

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P180 UNDIAGNOSED DEPRESSION IN AXIAL SPONDYLOARTHROPATHY NEGATIVELY AFFECTS DISEASE ACTIVITY AND QUALITY OF LIFE

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Background/Aims

Previous research in axial spondyloarthritis (axSpA) has shown this population to have a high prevalence of depression. This co-morbidity has been previously shown to impact disease activity in patients with rheumatic disease. The purpose of this study was to screen for signs of depression using two validated tools, the Patient Health Questionnaire-9 (PHQ-9) and the Hospital Anxiety and Depression Scale for depression (HADS-D) in axSpA patients.

Methods

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 PHQ-9 and the HADS-D. Scores from the HADS-D yielded a numerical result which was then categorised as normal, borderline or abnormal. PHQ-9 numerical results were categorised as normal, mild, moderate, moderate/severe or severe. Patients with a known diagnosis of depression were excluded. In addition to baseline demographics, patient reported outcomes were also recorded. Data analysis was performed using IBM SPSS version 26. Continuous variables were recorded as means, categorical variables as frequencies with percentages. A one-way analysis of variance analysis (ANOVA) determined significance of variation in outcomes between patient outcomes as determined by the HADS-D and PHQ-9. A p-value of <0.05 was deemed significant. Consent was obtained prior to participation. Approval was received from the St James'/Tallaght Hospital Joint Ethics Committee.

Results

In total 71 axSpA patients took part in the survey. The population was 70.4% (50) males and 29.5% (21) female, with an average age 47.9 years and mean disease duration 19.7 years (mean outcomes: BASDAI 4.08, BASFI 3.62, BASMI 3.54, ASQoL 6.79). Overall, 7 (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 (6.27 vs 3.42, $p<0.01$) and AqoL scores (12.57 vs 5.26, $p<0.01$) in axSpA patients with abnormal compared to normal HADS D scores. 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 2.55, $p<0.01$), BASFI (8.05 vs 2.33, $p<0.01$) and ASQoL (19.5 vs 2.62, $p<0.01$) noted in those scoring as severe compared to normal. No significant differences were detected in BASMI scores or baseline demographics.

Conclusion

A high percentage of axSpA patients recorded high HADS D and PHQ-9 scores for undiagnosed depression. These patients had significantly worse disease activity and quality of life as compared to patients with normal scores. Clinicians treating axSpA should consider screening for depression in this population.

DISEASE ASSESSMENT

O11 EXAMINING BASDAI BY GENDER: DIFFERING SCORES, BUT SIMILAR PATTERNS OF DISEASE

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Background/Aims

Research has shown that females with axial spondyloarthritis (axSpA) score worse on patient reported outcomes (PROs) than males. However, this does not always correlate to worse clinical findings. The purpose of this study was to understand why women with axSpA have worse BASDAI scores than men, by examining how both genders score across the components of the BASDAI. The Ankylosing Spondylitis Registry of Ireland (ARSI) is a national registry on patients with axSpA in Ireland and a source of epidemiological data.

Methods

Analysis of the ASRI was performed using IBM SPSS version 26. Patients were analysed on the basis of gender. Comparison of baseline characteristics and mean BASMI, BASFI, HAQ and ASQoL were tested for significance using an independent two tailed t-test and a Mann Whitney U test. Mean total BASDAI score and mean score for each component of the BASDAI were compared and tested for significance with the same statistical tests. A chi-squared test for independence was used to determine significance in variation of HLA-B27 status and radiographic findings.

Results

A total of 857 patients were included in the analysis. Patient population was 24.9% (213) female and 75.1% (644) male with a mean age of 45.9 years and mean disease duration of 19.4 years (means: BASDAI 4.02, BASMI 4, BASFI 3.67, HAQ 0.53, ASQoL 6.48). Females had worse BASDAI (4.6 vs 3.83, $p < 0.01$), HAQ (0.6 vs 0.51, $p = 0.03$) and ASQoL scores (7.62 vs 6.12, $p < 0.01$) than males. BASFI scores were worse in females which did not reach significance (3.89 vs 3.63, $p = 0.26$). However, females had significantly better BASMI scores than males (3.51 vs 4.16, $p < 0.01$). Within the BASDAI, females scored significantly worse than males across all components (Fatigue: 5.56 vs 4.51, $p < 0.01$; Spinal pain: 5.51 vs 4.63, $p < 0.01$; Other pain: 3.82 vs 3.19, $p = 0.01$; Discomfort: 4.05 vs 3.29, $p < 0.01$; EMS: 4.55 vs 3.94, $p = 0.01$), however duration of EMS did not reach significance (3.54 vs 3.12, $p = 0.07$) (table 1). Within the BASDAI, females recorded highest mean scores for fatigue (5.56), while males recorded highest mean scores for spinal pain (4.63). Lowest mean scores for both genders was for EMS duration (3.54 vs 3.12). Ranking of the BASDAI components by mean scores show similarity in the ranking of discomfort, EMS, other pain and EMS duration.

Conclusion

AxSpA females have consistently worse PROs but have better spinal mobility than males. Despite females recording worse BASDAI scores than males, the pattern of disease activity manifestation is similar in 4 of the 6 components of the BASDAI. However, fatigue is the most problematic symptom in females with active axSpA while spinal pain is the most problematic symptom for males. This variation by gender should be kept in consideration when evaluating a patient with suspected active axSpA.

Disclosure

S. Maguire: None. **P. Gallagher:** None. **F. O'Shea:** None.

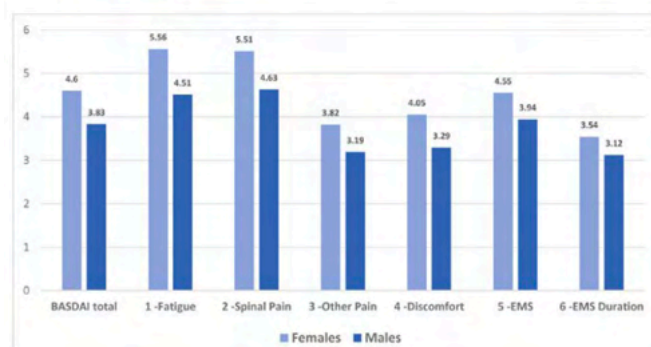
S. Maguire^{1,2}, P. Gallagher³, F. B. O'shea^{1,2}. ¹St James' Hospital, Department of Rheumatology, Dublin, Ireland; ²Trinity College Dublin, School of Medicine, Dublin, Ireland; ³St Vincent's Hospital, Department of Rheumatology, Dublin, Ireland

Background: Females with axial spondyloarthritis (axSpA) average scores on patient reported outcomes (PROs) than males. However, this does not necessarily correlate to worse clinical findings. The Ankylosing Spondylitis Registry of Ireland (ARSI) is a national registry on patients with axSpA in Ireland and a source of epidemiological data.

Objectives: The purpose of this study was to compare the scores of each sex across the individual components of the BASDAI to understand why females report worse scores than males.

Methods: Analysis of the ARSI was preformed using IBM SPSS version 26. Patients were analyzed on the basis of gender. Comparison of baseline characteristics and mean BASMI, BASFI, HAQ and ASQoL were tested for significance using an independent two tailed t-test and a Mann Whitney U test. Mean total BASDAI score and mean score for each component of the BASDAI were compared and tested for significance with the same statistical tests. A chi-squared test for independence was used to determine significance in variation of HLA-B27 status and radiographic findings.

Results: A total of 857 patients were included in the analysis. Patient population was 24.9% (213) female and 75.1% (644) male with a mean age of 45.9 years and mean disease duration of 19.4 years (means: BASDAI 4.02, BASMI 4, BASFI 3.67, HAQ 0.53, ASQoL 6.48). Females had worse BASDAI (4.6 vs 3.83, $p<0.01$), HAQ (0.6 vs 0.51, $p=0.03$) and ASQoL scores (7.62 vs 6.12, $p<0.01$) than males. BASFI scores were worse in females which did not reach significance (3.89 vs 3.63, $p=0.26$). However, females had significantly better BASMI scores than males (3.51 vs 4.16, $p<0.01$). Within the BASDAI, females scored significantly worse than males across all components (Fatigue: 5.56 vs 4.51, $p<0.01$; Spinal pain: 5.51 vs 4.63, $p<0.01$; Other pain: 3.82 vs 3.19, $p=0.01$; Discomfort: 4.05 vs 3.29, $p<0.01$; EMS: 4.55 vs 3.94, $p=0.01$), however duration of EMS did not reach significance (3.54 vs 3.12, $p=0.07$) (graph 1). Within the BASDAI, females recorded highest mean scores for fatigue (5.56), while males recorded highest mean scores for spinal pain (4.63). Lowest mean scores for both genders was for EMS duration (3.54 vs 3.12). Ranking of the BASDAI components by mean scores show similarity in the ranking of discomfort, EMS, other pain and EMS duration (Table 1).



Graph 1. Breakdown of BASDAI scores in Females compared to Males

Table 1. Ranking in order of severity by mean score

	Females	Males
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

Conclusion: AxSpA females have consistently worse PROs but have better spinal mobility than males. Despite females recording worse BASDAI scores than males, the pattern of active disease is similar in 4 of the 6 components of the BASDAI. However, fatigue is the most problematic symptom in females with active axSpA while spinal pain is the most problematic symptom for males. This variation by gender should be kept in consideration when evaluating a patient with suspected active axSpA.

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Background: Worldwide prevalence of obesity has been steadily increasing, despite significant public health campaigns to raise health awareness. In axial spondyloarthritis (axSpA) obesity has been shown to be associated with higher levels of disease activity and decreased response to treatment. The waist to hip ratio (WtHpR) is a tool to screen for abdominal obesity. Abdominal deposition of adipose tissue is associated with increased risk of cardiovascular disease, type II diabetes and premature death. Abdominal obesity is more commonly found in males, while females are more prone to gluteal-femoral fat deposition. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data of axSpA patients in Ireland.

Objectives: To capture the prevalence of abdominal obesity in a large cohort of axSpA patients and assess for variation in prevalence between sexes.

Methods: Participants were analysed on the basis of sex and presence of obesity by BMI and WtHpR. Obesity was defined by body mass index (BMI) with a result of >30 categorised as obese as per CDC definitions. Abdominal obesity was assessed by WtHpR and defined as per WHO guidelines. Categorical variables were recorded as frequencies, with a χ^2 test for independence used to test for statistical significance. Numerical variables were recorded as means within each group and an independent t-test or Mann Whitney U test was used to test for statistical significance between groups. A p-value of <0.05 was deemed significant. IBM SPSS version 26 was used for statistical analysis of the patient population captured within the ASRI.

Results: At the time of analysis, physical measurements were available on 692 patients in the ASRI made up of 96.2% (666) Caucasians with 22.3% (154) females and 77.7% (538) males. The average age was 45.9 years with a mean disease duration of 18.8 years (mean scores: BASDAI 4.09, BASFI 3.71, BASMI 3.99, HAQ 0.54, ASQoL 6.72). 80.9% (560) of patients had radiographic sacroiliitis while 49.1% (340) had sacroiliitis on MRI.

Overall 29.5% (215) patients were obese based on BMI results, while 37.5% (274) were centrally obese as per the WtHpR. Analysis on the basis of sex revealed no significant variation in mean BMI (28.1 vs 27.7, $p=0.45$) or prevalence of obesity as assessed by BMI (29.9% vs 28.6%, $p=0.49$) between males and females (table 1). As expected analysis of WtHpR revealed higher mean ratios in males compared to females (0.96 vs 0.89, $p<0.01$), however there was a significantly higher prevalence of abdominal obesity in females (29.9% vs 68.2%, $p<0.01$).

Conclusion: There is a high prevalence of abdominal obesity as assessed by WtHpR in axSpA, this is especially high in females with axSpA. Use of WtHpR should be considered when screening for obesity in this population.

Table 1. Assessment of Obesity by Sex

	Males	Females	p value
n	77.7% (538)	22.3% (154)	
Weight (kg)	84.98	72.76	<0.01
BMI	28.08	27.69	0.45
Underweight	0.9% (5)	0.06% (1)	0.49
Normal Weight	29.2% (157)	36.4% (56)	
Overweight	39.2% (211)	34.4% (53)	
Obese	29.9% (161)	28.6% (44)	
Waist Circumference (cm)	97.43	90.03	<0.01
Hip Circumference (cm)	102.11	101.27	0.56
Waist to Hip Ratio	0.956	0.8901	<0.01
Normal Weight	23.8% (128)	17.5% (27)	<0.01
Overweight	46.3% (249)	14.3% (22)	
Obese	29.9% (161)	68.2% (105)	

THE NEGATIVE IMPACT OF UNDIAGNOSED DEPRESSION IN AXIAL SPONDYLOARTHRITIS: RESULTS OF A SCREENING STUDY

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Background: Previous research in axial spondyloarthritis(axSpA) has shown this population to have a high prevalence of depression. This co-morbidity has been previously shown to impact disease activity in patients with rheumatic disease.

Objectives: The purpose of this study was to screen for early signs of depression using two validated tools, the Patient Health Questionnaire-9 (PHQ-9) and the Hospital Anxiety and Depression Scale for depression (HADS-D) in patients with known axSpA.

Methods: 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 PHQ-9 and the HADS-D. Scores from the HADS-D yielded a numerical result which was then categorised as normal, borderline or abnormal. PHQ-9 numerical results were categorised as normal, mild, moderate, moderate/severe or severe. Patients with a known diagnosis of depression were excluded. In addition to baseline demographics, patient reported outcomes from the clinic visit were also recorded.

Data analysis was performed using IBM SPSS version 26. Continuous variables were recorded as means, categorical variables as frequencies with percentages. 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 p-value of <0.05 was deemed significant. Consent was obtained prior to participation. Approval was received from the St James'/Tallaght Hospital Joint Ethics Committee.

Results: In total 71 axSpA patients took part in the survey. The population was 70.4%(50) males and 29.5%(21) female, with an average age 47.9 years and mean disease duration 19.7 years (mean outcomes: BASDAI 4.08, BASFI 3.62, BASMI 3.54, ASQoL 6.79). Overall, 7 (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 (6.27 vs 3.42, p<0.01) and AqoL scores (12.57 vs 5.26, p<0.01) in axSpA patients with abnormal compared to normal HADS-D scores. 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 2.55, p<0.01), BASFI (8.05 vs 2.33, p<0.01) and ASQoL (19.5 vs 2.62, p<0.01) noted in those scoring as severe compared to normal. No significant differences were detected in BASMI scores or baseline demographics.

Conclusion: A high percentage of axSpA patients recorded high HADS-D and PHQ-9 scores concerning for undiagnosed depression. These patients were noted to have significantly worse disease activity and quality of life as compared to patients with normal scores. Clinicians treating axSpA should consider screening for depression in this population.

SEX DIFFERENCES IN CORRELATION OF SPINAL MOBILITY AND FUNCTIONAL IMPAIRMENT IN AXIAL SPONDYLOARTHROPATHY

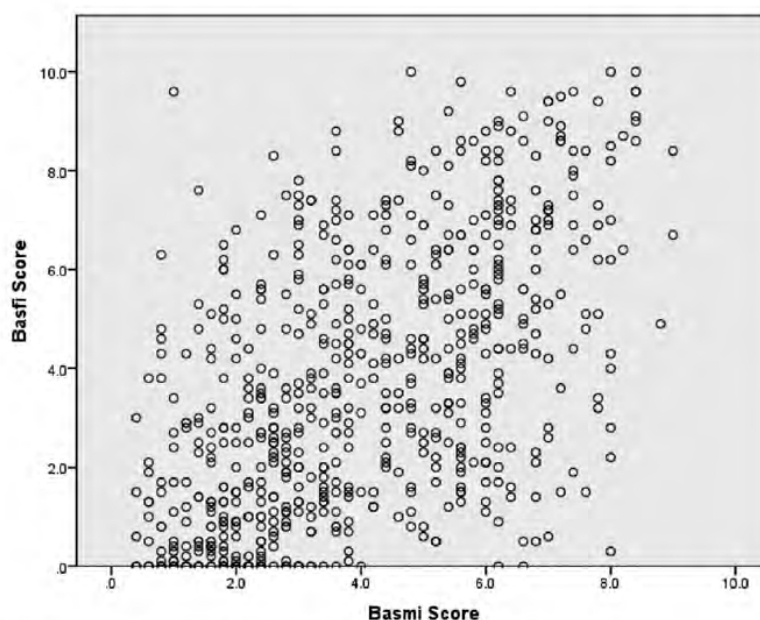
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Introduction. Axial spondyloarthritis (axSpA) is an inflammatory arthritis affecting the axial skeleton. Persistent disease activity can restrict spinal mobility over time, impairing function. The Ankylosing Spondylitis Registry of Ireland (ASRI) is an epidemiological data source on Irish patients with axSpA. The aim of this study was to examine the relationship between degree of spinal mobility and effect on function.

