# Clinical characteristics and patient-reported outcome measures in patients with axial spondyloarthritis:

## *Statistical Analysis Plan for a prospective cross-sectional study from southern Denmark*

**SAP Version 2.1, October 30, 2018**

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**Trial registration**

The study was approved by the Region of Southern Denmark's Ethics committee (S-20150219) and the study protocol is available from www.Parkerinst.dk.

**Protocol version**

This document has been written based on information contained in the study protocol version 3, dated 20 December 2015.

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Statistical Analysis Plan (SAP)

**Purpose of the Statistical Analysis Plan**

The SAP was initiated after the study protocol was registered and published online (www.Parkerinst.dk), but prior to reviewing data or conducting final analyses. The purpose of the SAP is to give a more transparent and detailed elaboration on the statistical analyses of the variables prospectively collected. Deviations from the pre-specified protocol are explained in the SAP. The reporting of the study will follow the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) (1).

**Background and rationale**

Spondyloarthritis (SpA) is a heterogenous group of chronic rheumatic diseases; it can be dominated by peripheral joint involvement, classified as peripheral SpA (pSpA), or by inflammatory back pain, classified as axial SpA (axSpA). Furthermore axSpA is subdivided into two stages: Nonradiographic (nr-axSpA) and radiographic (r-axSpA, formerly known as ankylosing spondylitis, AS). Next to the spinal and articular symptoms, many patients with axSpA also have extra-articular manifestations (EAMs; e.g. uveitis, enthesitis, psoriasis, inflammatory bowel disease) which contribute to reduced health-related quality of life (2). We anticipate that EAMs among patients with axSpA are underestimated and therefore undertreated. Besides EAMs, axSpA patients have a higher risk of comorbidities, including diabetes mellitus, renal disease, cardiovascular disease (CVD), and pulmonary disease (3-5). Awareness of comorbidities among clinicians is important in view of their role for treatment choices for axSpA patients. Other medical specialists and care professionals do of course also have their place. AxSpA disorders are generally diagnosed more often in men than in women (6). In reference to the most representative form of these disorders, r-axSpA, three male cases are documented for every female case (6). In contrast to r-axSpA, nr-axSpA patients show little difference in prevalence among males and females (7). Nevertheless, little is known of the differential clinical expression of axSpA between males and females, and females are often underrepresented in clinical research (8, 9). The higher incidence of r-axSpA in males compared to females has stimulated research on gender differences in axSpA. Few studies have analysed gender as a prognostic factor for course of disease in axSpA patients (8, 10, 11) and there is a need to determine the particularities and severity of axSpA in the female gender.

**Aims**

The overall objective of this cross-sectional study is to present a characterisation of axSpA patients, to

illuminate patient-reported outcome measures, and ultimately elucidate factors associated with disease outcome.

**Hypotheses**

We hypothesise that the amount of self-reported disease activity is more pronounced in women than in men (i.e. Bath Ankylosing Spondylitis Disease Activity Index [BASDAI (12)], and Bath Ankylosing Spondylitis Functional Index [BASFI (13)]).

**Objectives**

The primary objective of this study is to analyse the impact of gender on self-reported disease activity in axSpA patients based on the type of clinical diagnosis.

Secondary objectives are:
a. To determine the relationship between the continuous measure of muscular tenderpoints (TP (14)) and the self-reported disease activity (i.e. BASDAI).

b. To determine the prevalence of EAMs and comorbidities, as defined by the Charlson comobidy index, in axSpA patients.

c. To compare the impact on health-related quality of life of axSpA patients, specifically in terms of how axSpA classification differentially affects aspects of physical, mental and social wellbeing.

**Sample size considerations**

This study was designed as an exploratory study. A sample size of 100 individuals was considered sufficient to test the hypothesis: ‘is there a difference between reported BASDAI scores in axSpA patients by men vs women? For a two-sample pooled t test of a normal mean difference with a two-sided significance level of 0.05, assuming a common standard deviation of 1.5 BASDAI units, a total sample size of 100 assuming a balanced design (1:1 male-female ratio) has sufficient power (91%) to detect a mean difference of 1 BASDAI units. All descriptive statistics and tests will be reported in accordance with the recommendations of the

"Enhancing the QUAlity and Transparency Of health Research" (EQUATOR) network (15): the STROBE Statement (1). We consider p values less than 0.05 (and 95% confidence intervals excluding the null) to be statistically significant.