Methods. IBM SPSS was used for the analysis. Patients with both BASFI and BASMI scores were included. Variables were assessed with a Shapiro-Wilk's test for normal distribution and presence of a monotonic relationship by visual inspection of a scatterplot of the two variables. Then a Spearman's rank-order correlation was analyzed. A Pearson's partial correlation was performed to control for gender. Records were then split by gender and Spearman's rank-order correlation was undertaken to assess correlation of scores within each gender.

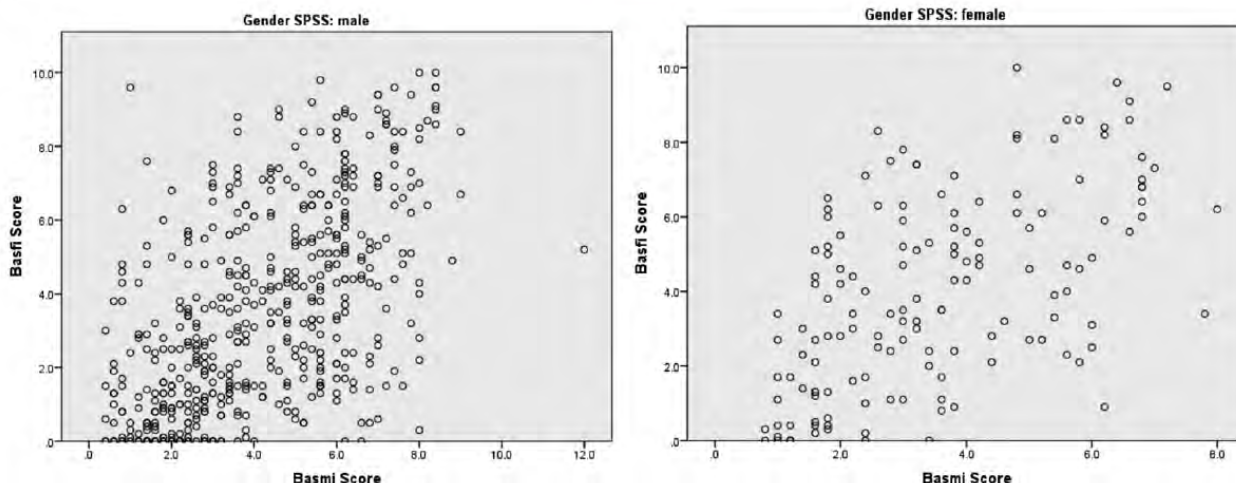
Results. Data on BASMI and BASFI scores were available on 647 patients. Variables were not normally distributed as assessed by Shapiro-Wilk's test ($p < 0.01$). The relationship was monotonic, as determined by visual inspection of the scatterplot. There was a significant, strong positive correlation between BASMI and BASFI scores in axSpA patients, $r_s(645) = 0.509$, $p = 0.001$ (Fig. 1) based on a Spearman's rank-order correlation. A Pearson's partial correlation showed this correlation was stronger when controlled for gender, $r_{\text{partial}}(645) = 0.521$, and remained significant $p < 0.001$. A Spearman's rank-order correlation analysis following splitting of records by gender showed the correlation becomes stronger if assessed within each gender (Females $r_s(144) = 0.577$, $p < 0.01$; Males $r_s(509) = 0.576$, $p < 0.01$) and has a slightly stronger association in females (Fig. 2).



P50. Fig. 1. Correlation between BASMI and BASFI scores overall.

Conclusions. Restriction of spinal mobility in axSpA has a strong positive association with functional impairment in axSpA. This correlation is more significant compared within each gender and is slightly stronger in females.

Acknowledgements. ASRI is supported by funding from AbbVie, Pfizer and UCB.



P50. Fig. 2. Sex specific correlation in (a) Males vs (b) Females

P51

NEGATIVE IMPACT OF UNEMPLOYMENT IN AXIAL SPONDYLOARTHROPATHY: RESULTS FROM THE ANKYLOSING SPONDYLITIS REGISTRY OF IRELAND

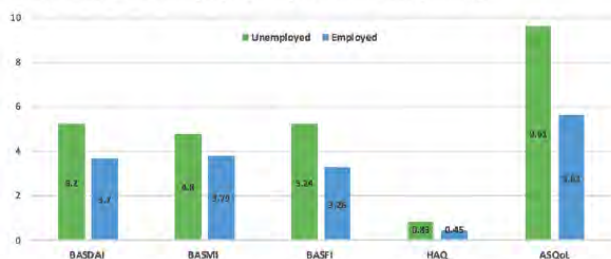
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Introduction. Persistent disease activity in axial spondyloarthritis (axSpA) can cause disability and affect ability to maintain employment. With advances in management, it was expected that employment levels in axSpA would be similar to nationally reported averages of the general population. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a valuable source of epidemiological data on axSpA in Ireland. The aim of this study was to determine prevalence of unemployment in axSpA and the impact on patient outcomes.

Methods. IBM SPSS v.26 was used for statistical analysis. Patients were analysed on the basis of employment and categorised as employed or unemployed. A two tailed t-test was tested differences between mean continuous variables between the groups. For categorical variables a chi-squared test of independence determined significance. An alpha level of $p < 0.05$ was deemed significant.

Results. Employment status was available for 876 patients. The population comprised 72.6% (644) males and 26.2% (232) females. Mean age was 45.9 years, disease duration was 19.4 years and delay in diagnosis was 8 years (mean scores: BASDAI 4.02, BASFI 3.67, BASMI 4.01, HAQ 0.53, ASQoL 6.47). Overall 21.6% (189) of the population was unemployed, considerably higher than national averages of 6.2-13.1% during the same period. In addition, 24% (213) reported axSpA as a factor limiting ability to work. Unemployed patients reported significantly worse BASDAI (5.2 vs 3.7, $p < 0.01$), BASMI (4.8 vs 3.79, $p < 0.01$), BASFI (5.24 vs 3.26, $p < 0.01$), HAQ (0.83 vs 0.45, $p < 0.01$), and ASQoL scores (9.61 vs 5.63, $p < 0.01$) compared to employed axSpA patients. A higher proportion of males were unemployed, compared to females (Table I).



P51. Fig. 1. Comparison of outcomes on the basis of employment, all differences significant at the $p < 0.05$ level.

P51. Table I. Characteristics of the employed versus unemployed cohorts.

	Unemployed	Employed	p-value
N	189 (21.6%)	687 (78.4%)	
Males	155 (82%)	489 (71.2%)	<0.01
Females	34 (18%)	198 (28.8%)	
Age	45.66	45.95	0.79
Disease duration	18.9	19.6	0.51
Delay to diagnosis	7.39	8.14	0.28
Symptom onset age	26.76	26.37	0.66
Caucasian	177 (93.7%)	622 (90.5%)	0.1
HLA-B27 +	130 of 145 (89.7%)	472 of 480 (98.3%)	0.98
Radiographic sacroiliitis	154 (81.5%)	529 (77%)	0.41
MRI sacroiliitis	72 (38.1%)	317 (46.1%)	0.13
Arthritis	60 (31.7%)	206 (30%)	0.89
Enthesitis	41 (21.7%)	111 (16.2%)	0.15
Dactylitis	13 (6.9%)	42 (6.1%)	0.49
Psoriasis	32 (16.9%)	112 (16.3%)	0.87
Uveitis	64 (33.9%)	233 (33.9%)	0.29
Colitis	12 (6.3%)	79 (11.5%)	0.07
NSAIDs	98 (51.9%)	349 (50.8%)	0.59
DMARDs	45 (23.8%)	153 (22.3%)	0.46
Biologic	141 (74.6%)	453 (65.9%)	0.07

Conclusions. Unemployment in axSpA remains considerably higher than the nationally reported average. Unemployed axSpA patients have worse quality of life, poorer levels of function and higher levels of disease activity. Further research is needed to determine how disease activity influences ability to engage in employment.

Acknowledgements. The ASRI is supported by funding from AbbVie, Pfizer and UCB.

Identifying Predictors of Unemployment in Axial Spondyloarthropathy: Data from the Ankylosing Spondylitis Registry of Ireland

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Meeting: ACR Convergence 2021

Keywords: Ankylosing spondylitis (AS), Economics, Employment, Spondylarthropathies, spondyloarthritis

SESSION INFORMATION

Date: Saturday, November 6, 2021

Session Type: Poster Session A

Session Title: Spondyloarthritis Including PsA – Diagnosis, Manifestations, & Outcomes Poster I: Clinical Aspects of Axial Spondyloarthritis (0357-0386)

Session Time: 8:30AM-10:30AM

Background/Purpose: Axial spondyloarthropathy (axSpA) is an inflammatory arthritis of the axial skeleton. Persistent disease activity can result in significant disability and affect ability to maintain employment. 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 unemployment in axSpA and quantify the impact on burden of disease, level of function and quality of life.

Methods: For the purposes of this analysis data was extracted from the ASRI on participants with employment data recorded. Patients were analysed on the basis of employment and categorised as employed or unemployed. A two tailed t-test was used to test for statistical significance in mean continuous variables between groups. For categorical variables, an independent chi-squared test of independence determined statistical significance. An alpha level of $p < 0.05$ was deemed significant. IBM SPSS v.26 was used for data and statistical analysis.

Results: Employment status was available for 876 patients enrolled in the ASRI. Overall 21.6% (189) of the population was unemployed, which is considerably higher than national averages of 6.2-13.1% during the same period. In addition, 24% (213) reported axSpA as a limitation in work ability. Unemployed patients reported significantly worse BASDAI (5.2 vs 3.7, $p < 0.01$), BASMI (4.8 vs 3.79, $p < 0.01$), BASFI (5.24 vs 3.26, $p < 0.01$), HAQ (0.83 vs 0.45, $p < 0.01$), and ASQoL scores (9.61 vs 5.63, $p < 0.01$) compared to employed axSpA patients (figure 1). A higher proportion of males were unemployed as compared to females (table 1). No significant differences were noted in pattern of disease, medication usage or baseline demographics. Male sex (OR 2.31, 95% CI 1.32-4.04), worse BASMI (OR 1.19, 95% CI 1.05-1.35) and worse ASQoL scores (OR 1.07, 95% CI 1.01-1.14) were found to

be significant predictors of unemployment (table 2).

Conclusion: Prevalence of unemployment in axSpA is 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. Predictors of unemployment were male sex, worse spinal mobility and poorer quality of life. In males, higher average BASMI scores were a significant contributing factor to the higher rates of unemployment observed. Prompt intervention for patients with worsening outcome measures, in particular spinal restriction, would provide an opportunity for occupational supports and prevent progression to unemployment.

	Unemployed n (%)	Employed n (%)	<i>p value</i>
n	189 (21.6%)	687 (78.4%)	
Males	155 (82%)	489 (71.2%)	0.01
Females	34 (18%)	198 (28.8%)	
Age	45.66	45.95	0.79
Disease duration	18.9	19.6	0.51
Delay to diagnosis	7.39	8.14	0.28
Age at Symptom onset	26.76	26.37	0.66
Caucasian	177 (93.7%)	622 (90.5%)	0.1
HLA-B27 +	130 of 145 (89.7%)	472 of 480 (98.3%)	0.98
Radiographic sacroiliitis	154 (81.5%)	529 (77%)	0.41
MRI sacroiliitis	72 (38.1%)	317 (46.1%)	0.13
Arthritis	60 (31.7%)	206 (30%)	0.89
Enthesitis	41 (21.7%)	111 (16.2%)	0.15
Dactylitis	13 (6.9%)	42 (6.1%)	0.49
Psoriasis	32 (16.9%)	112 (16.3%)	0.87
Uveitis	64 (33.9%)	233 (33.9%)	0.29
Colitis	12 (6.3%)	79 (11.5%)	0.07
NSAIDs	98 (51.9%)	349 (50.8%)	0.59
DMARDs	45 (23.8%)	153 (22.3%)	0.46
Biologic	141 (74.6%)	453 (65.9%)	0.07

Abbreviations: HLA-B27 -human leukocyte antigen B27; MRI -magnetic resonance imaging; NSAIDs -non-steroidal anti-inflammatory medications; DMARDs -disease modifying anti-rheumatic drugs

Table 1: Characteristics of the employed versus unemployed cohort in the ASRI

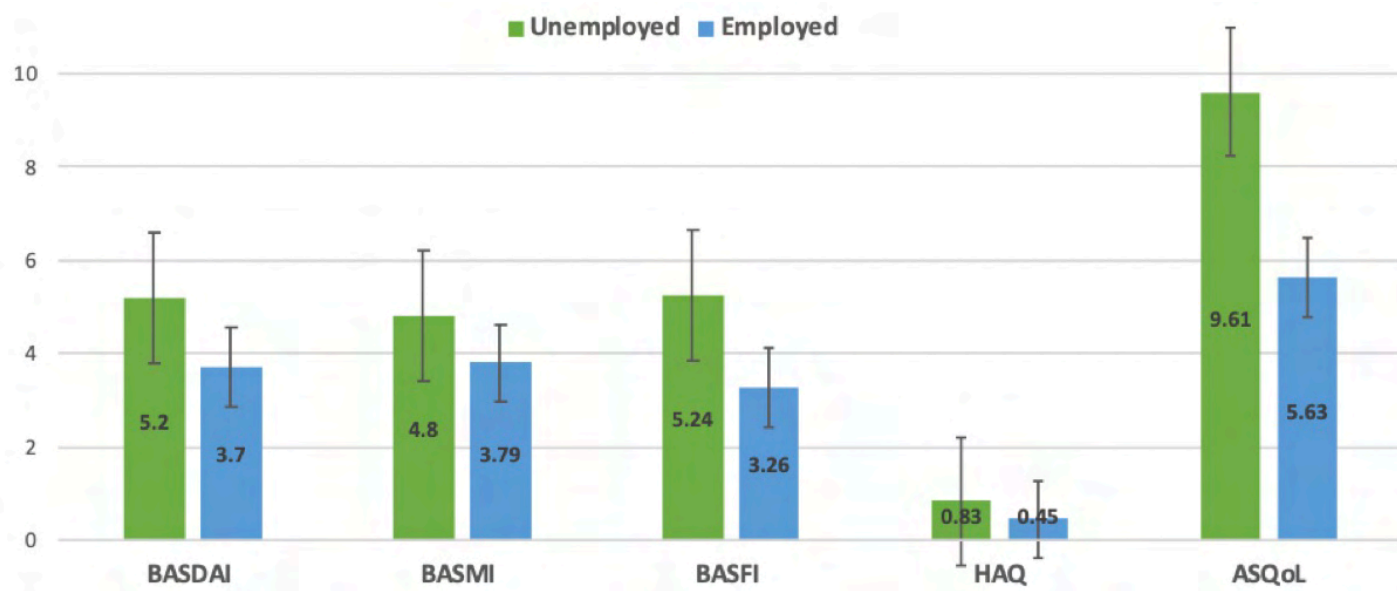


Figure 1: Comparison of mean outcomes on the basis of employment, all differences were statistically significant at the $p<0.01$ level

	Odds Ratio	95% CI	<i>p value</i>
Gender	2.31	1.32 - 4.04	<0.01
Age	0.98	0.95 - 0.99	0.02
Delay to diagnosis	0.99	0.96 - 1.02	0.51
Disease duration	1.00	0.98 - 1.02	0.81
BASDAI	1.09	0.96 - 1.23	0.19
BASMI	1.19	1.05 - 1.35	0.01
BASFI	1.02	0.93 - 1.13	0.68
HAQ	1.48	0.84 - 2.16	0.18
ASQoL	1.07	1.01 - 1.14	0.02

Table 2: Prediction model for risk of unemployment in AxSpA

Disclosures: S. Maguire, Gilead, 5; W. Fiona, None; P. Gallagher, None; F. O'Shea, None.

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High Frequency of Complications in Axial Spondyloarthropathy Pregnancies: Emerging Data from the Ankylosing Spondylitis Registry of Ireland

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Meeting: ACR Convergence 2021

Keywords: Ankylosing spondylitis (AS), gender, pregnancy, spondyloarthritis, Spondyloarthropathies

SESSION INFORMATION

Date: Saturday, November 6, 2021

Session Type: Poster Session A

Session Title: Spondyloarthritis Including PsA – Diagnosis, Manifestations, & Outcomes
Poster I: Clinical Aspects of Axial Spondyloarthritis (0357–0386)

Session Time: 8:30AM-10:30AM

Background/Purpose: National registries are excellent sources of data to allow analysis of inflammatory arthritis such as axial spondyloarthropathy (axSpA). Our understanding of axSpA has evolved rapidly over time resulting in improved recognition of the disease. Unfortunately, for women with axSpA there is limited data on pregnancy outcomes in this population. To address this issue, data was collected on pregnancy within the Ankylosing Spondylitis Registry of Ireland (ASRI), which is a source of epidemiological data on axSpA in Ireland. The aim of this study is to examine the prevalence of pregnancy and fetal complications in females with axSpA.

Methods: The ASRI records information on baseline demographics, imaging, medications, patient outcomes and comorbidities. To be considered for enrolment patients must have been diagnosed with axSpA by a Rheumatologist and meet the ASAS criteria for axSpA. Informed consent was obtained from all patients by a trained investigator, with ethical approval obtained from local hospital ethics committees. A dedicated section within the ASRI collects data on pregnancy, fertility and breastfeeding. Data on these outcomes was then recorded retrospectively for axSpA females enrolled in the ASRI.

Results: At the time of analysis 220 females were enrolled in the ASRI, representing 24.3% of the total population of the registry. Mean age of females was 43.9 years, with a mean disease duration of 18 years and mean delay to diagnosis 7.86 years. 68.6% (151) had radiographic sacroiliitis, while 49.5% (109) had sacroiliitis on MRI. Mean scores for females in the ASRI were: BASDAI 4.6, BASFI 3.82, BASMI, HAQ 0.6, and ASQoL 7.65.

Data on pregnancy was available in 76 women, with 61 women reporting a total of 210 pregnancies

resulting in 166 live births. Of these pregnancies 58.1% (122) were uncomplicated and 41.9% (88) were complicated, with 11.4% (24) of pregnancies encountering multiple complications (figure 1).

The frequency of miscarriage was high affecting 20.5% (43) of pregnancies overall in 37.7% (23) of women with a history of pregnancy. Of the pregnancies resulting in live births, the most common pregnancy complication was caesarean section in 10.8% (18) followed by preterm delivery in 11.4% (15), while the most common fetal complication was NICU admission in 11.4% (19) (figure 2). Only 4 women (5.3%) reported difficult conceiving and need for fertility specialist referral, but none underwent assisted reproductive therapy. Prevalence of breastfeeding was low, reported in 33.7% (56) of live births.

Conclusion: Data from the ASRI indicates a high frequency of pregnancy and fetal complications in women with axSpA. These results represent a preliminary analysis of pregnancy outcomes in axSpA pregnancies collected via a large national registry. Ongoing data collection will allow comparison to national averages. This provides much needed insight into the impact of axSpA on pregnancy, which can be used to improve monitoring and management of axSpA women during their pregnancies. Furthermore, data on prevalence of breastfeeding can be used to encourage discussion of benefits and safety while on medication of breastfeeding between Rheumatologists and axSpA women.

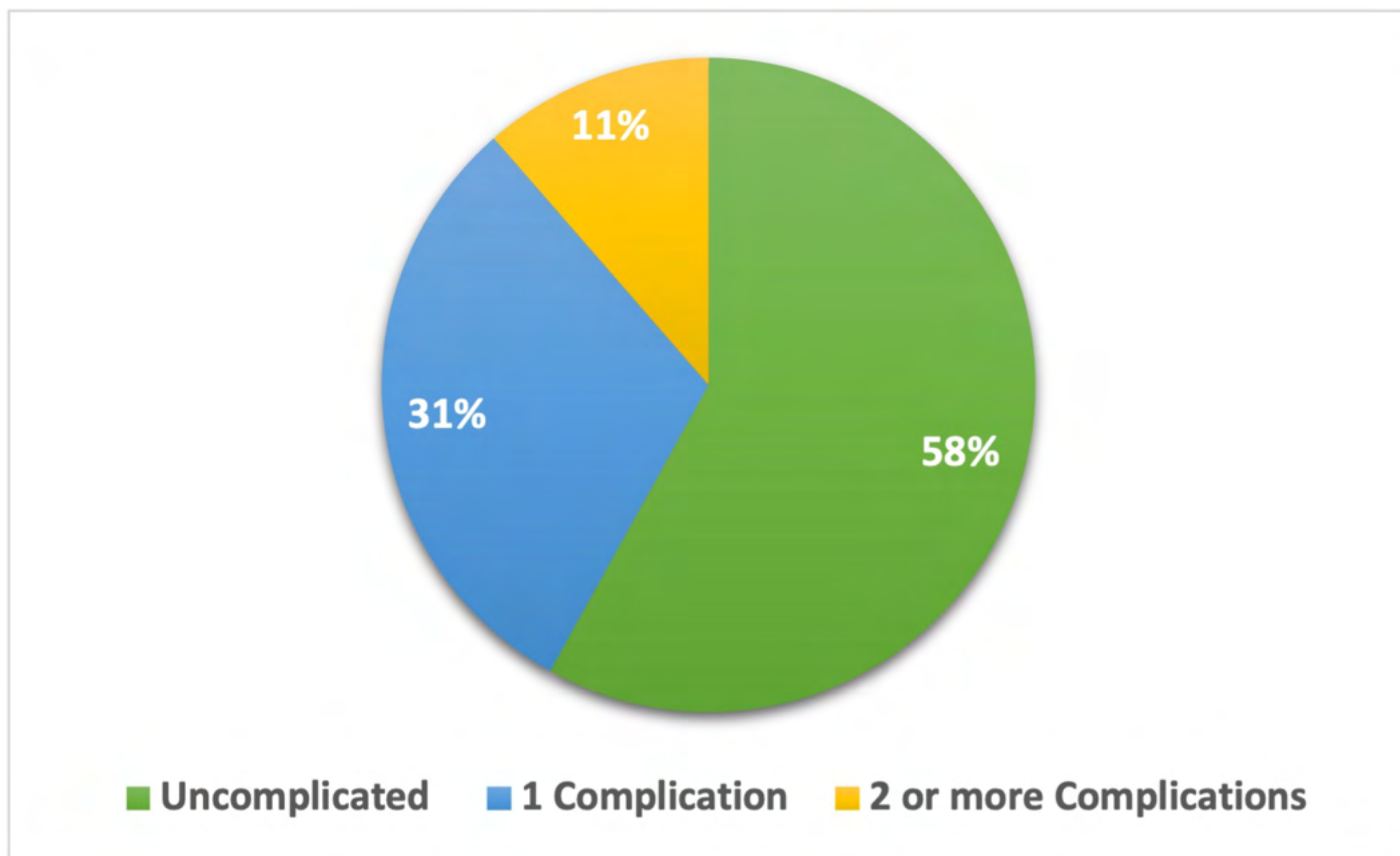


Figure 1: Frequency of Complications per Pregnancy

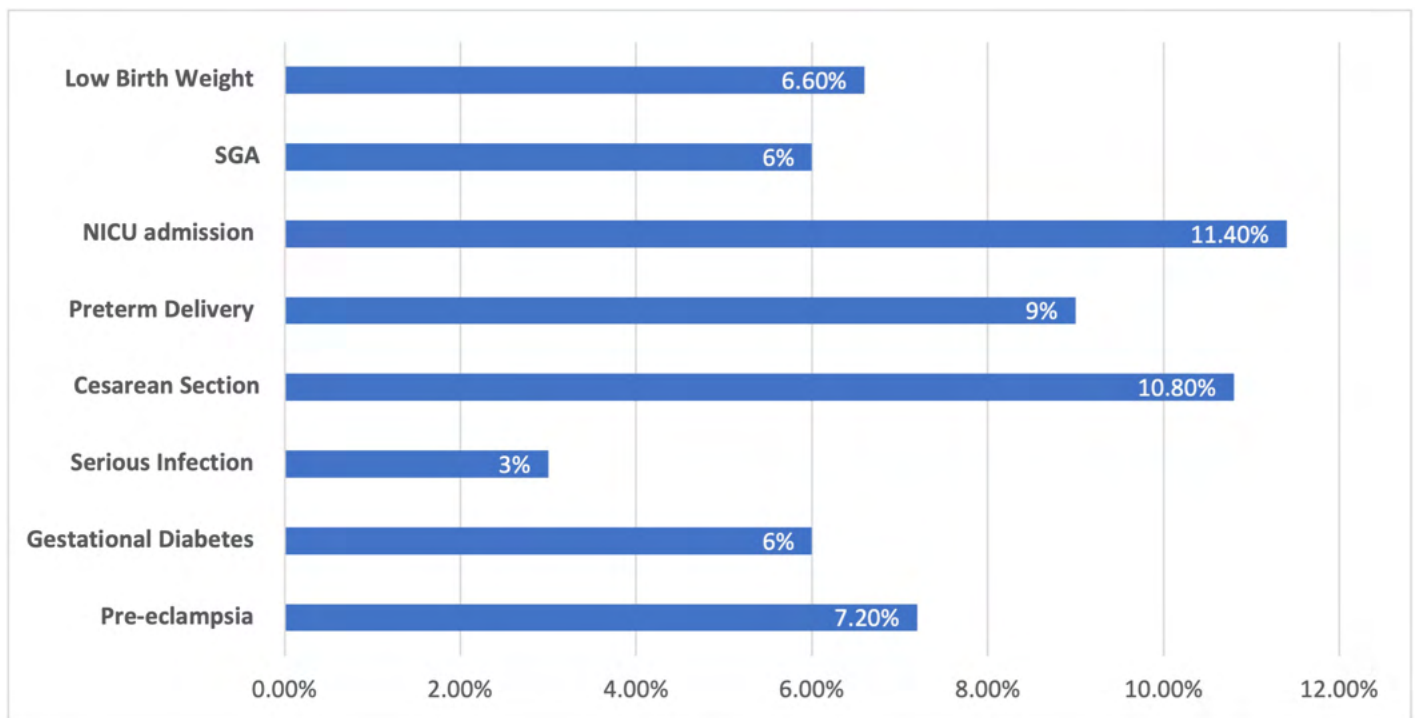


Figure 2: Prevalence of Pregnancy & Fetal Complications in Pregnancies resulting in Live Births

Disclosures: **S. Maguire**, Gilead, 5; **P. Gallagher**, None; **F. O'Shea**, None.

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Undiagnosed Depression in Axial Spondyloarthritis and the Negative Impact on Patient Outcomes: Results of a Screening Study

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Meeting: ACR Convergence 2021

Keywords: Ankylosing spondylitis (AS), depression, Patient reported outcomes, Spondylarthropathies, spondyloarthritis

SESSION INFORMATION

Date: Monday, November 8, 2021

Session Type: Poster Session C

Session Title: Spondyloarthritis Including PsA – Diagnosis, Manifestations, & Outcomes III: Comorbidities, Extra-musculoskeletal Manifestations, & Related Conditions (1304–1328)

Session Time: 8:30AM-10:30AM

Background/Purpose: Previous research in axial spondyloarthritis(axSpA) has shown this population to have a high prevalence of depression. This co-morbidity has been previously shown to impact disease activity in patients with rheumatic disease.

The purpose of this study was to screen for early signs of depression using two validated tools, the Patient Health Questionnaire-9 (PHQ-9) and the Hospital Anxiety and Depression Scale for depression (HADS-D) in patients with known axSpA.

Methods: 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 PHQ-9 and the HADS-D. Scores from the HADS-D yielded a numerical result which was then categorised as normal, borderline or abnormal. PHQ-9 numerical results were categorised as normal, mild, moderate, moderate/severe or severe. Patients with a known diagnosis of depression were excluded. In addition to baseline demographics, patient reported outcomes from the clinic visit were also recorded.

Data analysis was performed using IBM SPSS version 26. Continuous variables were recorded as means, categorical variables as frequencies with percentages. 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 p-value of < 0.05 was deemed significant. Informed consent was obtained prior to participation. Approval for this study was received from the St James'/Tallaght Hospital Joint Ethics Committee.

Results: In total 71 axSpA patients took part in the survey. The population was 70.4%(50) males and 29.5%(21) female, with an average age 47.9 years and mean disease duration 19.7 years (mean outcomes: BASDAI 4.08, BASFI 3.62, BASMI 3.54, ASQoL 6.79). Overall, 7 (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 (6.27 vs 3.42, $p < 0.01$) and AqoL scores (12.57 vs 5.26, $p < 0.01$) in axSpA patients with abnormal compared to normal HADs-D scores (figure 1). 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 2.55, $p < 0.01$), BASFI (8.05 vs 2.33, $p < 0.01$) and ASQoL (19.5 vs 2.62, $p < 0.01$) noted in those scoring as severe compared to normal (figure 2). No significant differences were detected in BASMI scores or baseline demographics.

Conclusion: A high percentage of axSpA patients recorded high HADs-D and PHQ-9 scores concerning for undiagnosed depression. These patients were noted to have significantly worse disease activity and quality of life as compared to patients with normal scores. Clinicians treating axSpA should consider actively screening for depression in this population.

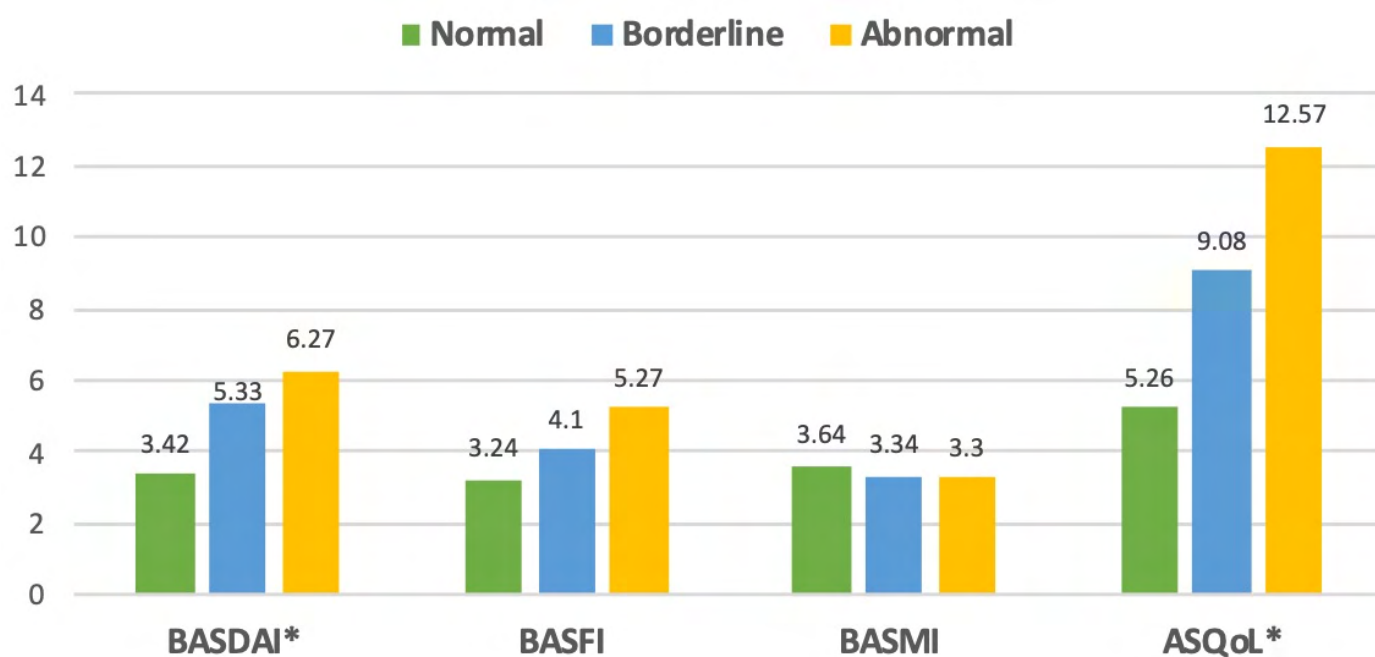


Figure 1: Patient outcomes by HADs-D scores (*indicates significant differences at the $p < 0.05$ level)

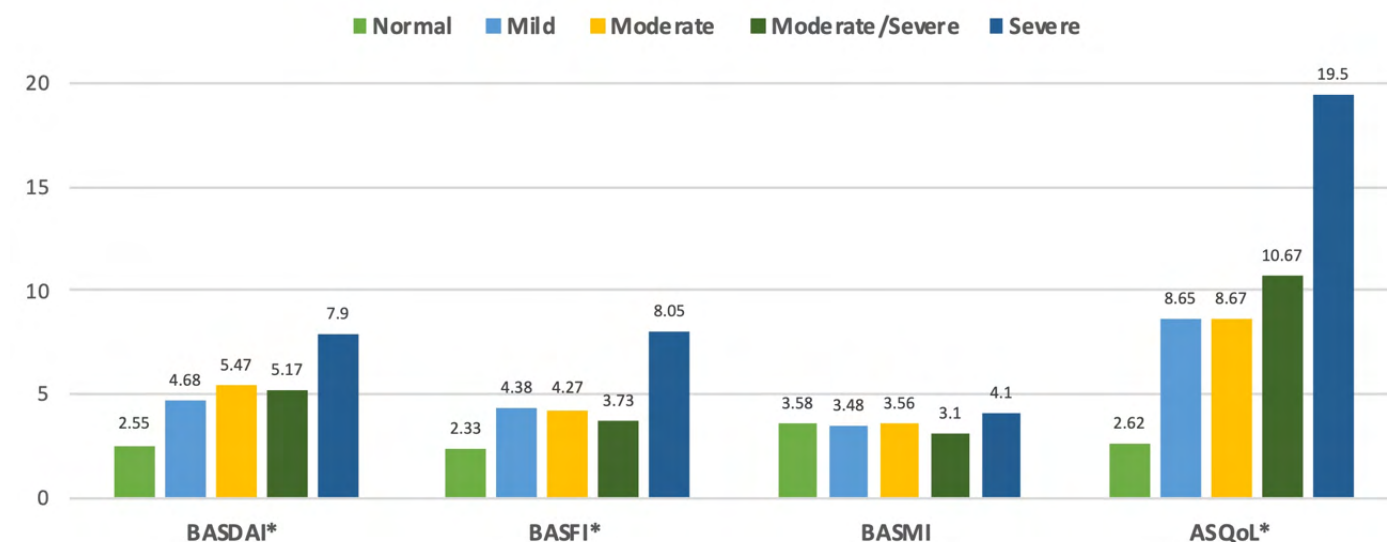


Figure 2: Patient outcomes by PHQ-9 scores (*indicates significant differences between normal, mild and severe groups at the $p < 0.05$ level)

Disclosures: S. Maguire, Gilead, 5; P. Gallagher, None; F. O'Shea, None.