Statistical Analysis Plan (SAP)

**Study design**

The study is designed as a cross-sectional study with prospective enrolment of axSpA patients. Information about the patients and their exposures were collected at a single centre at one visit according to the clinical standards in Denmark. Examinations were conducted on the same day. The inclusion period was between 1st of April 2016 and 30th of March 2018.

**Study participants**

Patients with axSpA seen in the Department of Rheumatology, Odense University Hospital, Svendborg/Odense were recruited. We used the ASAS classification criteria for axSpA (imaging arm) (16), and the modified New York criteria for r-axSpA (17). To be considered for inclusion, participants must have the ability and willingness to give written informed consent and to meet the requirements of the pre-specified protocol. Participants were excluded from the study if any of the following criteria were present: (1) no consent, (2) does not understand Danish, (3) age < 18 years.

**Statistical interim analyses and stopping guidance**

Preliminary results have been presented at the EULAR congress in 2017 in Madrid (18). 80 participants were included at that time point.

**Timing of final analysis**

The first main report/publication of the trial will be prepared when the SAP is completed, and the research team has approved it (anticipated to be November 2018).

Urine samples were collected in this study to analyse whether the urine electrolytes were altered and related to nephrolithiasis in axSpA patients. The results will not be part of the proposed manuscript, but will be presented in a separate future paper.

**Confidence intervals and P values**

*Level of statistical significance and use of confidence intervals:* All applicable statistical tests will be 2-sided and will be performed using a 5% statistical significance level. No correction for multiple testing will be conducted; instead the results will be interpreted with caution in the context multiplicity.

**Protocol deviations**

To specify the aim of this study and to clarify the statistical analyses, some deviations from the pre-specified protocol were made.

**Aims:**

***Protocol:*** The overall objective of this cross-sectional study is to perform a characterisation of SpA patients, to identify clinical phenotypes of SpA and ultimately elucidate factors predictive of disease outcome.

***SAP:*** The overall objective of this cross-sectional study is to present a characterisation of axSpA patients, to illuminate patient-reported outcome measures, and ultimately elucidate factors associated with disease outcome.

***Rationale:*** Spondyloarthritis (SpA) is a heterogeneous group of chronic rheumatic diseases with overlapping symptoms including psoriatic arthritis (PsA), r-axSpA, arthritis associated with inflammatory bowel disease (enteropathic arthritis) and undifferentiated SpA . SpA can be dominated by peripheral joint involvement, classified as peripheral SpA (pSpA), or by inflammatory back pain, classified as axial SpA (ax-SpA).

**Eligibility**

The number of ineligible patients will be reported with reasons for ineligibility.

**Recruitment**

A flowchart template modified from http://www.consort-statement.org comprising the number of people screened, eligible, consented, and included in the analyses will be used (**Figure 1**).

**Collected variables**

The following information was collected at the study visit (**Table 1)**. Information on: (1) demographic, (2) disease characteristics, (3) medication, (4) axSpA features, (5) patient reported outcome measures (PROMs) (6) co-morbidities using Charlson Co-morbidity Index (CCI), (19). An experienced physician (RAA) performed a clinical examination and performed a 44 tender/swollen joint count, the Bath Ankylosing Spondylitis Metrology Index (BASMI), an 18-sites tender point count, and an enthesitis score. The core domains set recommended by the ASAS/OMERACT: physical function, pain, spinal mobility, patient's global

assessment (PGA), peripheral joints/enthuses, spinal stiffness, acute phase reactants and fatigue were assessed using the instruments explained below.