To cite this abstract in AMA style:

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Body Mass Index (BMI) Underestimates Obesity in Females with Axial Spondyloarthritis

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Meeting: ACR Convergence 2021

Keywords: Ankylosing spondylitis (AS), gender, obesity, spondyloarthritis, Spondyloarthropathies

SESSION INFORMATION

Date: Monday, November 8, 2021

Session Type: Poster Session C

Session Title: Spondyloarthritis Including PsA – Diagnosis, Manifestations, & Outcomes III: Comorbidities, Extra-musculoskeletal Manifestations, & Related Conditions (1304–1328)

Session Time: 8:30AM-10:30AM

Background/Purpose: Worldwide prevalence of obesity has been steadily increasing, despite public health campaigns to raise awareness. In axial spondyloarthritis (axSpA) obesity has been shown to be associated with higher levels of disease activity and decreased response to treatment. The waist to hip ratio (WtHpR) is a tool to screen for abdominal obesity. Abdominal deposition of adipose tissue is associated with increased risk of cardiovascular disease, type II diabetes and premature death. Abdominal obesity is more common in males, with females more prone to gluteal-femoral fat deposition. The Ankylosing Spondylitis Registry of Ireland (ASRI) is a source of epidemiological data of axSpA patients in Ireland. The aim of this study was to capture the prevalence of abdominal obesity in a large cohort of axSpA patients and assess for variation in prevalence between sexes.

Methods: Participants were analysed on the basis of gender and presence of obesity by BMI and WtHpR. Obesity was defined by body mass index (BMI) with a result of >30 categorised as obese as per CDC definitions. Abdominal obesity was assessed by WtHpR and defined as per WHO guidelines (table 1). Categorical variables were tested for statistical significance with a chi² test for independence, while continuous variables were tested with an independent t-test or Mann Whitney U test. A Spearman's correlation analysis was run to assess the strength of association between BMI and WtHpR. A p-value of < 0.05 was deemed significant. IBM SPSS version 26 was used for statistical analysis.

Results: At the time of analysis, physical measurements were available on 692 patients in the ASRI made up of 96.2% (666) Caucasians with 22.3% (154) females and 77.7% (538) males. The average age was 45.9 years with a mean disease duration of 18.8 years (mean scores: BASDAI 4.09, BASFI 3.71,

BASMI 3.99, HAQ 0.54, ASQoL 6.72). 80.9% (560) of patients had radiographic sacroiliitis while 49.1% (340) had sacroiliitis on MRI.

Overall 29.5% (215) patients were obese based on BMI results, while 37.5% (274) were centrally obese as per the WtHpR. Analysis on the basis of sex revealed no significant variation in mean BMI (28.1 vs 27.7, $p=0.45$) or prevalence of obesity as assessed by BMI (29.9% vs 28.6%, $p=0.49$) between males and females (table 2). As expected, analysis of WtHpR revealed higher mean ratios in males compared to females (0.96 vs 0.89, $p<0.01$), however there was a significantly higher prevalence of abdominal obesity in females (29.9% vs 68.2%, $p<0.01$) (figure 1).

A moderate positive correlation was detected between BMI and WtHpR ($r_s=0.454$, $p<0.01$). When cases were analysed within each sex the correlation was noted to be stronger in males than females ($r_s=0.543$ vs 0.304 , $p<0.01$).

Conclusion: There is a high prevalence of abdominal obesity as assessed by WtHpR in axSpA, especially in females with axSpA. BMI can underestimate obesity in axSpA women, as the association between BMI and WtHpR is stronger in axSpA males. Use of WtHpR should be considered when screening for obesity in axSpA.

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

Table 1: Waist to Height Ratio definitions for Abdominal Obesity as per the World Health Organisation (WHO) guidelines

	Males	Females	p value
n	77.7% (538)	22.3% (154)	
Weight (kg)	84.98	72.76	<0.01
BMI (kg/m²)	28.08	27.69	0.45
<i>Underweight</i>	0.9% (5)	0.06% (1)	0.49
<i>Normal Weight</i>	29.2% (157)	36.4% (56)	
<i>Overweight</i>	39.2% (211)	34.4% (53)	
<i>Obese</i>	29.9% (161)	28.6% (44)	
Waist Circumference (cm)	97.43	90.03	<0.01
Hip Circumference (cm)	102.11	101.27	0.56
Waist to Hip Ratio	0.956	0.890	<0.01
<i>Normal Weight</i>	23.8% (128)	17.5% (27)	<0.01
<i>Overweight</i>	46.3% (249)	14.3% (22)	
<i>Obese</i>	29.9% (161)	68.2% (105)	

Table 2: Assessment of Obesity by Sex

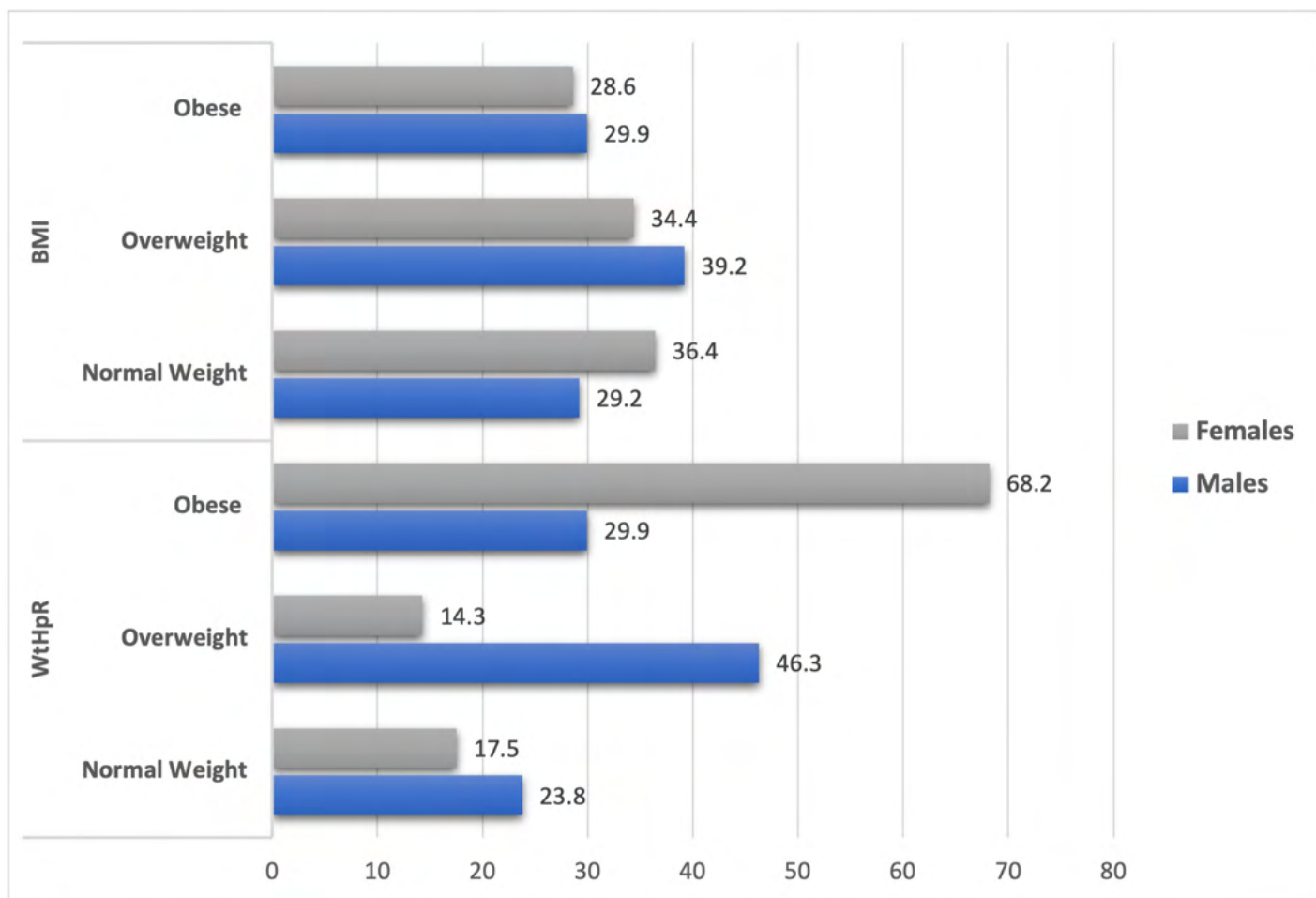


Figure 1: Prevalence of Obesity (%) in AxSpA as detected by Body Mass Index (BMI) and Waist to Hip Ratio (WtHpR) within each sex

Disclosures: S. Maguire, Gilead, 5; W. Fiona, None; P. Gallagher, None; F. O'Shea, None.

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P256 COMPLICATIONS IN PREGNANCY ARE COMMON IN WOMEN WITH AXIAL SPONDYLOARTHROPATHY: DATA FROM THE ANKYLOSING SPONDYLITIS REGISTRY OF IRELAND

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Background/Aims

National registries are excellent data sources to allow analysis of inflammatory arthritis such as axial spondyloarthritis (axSpA). Our understanding of axSpA has evolved rapidly over time resulting in improved recognition of the disease. Unfortunately for women with axSpA, there are limited data on pregnancy outcomes in this population. To address this issue, data were collected on pregnancy within the Ankylosing Spondylitis Registry of Ireland (ASRI), which 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 women with axSpA.

Methods

The ASRI records information on baseline demographics, imaging, medications, patient outcomes and comorbidities. For enrolment, all patients must have been diagnosed with axSpA by a rheumatologist and meet the ASAS criteria. Informed consent was obtained from all patients, with ethical approval obtained from local hospital ethics committees. A dedicated section collects data on pregnancy, fertility and breastfeeding. ASRI outcomes data for women with axSpA were recorded retrospectively.

Results

At the time of analysis, 220 women were enrolled in the ASRI, representing 24.3% of the total population of the registry. Mean age of women was 43.9 years, with a mean disease duration of 18 years and mean delay to diagnosis of 7.86 years. 68.6% (151) had radiographic sacroiliitis, while 49.5% (109) had sacroiliitis on MRI. Mean scores for women in the ASRI were: BASDAI 4.6, BASFI 3.82, BASMI, HAQ 0.6, and ASQoL 7.65. Data on pregnancy were available in 76 women, with 61 women reporting a total of 210 pregnancies resulting in 166 live births. Of these pregnancies, 58.1% (122) were uncomplicated and 41.9% (88) were complicated, with 11.4% (24) of pregnancies encountering multiple complications. The frequency of miscarriage was high, affecting 20.5% (43) of pregnancies overall in 37.7% (23) of women with a history of pregnancy. Of the pregnancies resulting in live births, the most common pregnancy complication was caesarean section in 10.8% (18) followed by preterm delivery in 11.4% (15), while the most common fetal complication was NICU admission in 11.4% (19). Only four women (5.3%) reported difficulty conceiving and the need for fertility specialist referral, but none underwent assisted reproductive therapy. Prevalence of breastfeeding was low, reported in only 33.7% (56) of live births.

Conclusion

Data from the ASRI indicates a high frequency of pregnancy and fetal complications in women with axSpA. These results represent a preliminary analysis of pregnancy outcomes in axSpA pregnancies collected via a large national registry. Ongoing data collection will allow comparison to national averages. This provides much needed insight into the impact of axSpA on pregnancy, which can be used to improve monitoring and management of women with axSpA during their pregnancies.

Appendix B Protocols

B.1 Study Protocol for the Ankylosing Spondylitis Registry of Ireland (ASRI)

B.2 Systematic Review Protocol

Ankylosing Spondylitis Registry of Ireland (ASRI)

Study Protocol

Chief Investigator

Dr. Barry O'Shea, Consultant Rheumatologist, St James's Hospital, Dublin 8, Ireland.

Introduction

Ankylosing Spondylitis (AS) is a chronic, disabling rheumatic disease characterized by inflammatory back pain, restricted spinal mobility, and frequently peripheral arthritis, enthesitis, and acute anterior uveitis. Patients fulfill classification criteria fAS if characteristic radiological changes of the sacroiliac joint (SIJ) are present, together with defined clinical symptoms and physical findings **(1)**. Symptoms of AS commonly begin in late adolescence and early adulthood, thus at a normally productive time of life. If undiagnosed or inadequately treated, continuous pain, stiffness, and fatigue are the consequences. Furthermore, a potentially progressive loss of spinal mobility and function result in a reduction in the quality of life **(2)**.

In the context of all the inflammatory rheumatic diseases, there is an unacceptably long delay between the onset of symptoms and the time of diagnosis for AS – an average interval of 8-11 years has been reported **(3,4)**. Until recently, treatment options for AS were limited. NSAIDs and Physiotherapy form the mainstay of therapy. Conventional disease-modifying anti-rheumatic drugs, which are effective in other chronic inflammatory diseases such as rheumatoid arthritis, have only a very limited effect on spinal inflammation. Anti-tumor necrosis factor (TNF) agents offer an exciting option for effective treatment. It has been shown that the anti-TNF agents have a prompt and robust effect on almost all aspects of active disease - most notably pain and fatigue, but also function, spinal mobility, peripheral arthritis, enthesitis, bone density, and acute inflammation as reflected by acute phase reactants and MRI **(5-7)**.

Exact figures for the incidence and prevalence of AS in the general population have been the subject of much debate in the literature. The disorders show striking familial aggregation and are typically associated with genes of the major histocompatibility complex (MHC), particularly HLA-B27 **(8)**. HLA-B27 is found in up to 95% of patients of European ancestry with AS **(9)**. However, fewer than 5% of HLA-B27 positive individuals in the general population develop these diseases. On the other hand, 20% of HLA-B27 positive relatives of patients with AS will themselves become affected **(10)**. Incidence rates of 0.5–8.2/100 000 population and prevalence rates of 0.1–1.2% have been described for AS **(11)**. An exact figure for the number of AS patients in Ireland doesn't exist, however it is felt that there is probably a minimum of 4000 cases here.

The ASRI database will document all AS patients attending Rheumatology clinics in participating centres in Ireland. It will be used to study outcome measures as well as responses to therapy. The identification of factors that might predict a poor prognosis will be a major area research focus. This database will record patient demographics, treatment including biologic therapy and outcomes. The primary objective is to measure the burden of AS in the population, primary and secondary care. We would then establish an inception cohort in order to identify early predictors of a poor outcome.

Study Objectives

Primary Objectives

The primary objectives of the study are to provide basic descriptive epidemiological data on the AS population in Ireland, and to establish an AS registry for potential future studies of genetics, aetiology and therapeutics. Specifically, we will measure the burden of AS in the population in primary and secondary care and to identify early predictors of a poor outcome.

Secondary Objectives

To collect measures of severity and function:

- (a) Back Pain Questionnaire (Back Pain scores, BASDAI, BASFI)
- (b) Generic measures of function (Short Form 12)
- (c) Disease specific measures of function (ASQoL)
- (d) Measure of Fatigue
- (e) Measures of impact on employment including Work Productivity and absenteeism);
- (f) Quality of Life (EuroQoL);
- (g) Measures of pain status.

Participating patients will be asked to provide biologic samples (serum and DNA). This will allow ASRI to contribute samples to an international collaboration examining genetic influences on AS and to analyse our data on outcome (and responses to therapy) utilising this genetic information. Specifically, we plan to examine, within, ASRI whether genetic and serological factors predict poor outcome (functional and radiographic)

Methods

Design

A registry will be established which will include adult patients who have been diagnosed with AS and have been reviewed in a hospital setting within the past 3 years.

Study Design - key points:

1) Inclusion Criteria:

All patients with a clinical diagnosis of AS and who have had a consultation within secondary care within the past three years will be registered irrespective of whether they are taking biologics.

2) Exclusion Criteria:

- a. Has not attended outpatient clinic within the past three years.
- b. Less than 18 years old
- c. Inability to give informed consent

Recruitment Sites

All Rheumatology where clinics that assess AS patients in Ireland will be approached for inclusion in ASRI. Each participating hospital will obtain Ethics approval from their local Ethics committee.

Number of Participants

One of the aims of this study is to determine how many patients with AS are currently treated in secondary care in Ireland – and therefore we aim to try to recruit and collect information on all such patients.

Procedures for Recruitment

Patients will be identified in the Rheumatology outpatient clinics. Once patients are identified a member of the Research team will meet them to explain the study. Informed consent will be obtained from all patients.

Patient Assessment

A standardized clinical assessment of patients will be undertaken to document history and clinical examination findings. Results of relevant laboratory parameters (e.g. ESR, CRP, FBC, HLA-B27,) and clinically appropriate imaging studies will be documented. Clinical data will be stored using an **SQL database hosted on a virtual private server owned by ASRI. The server will be protected by using SSL, a protocol for encrypting information over the internet.**

The following clinical measures will be obtained on each patient at the baseline visit .

Demographics (age, sex, level of education, status of employment);

Family History of AS and other SpA conditions, smoking status, alcohol consumption

Generic measures of function (Short Form 12)

Disease specific measures of function (ASQoL)

Measure of Fatigue

Measures of impact on employment

Quality of Life (EuroQoL);
Measures of pain status
Back Pain Questionnaire (Back Pain scores, BASDAI, BASFI
(All questionnaires attached in booklet form)

A once off sample of blood (three 3ml tubes of blood) will be collected from patients. Samples for serum, and DNA will be stored in St. James's hospital for future use. Prospective collection of serum and blood will allow measurement of various pro-inflammatory cytokines/biomarkers, which will be subsequently used to correlate with clinical data. DNA will be isolated and stored to facilitate genetic studies.

Confidentiality

Processing of the samples is performed in the research laboratory in St James's hospital.. All samples will be coded and rendered anonymous once collected. Participants will be issued with a unique study number immediately after being commenced onto the study. Participant's personal identifiers will be kept separate to disease defining information. Only the Co-Principal Investigators and personnel assigned by them are allowed to access clinical data. The personnel involved in collecting samples and consenting participants will be responsible for safeguarding anonymity.

Possible risk to participants

The risks of the procedures involved are the standard risk associated with phlebotomy. These are slight pain at the site of venous puncture at the time of needle insertion, occasional bleeding and/or bruising, and the occasional vasovagal episode. To minimise these complications a medical doctor, a trained phlebotomist or a research nurse will perform phlebotomy.

Serious Adverse Events

This study does not involve the administration of any experimental drug products to patients. No specific pharmaceutical treatment is mandated by the protocol. Treatment will be as per routine clinical practice, and as per the physicians professional opinion. During the course of the study, investigators may become aware of Adverse Events and Serious Adverse Events and should report these to the relevant Marketing Authorisation Holder of the marketed product.

Planned Analysis

The data will be analysed to produce simple descriptive epidemiological statistics about the burden and natural history of AS. It is anticipated, however, that the registry will also be used as a platform for future studies – all of which will require peer review, patient consent, and ethical approval.

Cost Implication There is no cost implication to St. Vincent's University Hospital.

References

1. van der Linden S, Valkenburg HA, Cats A.
Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984;27:361-8.
2. O'Shea FD, Boyle E, Riarh R, Tse SM, Laxer RM, Inman RD.
Clinical and Radiographic Severity of Ankylosing Spondylitis is associated with Age of Onset. *Ann Rheum Dis.* 2009 Sep;68(9):1407-12.
3. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J.
Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int.* 2003 Mar;23(2):61-6.
1. O'Shea F, Salonen D, Inman R.
The challenge of early diagnosis in ankylosing spondylitis. *J Rheumatol.* 2007 Jan;34:5-7.
5. van der Heijde D, Dijkmans B, Geusens P et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum.* 2005 Feb;52(2):582-91.
6. Davis JC, van der Heijde DM, Braun J et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann Rheum Dis.* 2005 Nov;64(11):1557-62.
7. van der Heijde D, Kivitz A, Schiff MH et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2006 Jul;54(7):2136-46.
8. Brown MA, Laval SH, Brophy S, Calin A.
Recurrence risk modeling of the genetic susceptibility to ankylosing spondylitis. *Ann Rheum Dis.* 2000;59:883-886.
9. van der Linden SJ, van der Heijde D.
Spondylarthropathies: ankylosing spondylitis. In Ruddy S, Harris ED, Sledge CB eds. *Kelley's Textbook of Rheumatology*, 6th ed. Philadelphia: WB Saunders, 2000:1039-1053.
10. van der Linden SM, Valkenberg HA, de Jongh BM, Cats A.
The risk of developing ankylosing spondylitis in HLA-B27 positive individuals. A comparison of relatives of spondylitis patients with the general population. *Arthritis Rheum.* 1984 Mar;27(3):241-9.
11. Sieper J, Rudwaleit M, Khan MA, Braun J.
Concepts and epidemiology of spondyloarthritis. *Best Pract Res Clin Rheumatol.* 2006 Jun;20(3):401-17.

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Pregnancy in Axial Spondyloarthritis: a systematic review and meta-analysis

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

01/09/2019

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/06/2020

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Sinead Maguire

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Sinead Maguire

7. * Named contact email.

Give the electronic mail address of the named contact.

sineadmaguire@rcsi.ie

8. Named contact address

Give the full postal address for the named contact.

Dept of Rheumatology, St. James's Hospital, James's Street, Dublin 8, Ireland

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+353857766787

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

St James' Hospital, Dublin, Ireland

Trinity College Dublin

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Sinead Maguire, St James' Hospital

Professor Fiona Wilson, Trinity College Dublin

Dr Tom O'Dwyer, Independent Researcher
Mr David Mockler, Trinity College Dublin
Dr Finbar O' Shea, St. James's Hospital

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

This project forms part of an MD project.

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Yes. BOS has received unrestricted financial support from AbbVie, Pfizer, MSD, UCB, Novartis, Roche and Janssen to attend and/or present at conferences and other educational meetings.

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Do individuals with axSpA have similar rates of complications in pregnancy(pre-eclampsia, gestational diabetes, infections, intra-uterine growth restriction etc.) as the average female population?

What complications do women with axSpA encounter most during pregnancy?

What is the effect of pregnancy on disease activity in axSpA?

What is the association between disease activity and pregnancy outcomes?

Is there a difference in fetal outcomes of neonates of females with axSpA compared to females without axSpA?

Is there a difference in baseline demographics between pregnant axSpA females and the general pregnant female population?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following electronic bibliographic databases will be searched: EMBASE, MEDLINE (Ovid), CINAHL, Cochrane Library (central), Web of Science, MIDIRS Online, ACR & EULAR electronic conference abstract archive (limited to abstracts available electronically). The search terms will be adapted for use with each bibliographic database. A manual search of references for all eligible studies will also be carried out. No language or date restrictions will be placed on the search. Searches will be run again immediately prior to final analysis to ensure all possible studies are included.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy. Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Axial spondyloarthritis(axSpA) is a form of inflammatory arthritis which affects the sacroiliac joints and the spine. Although this chronic condition affects a wide range of ages, many females affected are of childbearing age. At present it is unclear how axSpA affects pregnancy, in terms of rates of pregnancy complications, fetal outcomes, and fertility. Similarly, the effects of pregnancy on axSpA regarding effect on disease activity and medication use, have not been studied in large numbers. Previous studies in these areas have been limited with a wide variation in conclusions drawn. Studies in other forms of inflammatory arthritis have suggested improved disease control during pregnancy with increased risk of flares postpartum. It is unknown if axSpA follows this pattern. Improved control of inflammatory arthritis during pregnancy has thought to result in improved fetal outcomes, but there is limited data to validate this theory.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria:

-Females

- >18 years of age

-diagnosed as having Axial Spondyloarthritis or Ankylosing Spondylitis according to the 1984 modified New York Criteria or the 2009 Assessment of Spondyloarthritis International Society (ASAS) criteria for axial spondyloarthritis

Exclusion Criteria:

-Male

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-Diagnosis of axSpA or AS not confirmed

-Age < 18 years old

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Exposure:

- Pregnancy
- Females actively trying to conceive
- axSpA or AS as defined by the 2009 assessment of spondyloarthritis modified New York Criteria or 2009 ASAS criteria for axial SpA
- Any pharmacological treatment for axSpA used in the 12 months prior to or during pregnancy

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Exclusion:

- Females (age 18 years or older)
- No previous diagnosis of axSpA as previously defined

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion:

- Randomised control studies
- Observational studies
- case-control studies
- cross-sectional studies
- case series with >5 patients

Exclusion:

- case reports
- commentaries
- expert opinion
- review articles

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

The focus of this study will be on pregnancy outcomes and disease activity in females with axSpA.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurements are made, if these are part of the review inclusion criteria.

Frequency of pregnancy related complications in females with axSpA

Timing and effect measures

Measured throughout the course of the pregnancy, minimum of 1 time point.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

- Fetal outcomes: NICU admission, small for gestational age
- Disease activity: BASDAI, ASDAS, CRP
- Level of function: BASFI, HAQ, ASQoL
- Medication usage during and in the 12 months prior to pregnancy

Timing and effect measures

26. * Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of

researchers involved and how discrepancies will be resolved. List the data to be extracted.

Two reviewers will independently screen the titles of records returned by the search strategy to identify records that potentially meet the inclusion criteria. Two reviewers will then screen the relevant abstracts to identify studies meeting eligibility criteria. Full-text of potentially relevant reports will be retrieved and assessed for eligibility by two reviewers. Any disagreements on inclusion will be resolved by discussion to achieve consensus and, failing agreement, a third reviewer will be consulted.

A standardised data collection form will be used by two independent researchers to extract relevant data from the included studies. The data extraction form will record variables related to study design, participant characteristics, condition-related factors, pharmacological/non-pharmacological intervention, control group, outcome measures and study results.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Two review authors will independently assess potential biases resulting from the trial design.

Discrepancies between review authors will lead to a discussion to achieve a consensus. If a consensus cannot be achieved, assessment from a third review author will be requested. The revised Cochrane risk-of-bias tool for randomised trials (RoB2) will be used with each study judged as low, some concerns or high risk of bias across five domains (randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result). The ROBINS-I tool will be used for observational studies, assessing the risk of bias across seven domains (confounding, selection of participants, classifications of interventions, deviation from intended intervention, missing data & selection of the reported result). Bias judgements will be recorded as low, moderate, serious or critical risk.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

A narrative synthesis of the findings from the included studies will be presented. Outcome summaries and comparison with the control group will be analysed for each study by calculating standardised mean differences with 95% confidence intervals for continuous outcomes. If data is suitable (i.e. homogeneous study designs), a meta-analysis will be conducted. If there is not adequate homogeneity between studies to allow for a meta-analysis, the results of included studies may still be displayed in a forest plot but without the pooled estimate.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of

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intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

If there is sufficient comparable data, subgroup analysis will be done for patient baseline characteristics including age, disease duration and ethnicity. Subgroup analysis by medication exposure during pregnancy could also be considered.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness

No

Diagnostic

No

Epidemiologic

Yes

Individual patient data (IPD) meta-analysis

No

Intervention

Yes

Meta-analysis

Yes

Methodology

No

Narrative synthesis

No

Network meta-analysis

No

Pre-clinical

No

Prevention

No

Prognostic

No

Prospective meta-analysis (PMA)

No

Review of reviews

No

Service delivery

No

Synthesis of qualitative studies

No

Systematic review

Yes

Other

No

Health area of the review

Alcohol/substance misuse/abuse

No

Blood and immune system

No

Cancer

No
Cardiovascular
No
Care of the elderly
No
Child health
No
Complementary therapies
No
Crime and justice
No
Dental
No
Digestive system
No
Ear, nose and throat
No
Education
No
Endocrine and metabolic disorders
No
Eye disorders
No
General interest
No
Genetics
No
Health inequalities/health equity
No
Infections and infestations
No
International development
No
Mental health and behavioural conditions
No
Musculoskeletal
Yes
Neurological
No
Nursing
No
Obstetrics and gynaecology
Yes
Oral health
No
Palliative care
No
Perioperative care
No
Physiotherapy
No

Pregnancy and childbirth
Yes

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Ireland

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is completed

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

A paper will be submitted to an appropriate high impact journal with the results of this review.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Ankylosing spondylitis

Axial spondyloarthropathy

Spondyloarthropathy

Pregnancy

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For new registrations the review must be Ongoing.

Please provide anticipated publication date

Review on going

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

Appendix C Outcome Measures

C.1 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

C.2 Bath Ankylosing Spondylitis Functional Index (BASFI)

C.3 Back Questionnaire

C.4 Ankylosing Spondylitis Quality of Life scale (ASQoL)

C.5 Health Assessment Questionnaire Disability Index (HAQ-DI)

C.6 Bath Ankylosing Spondylitis Metrology Index (BASMI)

C.7 Hospital Anxiety and Depression Scale (HADS)

C.8 Patient Health Questionnaire 9 (PHQ-9)

C.9 Patient Health Questionnaire 4 (PHQ-4)

C.10 Case Report Form (CRF) for the ASRI

4. **BASDAI**

Please tick the box that represents your answer. ☒ 10).
All questions refer to the **last week**.

4.1. How would you describe the overall level of fatigue / tiredness you have experienced?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

4.2. How would you describe the overall level of AS neck, back or hip pain you have had?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

4.3. How would you describe the overall level of pain / swelling in joints **other than** neck, back or hips you have had?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

4.4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

4.5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

4.6. How long does your morning stiffness last from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

0 hr 1 hr 2 or more hrs

5. BASFI

Please indicate your level of ability with each of the following activities during the last week.



). An aid is a piece of equipment which helps you to perform an action or movement.

- 5.1. Putting on your socks or tights without help or aids (e.g. sock aid).

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.2. Bending forward from the waist to pick up a pen from the floor without an aid.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.3. Reaching up to a high shelf without help or aids (e.g. helping hand).

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.4. Getting up out of an armless dining room chair without using your hands or any other help.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.5. Getting up off the floor without help from lying on your back.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.6. Standing unsupported for 10 minutes without discomfort.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.7. Climbing 12-15 steps without using a handrail or walking aid. One foot at each step.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.8. Looking over your shoulder without turning your body.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.9. Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports).

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

- 5.10. Doing a full days activities, whether it be at home or at work.

0	1	2	3	4	5	6	7	8	9	10
easy										impossible

Questionnaire 4: BACK QUESTIONNAIRE

1. PAIN

Please tick the box that represents your answer ☒).

1.1. Nocturnal Back Pain

Based on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

no pain most severe pain

1.2. Total Back Pain

Based on your assessment, please indicate what is the amount of back pain at any time that you experienced during the last week?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

no pain most severe pain

2. PATIENT GLOBAL DISEASE ACTIVITY

2.1. Tick a box to indicate your overall assessment of your disease activity during the last week?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none severe

3. BAS - G

3.1. Tick a box to indicate the effect your disease has had on your well-being over the last week?

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

3.2. Please indicate the effect your disease has had on your well-being over the last six months.

0	1	2	3	4	5	6	7	8	9	10
---	---	---	---	---	---	---	---	---	---	----

none very severe

6. ASQoI

Please read each statement carefully. We would like you to tick 'yes' if the statement applies to you, and tick 'no' if it does not.

Tick the **one** response that applies best to you **at the moment**.

- | | | |
|--|-----------------------------|------------------------------|
| 6.1. My condition limits the places I can go. | ☐ No | ☐ Yes |
| 6.2. I sometimes feel like crying. | ☐ No | ☐ Yes |
| 6.3. I have difficulty dressing. | ☐ No | ☐ Yes |
| 6.4. I struggle to do jobs around the house. | ☐ No | ☐ Yes |
| 6.5. It's impossible to sleep. | ☐ No | ☐ Yes |
| 6.6. I am unable to join in activities with my friends / family. | ☐ No | ☐ Yes |
| 6.7. I am tired all the time. | ☐ No | ☐ Yes |
| 6.8. I have to keep stopping what I am doing to rest. | ☐ No | ☐ Yes |
| 6.9. I have unbearable pain. | ☐ No | ☐ Yes |
| 6.10. It takes a long time to get going in the morning. | ☐ No | ☐ Yes |
| 6.11. I am unable to do jobs around the house. | ☐ No | ☐ Yes |
| 6.12. I get tired easily. | ☐ No | ☐ Yes |
| 6.13. I often get frustrated. | ☐ No | ☐ Yes |
| 6.14. The pain is always there. | ☐ No | ☐ Yes |
| 6.15. I feel I miss out on a lot. | ☐ No | ☐ Yes |
| 6.16. I find it difficult to wash my hair. | ☐ No | ☐ Yes |
| 6.17. My condition gets me down. | ☐ No | ☐ Yes |
| 6.18. I worry about letting people down. | ☐ No | ☐ Yes |

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____

Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

DRESSING & GROOMING

Are you able to:

Dress yourself, including shoelaces and buttons? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

Shampoo your hair? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

ARISING

Are you able to:

Stand up from a straight chair? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

Get in and out of bed? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

EATING

Are you able to:

Cut your own meat? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

Lift a full cup or glass to your mouth? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

Open a new milk carton? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

WALKING

Are you able to:

Walk outdoors on flat ground? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

Climb up five steps? ☐ WITHOUT ANY DIFFICULTY ☐ WITH SOME DIFFICULTY ☐ WITH MUCH DIFFICULTY ☐ UNABLE TO DO

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing
(button hook, zipper pull, etc.)