**Patient-reported outcome measures (PROMs)**

Touchscreen questionnaires were used for PROMs at the inclusion visit. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the patient's evaluation of disease activity. The BASDAI consists of a 6-item scale to measure severity of fatigue, spinal and peripheral joint pain, localised tenderness, morning stiffness (duration and severity), using the VAS scale (0-100 mm). To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken. The resulting 0 to 500 score is divided by 5 to give a final 0-100 BASDAI score. Scores of 40 or greater indicate suboptimal control of disease (12). Physical function was addressed using the Bath Ankylosing Spondylitis Functional Index (BASFI). The BASFI is a 10-item scale on which respondents rate the degree of difficulty they have in performing certain tasks, using visual analogue scales (VAS) from 0 (easy) to 100 (impossible). The mean of the 10 responses is the BASFI score (13). Pain was assessed by a Visual Analogue Scale (VAS) pain last week/spine/at night/due to AxSpA on a 0-100 mm scale. The intensity of fatigue was assessed by a VAS scale (0-100 mm). Health-related quality of life (HRQoL) was addressed using the Medical Outcomes Study SF-36; SF-36 is a generic health status questionnaire that was developed as a tool to compare various aspects of health status across a general and broad patient population (20-22). The SF-36 examines eight general health domains: physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health. Furthermore, a physical and mental component summary score will be calculated. We used the Danish version of SF-36 (23) which uses a 4-week recall period. The PGA was assessed by a single question with a range from 0 to 100 mm (VAS).

**Clinical examination**

Spinal mobility was addressed by the BASMI. The BASMI is a composite index of spinal mobility, and is used internationally in research and clinical practice and is recommended by the ASAS (24). RAA performed a 44 swollen/tender joint count, a SPARCC enthesitis score (25) and a tender point count (26).

**Para-clinical assessment**

Blood samples as specified in the protocol was collected by a trained laboratory technician and treated according to set procedures. Results on inflammation (C-reactive protein, Plasma Calprotectin), Human Leukocyte Antigen B27 (HLA-B27) and faecal calprotectin will be presented in this study.

**Analysis methods**

This study was designed as a descriptive cross-sectional study. The characteristics of the participants will be described for each gender and axSpA classification using descriptive statistics. Means and SDs or medians and IQRs and Binary outcomes will be presented as numbers and corresponding percentages. The primary variable of interest is BASDAI coded as a continuous variable. The primary analyses will be based on General Linear Models (GLM), investigating if there is an association between BASDAI and each of the covariates of interest (gender and axSpA classification). Furthermore, a test for interaction between gender and axSpA classification will be performed. The model will include gender, axSpA classification and interaction between them as fixed effects. Categorical outcome measures will be analysed with the use of logistic regression with the same fixed effects. A sensitivity analysis will be performed to assess the robustness of the primary analyses, by imputation missing data with the grand mean. Secondary analyses will include the same model using the secondary outcome measures (see **Table 1**).

The relationship between the continuous measure of tender point count and the patient-reported disease activity score (BASDAI) will be analysed by scatter plots with Spearman rank correlation coefficients. We will stratify on gender (**Figure 2A)**, and axSpA classification (**Figure 2B**) (Appendix A). All models will be tested for their assumptions.

**Missing data**

The number of participants with missing observations will be reported for each outcome variable. We will use a simple manual imputation by replacing missing data with the grand mean of the variables.

**Spydergrams**

The medical outcomes survey short form 36 (SF- 36) is a validated patient-reported outcome measure of health related quality of life. It includes 35 questions combined into eight domains, and a transition question; domains are summarised into physical component (PCS) and mental component (MCS) summary scores from 0 – 50 where 50 is considered normative (20-22).

The presentation and interpretation of health-related quality of life from SF-36 is complex, and the impact of patterns of disease can be difficult to evaluate (27). We will use 'Spydergrams' which provide a visual method to examine the eight domains of health-related quality of life scored from 0 – 100 simultaneously in a single figure (27); using spydergrams will enable us to compare the impact on health related quality of life of axSpA patients, specifically in terms of how axSpA classification differentially affects aspects of physical, mental and social wellbeing (**Figure 3**).

**Statistical software**

The analyses will be conducted using STATA (version 15). The program code for the primary analysis in the statistical program:

```
.glm BASDAI i.Gender i.axSpA-classification, family (gamma) link (identity)

.glm BASDAI i.Gender##i.axSpA-classification, family (gamma) link (identity)
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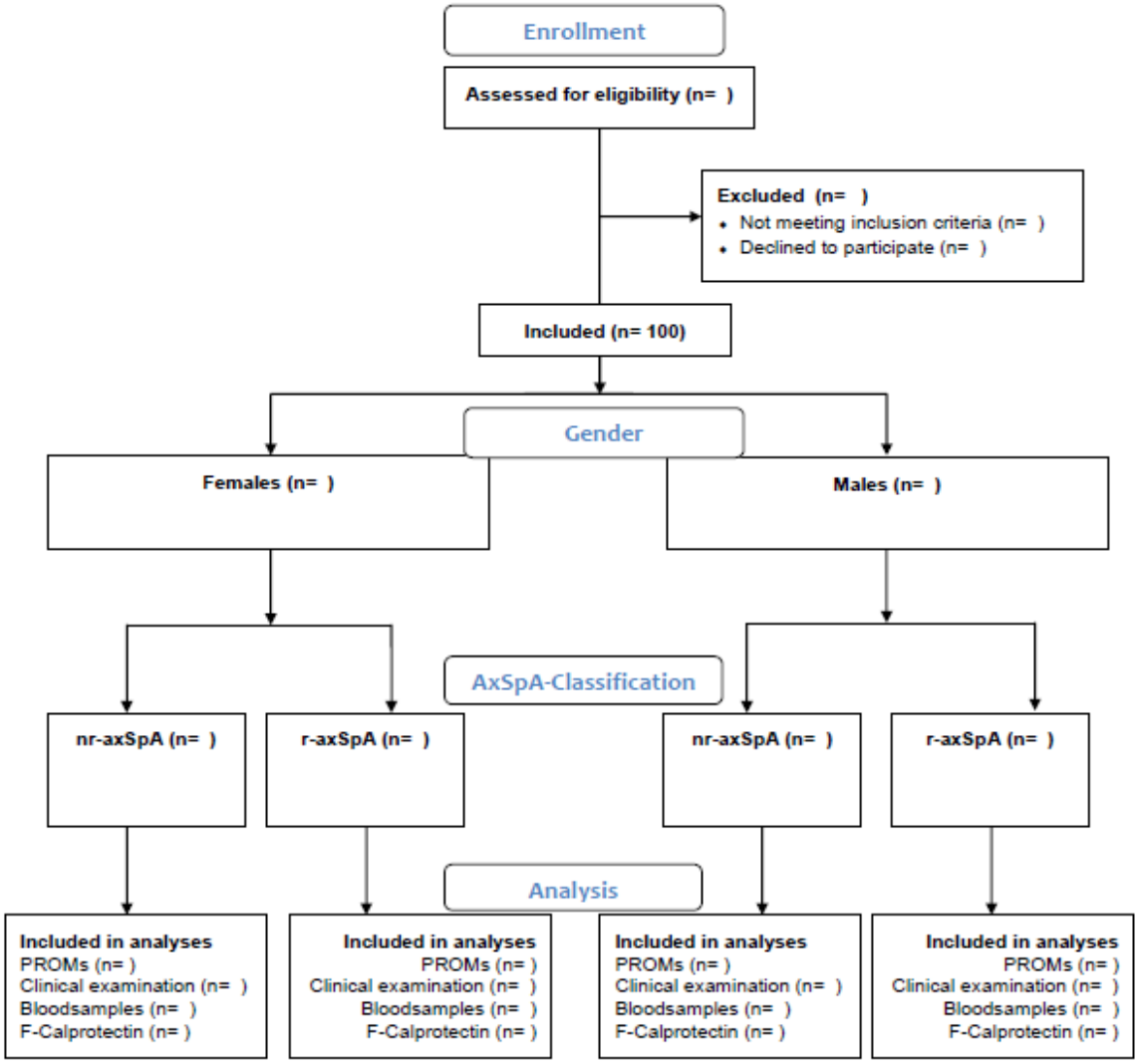


**Figure 1.** Numbers of axSpA patients who were screened, included in the study, and included in the analyses. Flow chart template modified from http://consort-statement.org.

**Table 1. Clinical characteristics and patient reported outcomes**

| | r-axSpA n = | | nr-AxSpA n = | | | |
|---|---|---|---|---|---|---|
| **Demographics** | Males, n = | Females, n = | Males, n = | Females, n = | Effect of gender | Effecf of axSpA classification |
| Age, years | | | | | | |
| BMI, kg/m$^2$ | | | | | | |
| Smoking (current), n (%) | | | | | | |
| AxSpA symptom month | | | | | | |
| Peripheral involvement, n (%) | | | | | | |
| **Co-morbidities** | | | | | | |
| Charlson Co-morbidity Index (CCI) | | | | | | |
| CCI = 0, n (%) | | | | | | |
| CCI = 1, n (%) | | | | | | |
| CCI ≥ 2, n (%) | | | | | | |
| **Medication** | | | | | | |
| NSAIDs daily use, n (%) | | | | | | |
| MTX use, n (%) | | | | | | |
| MTX dose (mg/week) | | | | | | |
| Sulfasalazine use, n (%) | | | | | | |
| Sulfasalazine dose (mg/daily) | | | | | | |
| No. of previous bDMARD used (if any) | | | | | | |
| Current bDMARD, n (%) | | | | | | |
| Glucocorticoid use, n (%) | | | | | | |