☐ Built up or special utensils

☐ Crutches

☐ Cane

☐ Wheelchair

☐ Special or built up chair

☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming

☐ Arising

☐ Eating

☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
--	---------------------------	-------------------------	-------------------------	-----------------

HYGIENE

Are you able to:

Wash and dry your body?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

Take a tub bath?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

Get on and off the toilet?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

REACH

Are you able to:

Reach and get down a 5 pound object (such as a bag of sugar) from above your head?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

Bend down to pick up clothing from the floor?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

GRIP

Are you able to:

Open car doors?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

Open previously opened jars?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

Turn faucets on and off?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

ACTIVITIES

Are you able to:

Run errands and shop?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

Get in and out of a car?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

Do chores such as vacuuming or yard work?

☐	☐	☐	☐
--------------------------	--------------------------	--------------------------	--------------------------

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

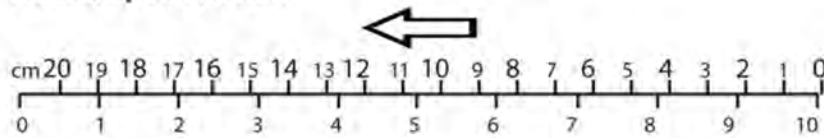
- | | | |
|---|--|--|
| ☐ Raised toilet seat | ☐ Bathtub bar | ☐ Long-handled appliances for reach |
| ☐ Bathtub seat | ☐ Long-handled appliances in bathroom | ☐ Jar opener (for jars previously opened) |

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

- | | | | |
|----------------------------------|--------------------------------|--|---|
| ☐ Hygiene | ☐ Reach | ☐ Gripping and opening things | ☐ Errands and chores |
|----------------------------------|--------------------------------|--|---|

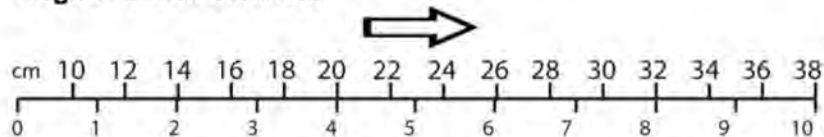
BASMI

1 Lateral spinal flexion



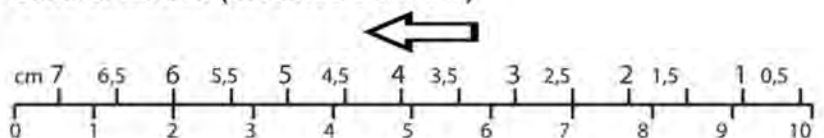
Mean of
right/left

2 Tragus-to-wall distance

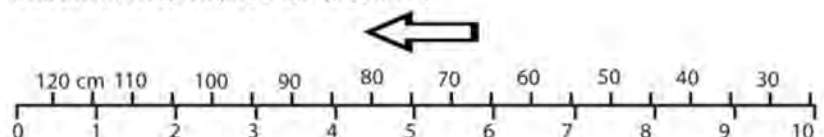


Mean of
right/left

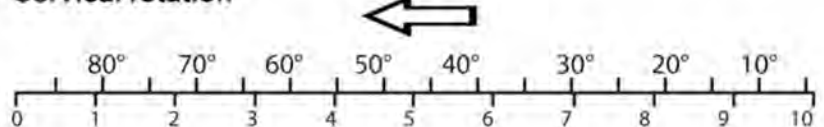
3 Lumbar flexion (modified Schober)



4 Maximal intermalleolar distance



5 Cervical rotation



Mean of
right/left

BASMI:
(Average
of 5 scores)

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.

Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much	0		Not at all
1		Not quite so much	1		Occasionally
2		Only a little	2		Quite Often
3		Hardly at all	3		Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could	3		Very much indeed
1		Not quite so much now	2		Quite a lot
2		Definitely not so much now	1		Not very much
3		Not at all	0		Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all	3		Very often indeed
2		Not often	2		Quite often
1		Sometimes	1		Not very often
0		Most of the time	0		Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered
by any of the following problems?
(Use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____
=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your
work, take care of things at home, or get along with other people?

Not difficult at all ☐	Somewhat difficult ☐	Very difficult ☐	Extremely difficult ☐
---	---	---	--

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

PHQ-4

Over the last 2 weeks , how often have you been bothered by the following problems? (Use “✓” to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Little interest or pleasure in doing things	0	1	2	3
4. Feeling down, depressed, or hopeless	0	1	2	3

Scoring

PHQ-4 total score ranges from 0 to 12, with categories of psychological distress being:

- None 0-2
- Mild 3-5
- Moderate 6-8
- Severe 9-12

Anxiety subscale = sum of items 1 and 2 (score range, 0 to 6)

Depression subscale = sum of items 3 and 4 (score range, 0 to 6)

On each subscale, a score of 3 or greater is considered positive for screening purposes

The PHQ scales were developed by Drs. Robert L. Spitzer, Janet B.W. Williams, and Kurt Kroenke and colleagues. The PHQ scales are free to use. For research information, contact Dr. Kroenke at kkroenke@regenstrief.org

Kroenke K, Spitzer RL, Williams JBW, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4 Psychosomatics 2009;50:613-621.

Ankylosing Spondylitis Registry of Ireland

Patient Details

Date of Birth ____/____/____

Gender Male ☐ Female ☐

Ethnicity

Caucasian – Irish	
Caucasian – Other	
Black	
Asian	
Hispanic	
Other	

Marital Status _____

Was patient diagnosed with ankylosing spondylitis? Yes ☐ No ☐

If yes, date of diagnosis (year) _____

Year of AS symptom onset _____

Year first seen by rheumatologist _____

Eligibility – please indicate which of the following **ARE/WERE** present

	Yes	No	Don't Know
Low back pain >3 months			
Low back pain onset <45 years			
Low back pain which improves with exercise (activity)			
Low back pain which worsens with rest			

Low back pain with insidious onset	Yes	No	Don't Know
Low back pain at night (with improvement upon getting up)			
Low back pain relieved by NSAIDs			
Reduced chest expansion relative to age and sex (Refer to appendix 1)			
Reduced lumbar spine movements in frontal and sagittal planes			
Sacroilitis >grade 2 bilaterally or grade 3-4 unilaterally grade 3-4 unilaterally(On plain x-ray)			
Active inflammation on MRI suggests sacroilitis associated with SpA			

SpA Features(Now or Ever)

	Yes	No	Don't Know
Arthritis			
Enthesitis (heel)			
Uveitis			
Dactylitis			
Psoriasis			
Crohns/Colitis			
HLA B27 positive			
Elevated CRP			
Chronic neck pain with early morning stiffness ≥ 30 mins			

Employment

Employment status _____

If employed, specify type _____

If unemployed/part-time employed, due to: AS/SpA ☐ Other reason ☐

Health

Do you drink alcohol? Current ☐ Past ☐ No ☐

If current/past drinker, # units per week _____

If current/past drinker, # years _____

Are you a smoker Current ☐ Past ☐ No ☐

If past/current smoker, # cigarettes per day _____

If past/current smoker, # years _____

Family History

First degree relative with:

AS/SpA Yes ☐ No ☐ Don't know ☐

If yes, which relative: Father ☐ Mother ☐ # Siblings ☐ # Children ☐

Psoriatic arthritis Yes ☐ No ☐ Don't know ☐

If yes, which relative: Father ☐ Mother ☐ # Siblings ☐ # Children ☐

PsoriasisYes ☐No ☐Don't know ☐

If yes, which relative:

Father ☐Mother ☐# Siblings ☐# Children ☐

Second degree relative with:

-AS/SpAYes ☐No ☐Don't know ☐

If yes:

Maternal grandfather ☐Maternal grandmother ☐Paternal grandfather ☐Paternal grandmother ☐Maternal aunts/uncles ☐# Paternal aunts/uncles ☐Maternal cousins ☐#Paternal cousins ☐**Psoriatic arthritis**Yes ☐No ☐Don't know ☐

If yes:

Maternal grandfather ☐Maternal grandmother ☐Paternal grandfather ☐Paternal grandmother ☐# Maternal aunts/uncles ☐# Paternal aunts/uncles ☐# Maternal cousins ☐#Paternal cousins ☐**-Psoriasis**Yes ☐No ☐Don't know ☐

If yes:

Maternal grandfather ☐Maternal grandmother ☐Paternal grandfather ☐Paternal grandmother ☐Maternal aunts/uncles ☐Paternal aunts/uncles ☐Maternal cousins ☐Paternal cousins ☐

Co-morbidities

Has the patient ever been treated for:

- Ischaemic heart disease Yes ☐ No ☐

If yes, what was first year of treatment _____

- Cerebrovascular disease Yes ☐ No ☐

If yes, what was first year of treatment _____

- Hypertension Yes ☐ No ☐

If yes, what was first year of treatment _____

- Hyperlipidaemia Yes ☐ No ☐

If yes, what was first year of treatment _____

- Diabetes mellitus Yes ☐ No ☐

If yes type 1 or type 2 _____

If yes, what was first year of treatment? _____

- Chronic lung disease _____ If yes, is it clinically significant? Yes ☐ No ☐

If yes, what was first year of treatment _____

Asthma If yes, is it clinically significant? Yes ☐ No ☐

If yes, what was first year of treatment _____

Bronchiectasis If yes, is it clinically significant? Yes ☐ No ☐

If yes, what was first year of treatment _____

Emphysema If yes, is it clinically significant? Yes ☐ No ☐

If yes, what was first year of treatment _____

Fibrosis

If yes, is it clinically significant?

Yes ☐

No ☐

If yes, what was first year of treatment _____

- Peptic ulcer disease Yes ☐ No ☐

If yes, what was first year of treatment _____

- Tuberculosis Yes ☐ No ☐

If yes, what was first year of treatment _____

- Osteoporosis Yes ☐ No ☐

If yes, what was first year of treatment _____

- DXA Yes ☐ No ☐

If yes, what date (most recent) _____

If yes, hip t-score _____ hip z-score _____

If yes, spine t-score _____ spine z -score _____

- Fragility Fracture Yes ☐ No ☐

If Yes drop down for wrist, hip, spine(vertebrae) tib/fib, other

- Depression Yes ☐ No ☐

If yes, what was first year of treatment _____

- Have you ever had joint replacement? Yes ☐ No ☐

If yes, select site(s):

Knee joint , Hip joint , Other joint

If other, which joint _____

- Spinal corrective surgery Yes ☐ No ☐

If yes, what year _____

- Other musculoskeletal surgery Yes ☐ No ☐

If yes, what year _____

- Cancer Yes ☐ No ☐

If yes, what was first year of treatment _____

If yes select site:

Skin – melanoma	
Skin – non-melanoma	
Lung	
Breast	
Gastrointestinal	
Genitourinary	
Lymphatic	
Haematological	
Other	

Female patient only

Previous pregnancies

Yes ☐

No ☐

If yes proceed to pregnancy questionnaire

Medication History

NSAIDS – has patient received:

Are you currently taking NSAIDs? Yes ☐ No ☐

If yes, taking them: Continually ☐ As required ☐

of years using NSAIDS _____

Synthetic DMARDS – has patient received:

• Sulfasalazine Yes ☐ No ☐

If yes, treatment duration (months) _____

Is medication still ongoing Yes ☐ No ☐

• Methotrexate Yes ☐ No ☐

If yes, treatment duration (months) _____

Is medication still ongoing Yes ☐ No ☐

Complete attached worksheet for all past Biologics

Biologic DMARDS – has patient received:

• Etanercept Yes ☐ No ☐

If yes, treatment duration (months) _____

Is medication still ongoing Yes ☐ No ☐

Frequency of treatment

Average dose (in mg)

Start of treatment

End of treatment

Treatment duration (months)

If treatment stopped, what was the reason?

Inefficacy from the start, loss of efficacy, Reoccurring infections,

Intolerance, Reaction, Toxicity, Economic, **Biosimilar switch**

If the reason was "reaction", what was type of reaction was it?

Local, Systemic, Anaphylaxis.

If the reason was "reaction", how strong was the reaction?

Mild, Moderate, Severe

• **Adalimumab** Yes ☐ No ☐

If yes, treatment duration (months) _____

Is medication still ongoing Yes ☐ No ☐

Frequency of treatment

Average dose (in mg)

Start of treatment

End of treatment

Treatment duration (months)

If treatment stopped, what was the reason?

Inefficacy from the start, loss of efficacy, Reoccurring infections,

Intolerance, Reaction, Toxicity, Economic, **Biosimilar switch**

If the reason was "reaction", what was type of reaction was it?

Local, Systemic, Anaphylaxis.

If the reason was "reaction", how strong was the reaction?

• **Infliximab** Yes ☐ No ☐

If yes, treatment duration (months) _____

Is medication still ongoing Yes ☐ No ☐

• **Golimumab**

Yes ☐

No ☐

If yes, treatment duration (months) _____ Is

medication still ongoing

Yes ☐

No ☐

• **Certolizumab**

Yes ☐

No ☐

If yes, treatment duration (months) _____ Is

medication still ongoing

Yes ☐

No ☐

• **Secukinumab**

Yes ☐

No ☐

If yes, treatment duration (months) _____ Is

medication still ongoing

Yes ☐

No ☐

• **Ustekinumab**

Yes ☐

No ☐

If yes, treatment duration (months)

Is medication still ongoing

Yes ☐

No ☐

• **Tocilizumab**

Yes ☐

No ☐

If yes, treatment duration (months)

• **Orencia (Abatacept)**

• **Benapali(Enbrel)**

• **Olimiant(Baricitinib)**

• **Inflectra**

• **Xeljanz(Tofacitinib citrate)**

• **Imraldi (Humira)**

- Amgevita (Humira)
- Ixekizumab (TALZ)

Complete attached worksheet for all past Biologics

Physical Examination

Spinal Mobility Measures

Tragus-to-wall (cm) _____

Cervical rotation (deg) _____

Chest expansion (cm) _____

Schober test (cm) _____

Lumbar side flexion (cm) _____

Intermalleolar distance (cm) _____

Add comment box here for unusual findings

Please comment on any unusual measurements

Clinical measurements

Current blood pressure _____ / _____

Height (cm) _____

Weight (kg) _____

Waist circumference (cm) _____

Hip circumference (cm) _____

Blood tests

Highest recorded ESR (mm/hr) _____

Current ESR (mm/hr) _____

Highest recorded CRP (mg/l) _____

Current CRP (mg/l) _____

Date consent signed _____

DNA/Serum collected Yes ☐ No

Appendix D Research Ethics Approval

D.1 Ethical Approval Details for all centres involved in the ASRI

D.2 Blackrock Clinic ASRI ethics letter

D.3 Navan Hospital ASRI ethics letter

D.4 St James' & Tallaght University Hospital ASRI ethics letter

D.5 Sligo University Hospital ASRI ethics letter

D.6 Midlands Regional Hospital Tullamore ASRI ethics letter

D.7 Waterford University Hospital ASRI ethics letter

D.8 Depression screening ethics letter

D.9 Coping with COVID-19 ethics letter

Supplementary Table 1: Ethical Approval details for all centres involved in the ASRI

Center	Ethics Review Board	Approval Number
St James' Hospital	St James' & Tallaght Hospital Joint Research Ethics Committee	2019-07(27)
Tallaght University Hospital	St James' & Tallaght Hospital Joint Research Ethics Committee	2019-07(27)
Sligo University Hospital	Research Ethics Committee of Sligo University Hospital	473
St Vincent's University Hospital	Research Ethics Committee of St Vincent's Healthcare Group	ACA-IREL-11-02
Galway University Hospital	Galway Clinical Research Ethics Committee	
Our Lady's Hospital Navan	Health Service Executive (HSE) Northeast Research Ethics Committee	No approval number issued
Cork University Hospital	Clinical Research Ethics Committee of the Cork University Teaching Hospitals (CREC)	
Waterford University Hospital	HSE South-Eastern Area Research Ethics Committee	No approval number issued
University Hospital Limerick	Research Ethics Committee, University of Limerick Hospitals Group, Mid-West Region	010/15
Blackrock Clinic	Blackrock Clinical Trials & Medical Research Ethics Committee	No approval number issued
Midland Regional Hospital Tullamore	HSE Midland Area Research Ethics Committee	050214
University Hospital Kerry	Clinical Research Ethics Committee of the Cork University Teaching Hospitals (CREC)	



Blackrock Clinic

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**BLACKROCK CLINIC CLINICAL TRIALS &
MEDICAL RESEARCH COMMITTEE**
28th February 2014

Project Title: Ankylosing Spondylitis Registry
Chief Investigator: Dr. Frances Stafford

Dear Dr. Stafford:

I hereby confirm that the above Committee has reviewed the application and personal submission on 19th February 2014. It has been decided following consideration of all risks, ethical and procedural implications to grant full approval for the Ankylosing Spondylitis Registry and allow the project to proceed.