| Glucocorticoid dose (mg/daily) | | | | | | |
| **Patient reported outcome measures (PROMs)** | | | | | | |
| BASDAI (0-100) | | | | | | |
| BASFI (0-100) | | | | | | |
| VAS pain due to AxSpA (0-100 mm) | | | | | | |
| VAS fatigue (0-100 mm) | | | | | | |
| VAS global (0-100 mm) | | | | | | |
| SF-36: MCS (0-100) | | | | | | |
| SF-36: PCS (0-100) | | | | | | |
| **Clinical examination** | | | | | | |
| Swollen joint count (0-44) | | | | | | |
| Tender joint count (0-44) | | | | | | |
| BASMI (0-100) | | | | | | |
| Tender point count (0-18) | | | | | | |
| SPARCC enthesitis score (0-16) | | | | | | |
| ASDAS-CRP | | | | | | |
| VAS physician (0-100) | | | | | | |
| **Extra-articular manifestations*** | | | | | | |
| Uveitis, n (%) | | | | | | |
| Inflammatory bowel disease, n (%) | | | | | | |
| Psoriasis, n (%) | | | | | | |
| Dactylitis, n (%) | | | | | | |
| Heel enthesitis, n (%) | | | | | | |
| Nephrolithiasis, n (%) | | | | | | |
| **Paraclinic assessment** | | | | | | |
| HLA-B27 positive, n (%) | | | | | | |
| CRP (mg/L) | | | | | | |
| P-Calprotectin ( $\mu$ g/ml) | | | | | | |
| F-calprotectin (mg/L) | | | | | | |
| **Urine samples**** | | | | | | |
| U-Sodium, U-Oxalate, U-Chloride, U-albumin, U-Calcium, U-Potassium | | | | | | |

BMI, Body Mass Index; NSAIDs, Nonsteroidal anti-inflammatory drugs; MTX, Methotrexate; bDMARD, biologic disease modifying drugs; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; VAS, Visual Analogue Scale; SF-36: MCS/PCS, Medical Outcomes Study Short Form 36 Mental/Physical Component Summary; BASMI, Bath Ankylosing Spondylitis