Sincerely,

**Daryl Simpson, Secretary, on behalf
of Dr. Mark Laher**

**Chairperson Clinical Trials & Medical
Research Committee**

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Dr. Frances Stafford
Dr. Daryl Simpson
Dr. Mark Laher
Dr. Stephen O'Brien
Dr. John O'Brien

Dr. Stephen O'Brien
Dr. John O'Brien
Dr. Mark Laher
Dr. Daryl Simpson
Dr. Frances Stafford

Accredited by Joint Commission International

From: Eimear.Dowling@hse.ie <Eimear.Dowling@hse.ie>
Sent: 25 July 2016 17:27
To: Gallagher, Phil (Bone and Joint)
Cc: Shawn.Chavrimootoo@maile.hse.ie
Subject: Study Title: "Ankylosing Spondylitis Registry of Ireland (ASRI)"

Dear Phil

I refer to your email correspondence of the 05/07/16 and the 19/07/16 and wish to advise that Dr MacMahon, Chair, HSE North East Area Research Ethics Committee has reviewed same.

I can confirm that approval dated 2nd October 2014 remains in place in relation to this study.

Dr MacMahon has also reviewed the revised Participant Information Leaflet and approval is given for the amendment as outlined.

You will receive a formal letter from Dr MacMahon, Chairperson advising of the above in due course.

Kind regards

Eimear Dowling
Research Ethics Administration

Eimear Dowling : Consumer Affairs : HSE Dublin North East : Bective St : Kells : Co Meath :
Tel: 046 9251264 : Fax: 046 9251774 : Email: eimear.dowling@hse.ie

...

[Message clipped] [View entire message](#)



Tallaght
University
Hospital

Ospidéal
Ollscoile
Thamhlachta

An Academic Partner of Trinity College Dublin

SJH/TUH Research Ethics Committee Secretariat
email: researchethics@tuh.ie

Mr Phil Gallagher,
St Vincent's Hospital,
196 Merrion Road,
Elm Park,
Dublin 4

19th July 2019

REF: ASRI (Ankylosing Spondylitis Registry of Ireland)

REC: 2019-07 List 27 (27)

(Please quote reference on all correspondence)

Date of Valid Submission to REC: 16.07.2019

Date of Ethical Review: 17.07.2019

R&I Application Number: N/A

Dear Mr Gallagher,

Thank you for your correspondence in which you sent in a response to the Committee's letter which detailed the Committee's queries and concerns in relation to the amendment submitted for the above referenced research study.

The Chairman, Prof. Richard Dean, on behalf of the Research Ethics Committee, has reviewed your correspondence and has given full approval.

The following documents were reviewed:

- Response to comments, dated 15.07.2019
- PIL and CF, V4, dated 11.06.2019

Applicants must submit an annual report for ongoing projects and an end of project report upon completion of the study. It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018. Additionally, please note for documents submitted for GDPR purposes that the REC and the Chair are not confirming that you're documents are GDPR compliant, they are approving the document from an ethical perspective.

Yours sincerely,

REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

Ospidéal na hOllscoile, Thamhlacht
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Príomhlíne: +353 1 414 2000
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Tallaght, Dublin, D24 NR0A, Ireland
Tel: +353 1 414 2000
www.tuh.ie

Tallaght University Hospital is a registered
business name of The Adelaide and Meath
Hospital, Dublin Incorporating The National
Children's Hospital.



www.ref-sligo.ie / ref.sligo@hse.ie



Research Ethics Committee
Chair: Dr. Miriam O'Sullivan

30/11/20

Re. Research Ethics Application No. 473

Dear Carmel,

The Research Ethics Committee (REC) at Sligo University Hospital has received your amendments for ethical review "**Ankylosing Spondylitis Registry of Ireland (ASRI)**"

The REC Chair has given **ethical approval** for the amendments for Sligo University Hospital.

Documents reviewed:

- Amendments Notification Form

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report (due annually from the date of your approval letter)
2. Report unexpected events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to SUH REC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from SUH REC.
4. Notify SUH REC of discontinuation of the study.
5. Submit a Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Dr. Miriam O'Sullivan
REC Chairperson

PLEASE ENSURE THAT DATA PROCESSING COMPLIES WITH THE NEW GDPR REGULATION WHICH CAME INTO EFFECT ON 25th May 2018. This submission has been reviewed from an ethical perspective only. It is the responsibility of the PI/sponsor/data controller and relevant Data Protection Officer to ensure and monitor compliance with any relevant legislation in the country where the study is due to take place or any local policy in the site where the study is due to take place. Your attention is drawn to new EU regulations concerning Data Protection, and provisions in Irish legislation for application of these regulations in Medical Research. Guidance is available from HRB on the following links:

<http://www.hrb.ie/funding/gdpr-guidance-for-researchers/health-research-regulations-2018-faq/>

<https://www.youtube.com/watch?v=jcfSRpvxY5A>

[The REC at SUH cannot interpret GDPR or approve consent waivers.](#)



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

Research Ethics Committee
HSE – Midland Area
HSE Area Offices
Arden Road
Tullamore
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Telephone: 057 9359894

Fax: 057 9359906

20th December 2013

Ref: 050214

Dr. Killian O'Rourke
Consultant Rheumatologist
Midland Regional Hospital Tullamore
Arden Road
Tullamore
Co. Offaly

Re: Ankylosing Spondylitis Registry of Ireland (ASRI)

Dear Dr. O'Rourke,

Thank you for your email dated December 12th requesting expedited Chairperson review of your research proposal titled "Ankylosing Spondylitis Registry of Ireland". This research proposal was reviewed by the Chairperson as requested.

The Chairperson has provided a **Favourable Opinion** with regard to this research but would like to note the following:

- In relation to the information provided in the participant information leaflet in the section on 'Future Studies'. An option is provided regarding either permission to use the participants sample and information for future research **without** further consent (A) **or** permission for samples and information to be stored for possible future research related to this study but only **if consent is obtained** at the time of the future research (B). The consent form notes option "A" above but has no reference to option B. It is not appropriate to offer the option as part of participant information and then not offer the option as part of informed consent so the consent form will require amendment accordingly.

We wish you well with your research.

Yours Sincerely,

Paul Marsden
Paul Marsden
Secretary – Research Ethics Committee
On behalf of
Dr. Una Fallon MCRN 014313
Chairperson – Research Ethics Committee

A favourable ethics review from the Research Ethics Committee (REC) is not the same as permission from the relevant HSE manager to proceed with the study. Authorisation from HSE management must be sought separately.
Please note that the REC submits details of all reviewed research to LENUS – the Irish Health Repository www.lenus.ie

Revised
on
21/1/14
↓
Approved
via
e-mail
on
21/1/14.



Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

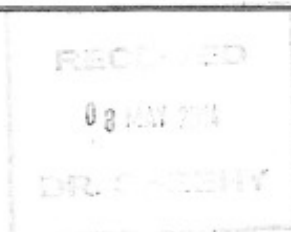
HSE South,
Waterford Regional Hospital,
Dunmore Road,
Waterford,
Ireland.

Telephone 051 848000
Fax 051 848572

RESEARCH ETHICS COMMITTEE,
HEALTH SERVICE EXECUTIVE, SOUTH EASTERN AREA

6th May 2014

Dr. Claire Sheehy
Consultant Rheumatologist
Waterford Regional Hospital



TITLE OF STUDY: Ankylosing Spondylitis Registry of Ireland (ASRI)

STUDY STATUS: APPROVED

Dear Dr. Sheehy,

The Research Ethics Committee, HSE, South East reviewed the above study at their meeting on Monday 10th March 2014.

The following documents were reviewed and approved:

1. Standard R.E.C. Application Form
2. Participant Information Sheet
3. Participant Questionnaires
4. Participant Consent Form
5. Participant Registry Form

The following documents were received:

1. C.V. of Principal Investigator – Dr. Claire Sheehy
2. Signed hard copy of Declaration

Please notify the Research Ethics Committee Office, Old School of Nursing, Waterford Regional Hospital on completion of Research.

Yours sincerely,

Waterford Regional Hospital Mission Statement:

"Together we will provide quality patient care delivered by skilled and valued staff through the best use of available resources".

Dr Sinead Maguire,
St James's Hospital,
James' Street,
Dublin 8

05th May 2020

REF: Screening for Depression in Ankylosing Spondylitis

REC: 2020-04 List 15 – Response to Comments (21)

(Please quote reference on all correspondence)

Date of Valid Submission to REC: 24.03.2020

Date of Ethical Review: 22.04.2020

Dear Dr Maguire,

The Chairman, Prof Richard Deane, has reviewed the response to comments and amendments you submitted for the above-named study and has given **FULL** ethical approval for the study to proceed. Please add that data will be kept and processed if the patient withdraws.

The following documents were reviewed:

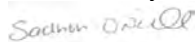
- Patient Information Leaflet

Please note that ethical approval for this study is only active under the following conditions:

- ✓ *Applicants must submit an annual report for ongoing projects.*
- ✓ *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
- ✓ *All adverse events must be reported to the JREC.*
- ✓ *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,



REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

Dr Finbar O'Shea,
St James's Hospital,
James' Street,
Dublin 8

23rd June 2020

REF: Coping with COVID-19 Pandemic for Patients with Rheumatic Diseases

REC: 2020-06 List 23 – Response to Comments (02)

(Please quote reference on all correspondence)

Date of Valid Submission to REC: 02.06.2020

Date of Ethical Review: 17.06.2020

Dear Dr O'Shea,

The Chairman, Prof. Richard Deane, on behalf of the Research Ethics Committee, has reviewed the Response to the Committees comments you submitted and has given **FULL** approval for the study to proceed. The following comments were made:

The following documents were reviewed:

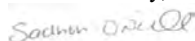
- Patient Information Leaflet

Please note that ethical approval for this study is only active under the following conditions:

- ✓ *Applicants must submit an annual report for ongoing projects.*
- ✓ *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
- ✓ *All adverse events must be reported to the JREC.*
- ✓ *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,



REC Officer – Dr Sadhbh O'Neill
SJH/TUH Research Ethics Committee

Appendix E Patient Information Leaflets & Consent

E.1 Screening for Depression in Ankylosing Spondylitis PIL

E.2 Coping with the COVID-19 Pandemic in Patients with Rheumatic Disease PIL

E.3 ASRI Consent form

PARTICIPANT INFORMATION LEAFLET

Screening for Depression in Ankylosing Spondylitis

Principal Investigator & Co-investigator: Dr Sinead Maguire, Dr Finbar O'Shea

You are invited to take part in a research project focusing on screening patients with ankylosing spondylitis for early signs of depression. This research project is run by the Rheumatology department in St James' Hospital. We would appreciate if you decided to take part, but before you decide please read this leaflet carefully. Ask your doctor in clinic today if any of the information leaflet is unclear or if you have additional questions.

THE STUDY

Why is this study being done?

Depression has been shown to be associated with poor outcomes in inflammatory arthritis. The impact of depression on ankylosing spondylitis(AS) is poorly understood. Early detection of depression using screening tools could help to improve energy levels, control of disease and overall quality of life. For these reasons the Rheumatology Department of St James' has begun to screen patient attending the AS clinic for early depression.

Why am I being asked to take part?

You are invited to take part due to your diagnosis of ankylosing spondylitis or the earlier form known as axial spondyloarthritis.

Do I have to take part? What happens if I say no? Can I withdraw?

Participation in this study is completely voluntary. If you decide not to participate it will not affect your medical care. If you do decide to take part but change your mind at a later date, you can choose to have your information removed from the study at any time. You do not need a reason to ask to be removed from the study. If you wish to opt out of this study please contact the Rheumatology Department and one of the Doctors responsible for the study will return your call.

How will the study be carried out?

Participation in the study involves completing two questionnaires on the day you attend clinic in the Rheumatology Department. On completion of the questionnaires the doctor will review your scores and discuss them with you if needed or if you have any questions.

What will happen to me if I agree to take part?

If you agree to take part you will be asked if you have any questions regarding this information leaflet. If you are happy to proceed, you will be asked to complete the following 2 questionnaires which will take less than 10 minutes total. Your scores will be reviewed by your doctor. All results are confidential.

Are there any benefits to me or others if I take part in the study?

Participation could result in early detection of depression which could lead to early intervention and improved outcomes.

Are there any risks to me or others if I take part in the study?

There are no direct risks anticipated by your participation in the study.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

The results of your questionnaire will be discussed with you and if further action should be considered (including referral to psychiatry etc) based on your score this will also be discussed. Anonymised study results will discuss the ASRI patient population as a whole. Your information will never be discussed on an individual basis. Results of the study overall will be presented at Rheumatology meetings and published in Rheumatology Journals.

DATA PROTECTION

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

Your identity will remain confidential. Your name and personal information will not be published or disclosed to any party other than the principal investigators and their staff. Your medical records will not be required for this study.

What will happen my personal data?

Your personal data will be stored in a password protected document on a secure computer in the hospital. Data will be retained for the duration of the study and the subsequent analysis. Only details relevant to the analysis will be processed and saved. Following completion of the analysis data will be securely stored in the Rheumatology Department. Your personal data will not leave the state.

Who will access and use my personal data as part of this study?

Only the principal investigators and assigned personnel are allowed access to the data.

Will my personal data be kept confidential? How will my data be kept safe?

St James Hospital operates and uses appropriate technical and physical security measures to protect your personal data. In particular measures are in place to protect your data from

accidental or unlawful destruction, loss, alteration, unauthorised disclosure of or access to results of this research study.

What is the lawful basis to use my personal data?

The processing of your personal data will be in compliance with the Data Protection Acts 1988 to 2018 (as amended) and the General Data Protection Regulation articles 6 & article 9.

What are my rights?

All study participants have the following rights in relation to their personal data:

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability
- Right to object to profiling

COSTS, FUNDING & APPROVAL

Will it cost me anything if I agree to take part?

Your participation in the study will not cost you any money. You will not receive any payment for participation in the study.

Who is funding this study? Will the results study be used for commercial purposes?

There are no grants or sponsorships funding this study.

Has this study been approved by a research ethics committee?

This project has been reviewed and approved by the St James' Hospital/Tallaght University Hospital Joint Research Ethics Committee.

Contact details: TUH/SJH REC Officer Dr Sadhbh O'Neill

Email: researchethics@tuh.ie / Sadhbh.oneill@tuh.ie

No persons carrying out the research have a link to the committee or the institution behind the committee.

FUTURE RESEARCH

Will my personal data and/or biological material be used in future studies? *(May not apply)*

No

FURTHER INFORMATION

Where can I get further information?

Provide the **contact details** for:

- Principal Investigator(s): Dr Sinead Maguire (simaguire@stjames.ie)
- Data Controllers: Dr Sinead Maguire
- Data Protection Officer: Cathal Kinsella, Freedom of Information Officer, St James' Hospital, Dublin 8, +35314162463; dataprotection@stjames.ie

What happens if I wish to make a complaint?

If you wish to make a complaint in relation to this study please contact the patient experience office at St James' Hospital on 014284248

Will I be contacted again?

No

PARTICIPANT INFORMATION LEAFLET

Coping with the Covid 19 Pandemic in Patients with Rheumatic Diseases

Principal Investigator & Co-investigator: Dr Sinead Maguire, Dr Finbar O'Shea

Living with a rheumatic disease during this period of social isolation and global pandemic is a considerable source of stress for many people. The Rheumatology Department at St James' Hospital wants to understand how these current conditions are affecting you (our patient) and how you are managing. Improved understanding of this issue will help us to better address your concerns during this time.

THE STUDY

Why is this study being done?

Living with a rheumatic disease during this period of social isolation and global pandemic is a considerable source of stress for many people. The Rheumatology Department at St James' Hospital wants to understand how these current conditions are affecting you (our patient) and how you are managing. Improved understanding of this issue will help us to better address your concerns during this time.

Why am I being asked to take part?

You are invited to take part as you are a patient attending the Rheumatology Department in St James' Hospital.

Do I have to take part? What happens if I say no? Can I withdraw?

Participation in this study is completely voluntary. If you decide not to participate it will not affect your medical care.

How will the study be carried out?

Participation in the study involves completing a short questionnaire on your experience during the self-isolation period of the covid 19 pandemic.

What will happen to me if I agree to take part?

If you agree to take part you will be asked to complete the following short survey. Your answers will be reviewed by the principal investigators. All results are confidential.

Are there any benefits to me or others if I take part in the study?

There are no direct benefits to participating. Participation could help Rheumatologists understand stressors encountered during the self-isolation period of the covid 19 pandemic.

Are there any risks to me or others if I take part in the study?

There are no direct risks anticipated by your participation in the study.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

Anonymised study results will only ever discuss patients who participated as a whole, your responses will never be discussed on an individual basis. Results of the study overall will be presented at Rheumatology meetings and published in Rheumatology Journals.

DATA PROTECTION

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

Your identity will remain confidential. Your name and personal information will not be published or disclosed to any party other than the principal investigators. Your medical records will not be required for this study.

What will happen to my personal data?

Your data will be stored in a password protected document on a secure computer. Data will be retained for the duration of the study and analysis. Only details relevant to the analysis will be processed and saved. Following completion of the analysis data will be stored in a secured location within the Rheumatology Department. Your personal data will not leave the state.

Who will access and use my personal data as part of this study?

Only the principal investigators and assigned personnel are allowed access to the data.

Will my personal data be kept confidential? How will my data be kept safe?

St James Hospital operates and uses appropriate technical and physical security measures to protect your personal data. In particular measures are in place to protect your data from accidental or unlawful destruction, loss, alteration, unauthorised disclosure of or access to results of this research study.

What is the lawful basis to use my personal data?

The processing of your personal data will be in compliance with the Data Protection Acts 1988 to 2018 (as amended) and the General Data Protection Regulation articles 6 & 9.

What are my rights?

All study participants have the following rights in relation to their personal data:

- Right to access data held
- Right to restrict the use of the data held

- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability
- Right to object to profiling

COSTS, FUNDING & APPROVAL

Will it cost me anything if I agree to take part?

Your participation in the study will not cost you any money. You will not receive any payment for participation in the study.

Who is funding this study? Will the results study be used for commercial purposes?

There are no grants or sponsorships funding this study.

Has this study been approved by a research ethics committee?

This project has been reviewed and approved by the St James' Hospital/Tallaght University Hospital Joint Research Ethics Committee.

Contact details: TUH/SJH REC Officer Dr Sadhbh O'Neill

Email: researchethics@tuh.ie / Sadhbh.oneill@tuh.ie

No persons carrying out the research have a link to the committee or the institution behind the committee.

FUTURE RESEARCH

Will my personal data and/or biological material be used in future studies?

No

FURTHER INFORMATION

Where can I get further information?

Provide the **contact details** for:

- Principal Investigator(s): Dr Sinead Maguire (simaguire@stjames.ie)
- Data Controllers: Dr Sinead Maguire
- Data Protection Officer: Cathal Kinsella, Freedom of Information Officer, St James' Hospital, Dublin 8, +35314162463; dataprotection@stjames.ie

What happens if I wish to make a complaint?

If you wish to make a complaint in relation to this study please contact the patient experience office at St James' Hospital on 014284248

Will I be contacted again?

No



OSPIDÉAL NAOMH SÉAMAS ST. JAMES'S HOSPITAL



Ospidéal Naomh Séamas, Sráid Shéamais, Baile Átha Cliath 8.
St. James's Hospital, James's Street, Dublin 8.
+353 1 410 3000 www.stjames.ie

ST JAMES'S HOSPITAL/TALLAGHT UNIVERSITY HOSPITAL JOINT RESEARCH ETHICS COMMITTEE

Patient Information and Consent

Title of study

Ankylosing Spondylitis Registry of Ireland (ASRI)

Principal Investigator:

Dr. Barry O'Shea

Introduction:

You are invited to participate in a research study at St James Hospital. Thank you for taking time to read this. Before you decide whether or not you wish to take part, you should read the information provided in this leaflet carefully. Take time to ask questions – don't feel rushed or under pressure to make a quick decision. You should understand the risks and benefits of taking part in this study so that you can make a decision that is right for you. You may wish to discuss it with your family, friends or GP.

You should be satisfied that all your questions concerning this study are answered and that you understand your rights as a study patient.

Purpose of the study:

The main aim of the study is to establish a registry of patients with Ankylosing Spondylitis (AS). This will include adult patients who have been diagnosed with AS and have been reviewed in a hospital setting within the past 3 years.

This database of patients will facilitate clinical and research studies to allow us to better understand the disease and measure its impact on those who suffer from this disease.



Why am I being asked to take part?

You are being asked to participate in this study as you have a diagnosis of Ankylosing Spondylitis (AS)

Do I have to take part?

Your participation is voluntary. You don't have to take part in this study. If you decide not to take part it won't affect your current or future medical care. You can change your mind about taking part in the study and opt out at any time even if the study has started. If you decide to opt out, it won't affect your current or future medical care and you will continue to be seen in the specialist clinic for AS. You don't have to give a reason for not taking part or for opting out.

If you wish to opt out, please contact Dr Barry O'Shea or a member of the Rheumatology team – 01 4162551 who will be able to organize this for you.

How will the study be carried out?

Your study visits will take part in the Rheumatology outpatients department at St James's hospital and each visit will take approximately one hour. All patients who present with Ankylosing Spondylitis will be invited to participate.

What will happen to me if I agree to take part?

- You are asked to carefully read this information leaflet and consent form. The doctor or research nurse will ask you if you understand all aspects of the study and what is involved for you. If you agree to participate, you will be asked to sign the attached consent form. You will be seen by Dr Barry O'Shea or a member of the Rheumatology team assigned by him.
- You will have a physical examination consistent with routine clinical practice.
- You will be asked to give a once off blood sample of approximately (3 tablespoons) of blood for genetic studies.
- If you are part of the subset of patients (new diagnosis and patients changing treatment) you may be asked return for follow up visits at 6 monthly or 12 monthly intervals (up to 5 years) to monitor disease progress and response to treatment and you will be asked to provide a serum sample for gene & protein studies.
- You will be asked to complete some questionnaires to assess your pain level, your disease activity and your physical function.

- We will also collect your medical details, as part of your routine consultations with the doctor on your first visit and all subsequent visits to the rheumatology clinic. The data we collect will be stored with no identifying details (this is called pseudonymised) on a secure database. This will allow us to match detailed medical assessment with the information gained from the samples we have collected from you. You will be aware of all the information that is collected about you.

Benefits:

There is no direct benefit to you in participating in this study but the knowledge gained from this study may be of help to other patients in the future.

Risks:

There will be no risks other than those associated with taking blood from a vein in your arm, which you would be having as part of your standard care. These are discomfort, pain or bruising. No additional risks to you are foreseen from participating in this study.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

You will not be told the outcome of the study and you will not be given individual results – anonymised results will be published in medical journals and will be presented at peer groups. Data is published in an aggregated form only (as a group as opposed to individual results) the information obtained may provide further knowledge of this condition.

DATA Protection:

What information about me personal data) will be used as part of the study? Will my medical records be assessed?

Your identity will remain confidential. A study number will identify you. Your name will not be published or disclosed to any party other than the Co-Principal Investigators and their staff.

It is a requirement that your involvement in this study is noted in your medical records. Direct access to your medical records by medical staff of St James's Hospital will be needed to check the information collected for the study. Information collected about you will include demographic (e.g. date of birth, sex, age etc.) medical history, clinical measures to assess disease level, biometric measures (height, weight, waist and hip circumference) medication history, x-ray and blood test results, family history relating to AS, questionnaires required to

measure response to treatment and current disease activity. When the blood sample is taken by the researcher it will be coded and pseudonymised so you are not identifiable outside the Rheumatology department. At no point in this study will you be identifiable to outside parties.

By signing this consent form you authorise access to this confidential information by the medical staff of St James's Hospital for the purpose of this study.

The confidentiality of your medical records will be maintained to the extent permitted by the applicable laws. If results of the study are published your identity will remain confidential.

You have the right of access to and the right to rectification of your medical records upon written request to one of the Principal/ Co- Investigators at the Department of Rheumatology at St James's Hospital.

What will happen my personal data?

All your data and samples will be coded and rendered pseudonymous (you can be identified by a number only) once collected. A unique study number will be assigned to this data. The personnel involved in collecting samples and the data will be responsible for safeguarding anonymity. All pseudoanonymised data will be kept as long as the registry is active. This is a safeguard to avoid duplication. Pseudoanonymised personal data may leave the state if relevant in the project involved. ie date of birth /and or gender might be necessary to accompany a genetic study.

Your research blood samples will be processed and stored at the Trinity Translational Medicine Institute, Department of Clinical Medicine, and Trinity Centre for Health Sciences, and St James's Hospital presently under the supervision of Ross McManus, PhD. Professor in Molecular Medicine.

Who will access and use my personal data as part of this study?

The Principal Investigator and personnel assigned by him are allowed to access the data.

We use a third party service provider to provide a database to store your information. This data base is hosted on a virtual server owned by Ankloysing Spondylitis Ireland (ASRI). This server will be protected by using SSL, a protocol for encrypting information over the internet. All data entered into the database will be pseudoanonymised and only the Principal Investigator or his staff can identify you. Once data is collected the researcher enters it into a web based

database described above. Your study number is a random number assigned by the computer. Only the staff at St James's hospital can identify you.

Will my personal data be kept confidential? How will my data be kept safe?

St James Hospital operates and uses appropriate technical and physical security measures to protect your personal data.

We have in particular taken appropriate security measures to protect your data from accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access, in connection with this research study. Access is only granted on a need –to – know basis to those people whose roles require them to process your personal data.

In addition our service providers are also selected carefully and required to use appropriate protective measures.

What is the lawful basis to use my personal?

The processing of your personal data will be in compliance with the Data Protection Acts 1988 to 2018 (as amended) and the General Data Protection Regulation (the "Data Protection Legislation") Article 6 & Article 9.

What are my rights?

All study participants have the following rights in relation to their personal data:

- Right to access data held
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted
- Right to data portability
- Right to object to profiling

Will it cost me anything if I agree to take part?

Your participation in this study will not cost you any additional money. You will not receive any payment for participation in this study

Your study doctors are covered by a standard clinical indemnity scheme.

Who is funding this study? Will the study results be used for commercial purposes?

The overall study is organised by Dr Barry O'Shea, Consultant Rheumatologist. There is a nominal fee paid to each Investigator participating to cover

administration costs. The overall project is presently being funded by a grant from Abbvie Pharmaceuticals and Pfizer Pharmaceuticals but in the future it is hoped that funding will be received from other pharmaceutical /commercial organisations (Novartis, UCB, GMI and others not yet identified)

The registry (ASRI) will not be disclosing results for commercial purposes but may collaborate with commercial organisations (GMI) who are for profit organisation. All donations to the registry from commercial organisations will be directly used to support work within ASRI.

Stopping the study:

You understand that your doctor may stop your participation in the study at any time without your consent.

Has the study been approved by a Research ethics Committee?

St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee have reviewed and approved this study.

Contact Details: TUH/SJH REC OFFICER:

Dr. Sadhbh O'Neill

Email: ResearchEthics@tuh.ie/ Sadbh.O'Neill@tuh.ie

Phone: 01-414 2199

No persons carrying out the research have a link to the committee or the Institution behind the committee.

Initial Approval was granted on 19th June 2013.

Anonymised results will published in medical journals and will be presented at peer groups. The information obtained may provide further knowledge of this condition.

Will my personal data and/ or biological material be used in future studies?

We will ask your permission for the blood sample and information collected about you to be stored for possible future research without any further consent being required and subject to approval by a Research Ethics Committee. Any future Research will always apply to AS only and may include DNA studies and may be carried out by other commercial/academic institutions that we wish to collaborate with in the interest of research into the disease. These collaborators may be outside the European Economic Area ("EEA"),

We will ensure adequate safeguards with respect to the protection of your privacy, fundamental rights and freedoms and the exercise of your rights, e.g. we will ensure any collaborators have an adequate level of data protection

through EU Standard Contractual Clauses based on the EU commission's model clauses.

What if I wish to make a complaint?

If you wish to make a complaint in relation to the study- please contact Patient experience office at St James's hospital on 014284248

You will only be contacted if there is a change to the protocol or to the data we collect. You will be asked to resign a consent form if we make a change that affects you or wish to seek any further information.

Further information:

For further information,

Please contact the following

Principal Investigator: Dr Barry O'Shea (01) 4162551 from 0900-1700 (Monday to Friday)

Data Controller: St James's hospital and Dr Barry O'Shea

Data Processor: Dr Barry O'Shea and research staff assigned by him

Data Protection Officer:

Cathal Kinsella

Freedom of Information Officer

St. James's Hospital

Dublin 8

Phone: +353 1 416 2463

**ST JAMES'S HOSPITAL/TALLAGHT UNIVERSITY HOSPITAL JOINT RESEARCH
ETHICS COMMITTEE**

CONSENT FORM

ANKYLOSING SPONDYLITIS REGISTRY OF IRELAND (ASRI)

To be completed by the **PARTICIPANT**:

I have read and understood the information leaflet.	YES ☐	NO ☐
I have had the opportunity to discuss the study, ask questions about the study and I have received satisfactory answers to all my questions.	YES ☐	NO ☐
I have received enough information about this study.	YES ☐	NO ☐
I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care.	YES ☐	NO ☐
I agree to allow the researchers use my information (personal data) as part of this study as outlined in the information leaflet.	YES ☐	NO ☐
I agree to allow the researchers access my medical records as part of this study.	YES ☐	NO ☐
I agree to be contacted by researchers as part of this study for the purpose of data clarification.	YES ☐	NO ☐
I agree to give blood samples as described in the patient information leaflet as part of this study.	YES ☐	NO ☐
I agree to take part in the study.	YES ☐	NO ☐
Future research I agree that the samples I have given and the Information gathered about me can be Pseudoanonymised and stored in the St James's Hospital, for use in future projects relating to Ankylosing Spondylitis without further consent being required and subject to the research being approved by a Research Ethics Committee. I am aware that some of these projects research projects may be carried out by researchers in Trinity College Dublin and researchers working for commercial/pharmaceutical companies including GMI.	YES ☐	NO ☐

Participant's Name (Block Capitals):	
Participant's Signature:	
Date:	

To be completed by the **RESEARCHER**:

I have fully explained the purpose and nature (including benefits and risks) of this study to the participant in a way that he/she could understand. I have invited him/her to ask questions on any aspect of the study.	YES ☐	NO ☐
I confirm that I have given a copy of the information leaflet and consent form to the participant.	YES ☐	NO ☐

Researcher's Name (Block Capitals):	
Researcher's Title & Qualifications:	
Researcher's Signature:	
Date:	

Appendix F: Systematic Review on Pregnancy in Axial Spondyloarthritis

Search Strategy

EMBASE

1. 'ankylosing spondylitis'/exp OR 'spondylarthritis'/exp
2. ((Ankylo*) NEAR/5 (spondyl* OR spondil* OR spine OR spinal)):ti,ab
3. (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis):ti,ab
4. (axial NEAR/2 spondyloarthropath*):ti,ab
5. #1 OR #2 OR #3 OR #4
6. 'pregnancy'/exp OR 'pregnancy disorder'/exp OR 'pregnant woman'/exp OR 'pregnancy rate'/exp OR 'parameters concerning the fetus, newborn and pregnancy'/exp
7. pregnan*:ti,ab
8. (labo*r NEAR/3 complication*):ti,ab
9. #6 OR #7 OR #8
10. #5 AND #9

Medline (OVID)

1. exp Spondylitis/
2. ((Ankylo*) adj5 (spondyl* OR spondil* OR spine OR spinal)):ti,ab.
3. (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis):ti,ab.
4. (axial adj2 spondyloarthropath*):ti,ab.
5. or/1-4
6. exp Pregnancy/ or exp Pregnancy Complications/ or Pregnant Women/ or Pregnancy Rate/
7. pregnan*.ti,ab.
8. (labo*r adj3 complication*):ti,ab.
9. or/6-8
10. and/5,9

CINAHL

1. (MH "Spondylarthritis+") OR (MH "Spondylosis+")
2. TI ((Ankylo*) N5 (spondyl* OR spondil* OR spine OR spinal)) OR AB ((Ankylo*) N5 (spondyl* OR spondil* OR spine OR spinal))
3. TI (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis) OR AB (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis)
4. TI (axial N2 spondyloarthropath*) OR AB (axial N2 spondyloarthropath*)
5. S1 OR S2 OR S3 OR S4
6. (MH "Pregnancy+") OR (MH "Pregnancy, Multiple+") OR (MH "Pregnancy Complications+") OR (MH "Pregnancy Outcomes") OR (MH "Expectant Mothers")
7. TI (pregnan*) OR AB (pregnan*)
8. TI (labo*r N3 complication*) OR AB (labo*r N3 complication*)
9. S6 OR S7 OR S8

10. S5 AND S9

Maternity and Infant Care (MIDIRS Online)

1. Ankylosing spondylitis.de.
2. ((Ankylo*) adj5 (spondyl* OR spondil* OR spine OR spinal)).ti,ab.
3. (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis).ti,ab.
4. (axial adj2 spondyloarthropath*).ti,ab.
5. or/1-4
6. (Pregnancy OR Pregnancy - high-risk or Pregnant or Labour complications).de.
7. pregnan*.ti,ab.
8. (labo*r adj3 complication*).ti,ab.
9. or/6-8
10. and/5,9

Web of Science

TS= (((Ankylo*) NEAR/5 (spondyl* OR spondil* OR spine OR spinal)) OR (Bechterew* OR Bekhterev* OR Marie-Struempell OR spondylarthritis OR spondylarthrosis) OR (axial NEAR/2 spondyloarthropath*)) AND (pregnan* OR ((labor OR labour) NEAR/3 complication*))

Searches run 06/09/19

Number of results from all databases = 1250

After duplication = 884

All database searches run from inception