Metrology Index; SPARCC, Spondyloarthritis Research Consortium of Canada; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score - C-eactive Protein; *either patient history or current diagnosis; P/F-Calprotectin, Plasma/Faecal Calprotectin; *Urine samples will be collected in this study, but will be presented in a seperate future paper. The primary analyses will be based on General Linear Models (GLM), investigating if there is an association between BASDAI and each of the covariates of interest (gender and AxSpA classification). Furthermore, a test for interaction between gender and axSpA classification will be performed. The model will include gender, axSpA classification and interaction between them as fixed effects. Categorical outcome measures will be analysed with the use of logistic regression with the same fixed effects. Secondary analyses will include the same model using the secondary outcome measures

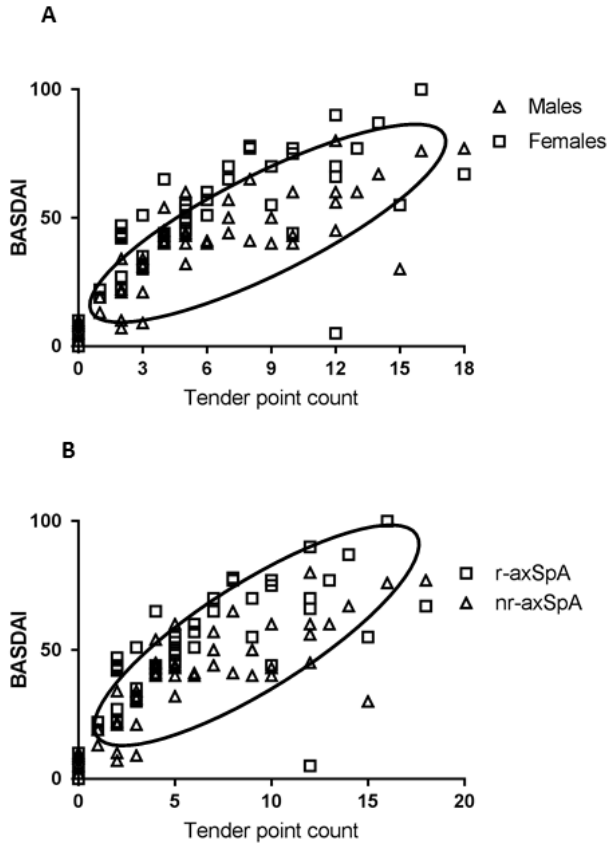


**Figure 2.** (Data are simulated for visual illustration) Correlation between tender point count and BASDAI. (A) Stratified on gender (B) Stratified on axSpA classification.

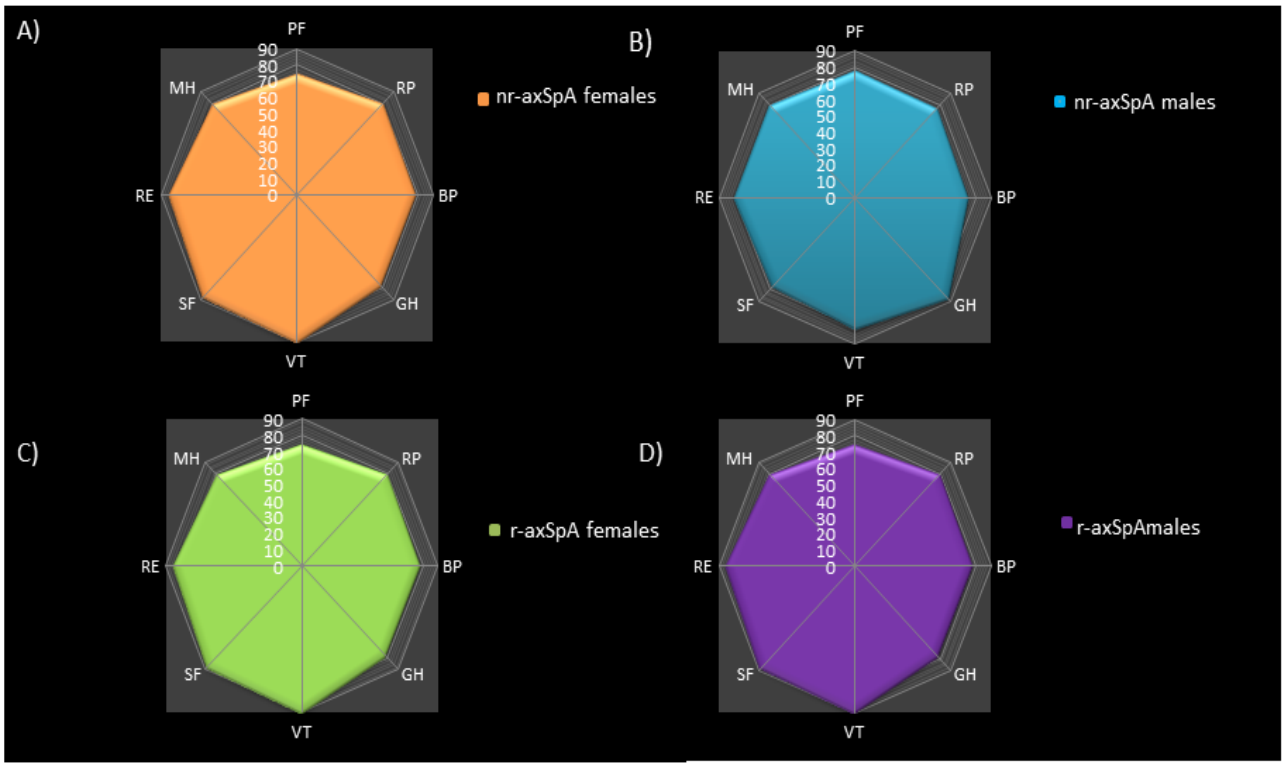


**Figure 3** (Data are simulated for visual illustration). Mean SF-36 scores are shown for axSpA patients. (A) nr-axSpA females (B) nr-axSpA males (C) r-axSpA females (D) r-axSpA males. PF, physical function; RP, role physical; BP, bodily pain; GH, general health; VT ,vitality; SF, social functioning; RE, role emotional; MH, mental health.

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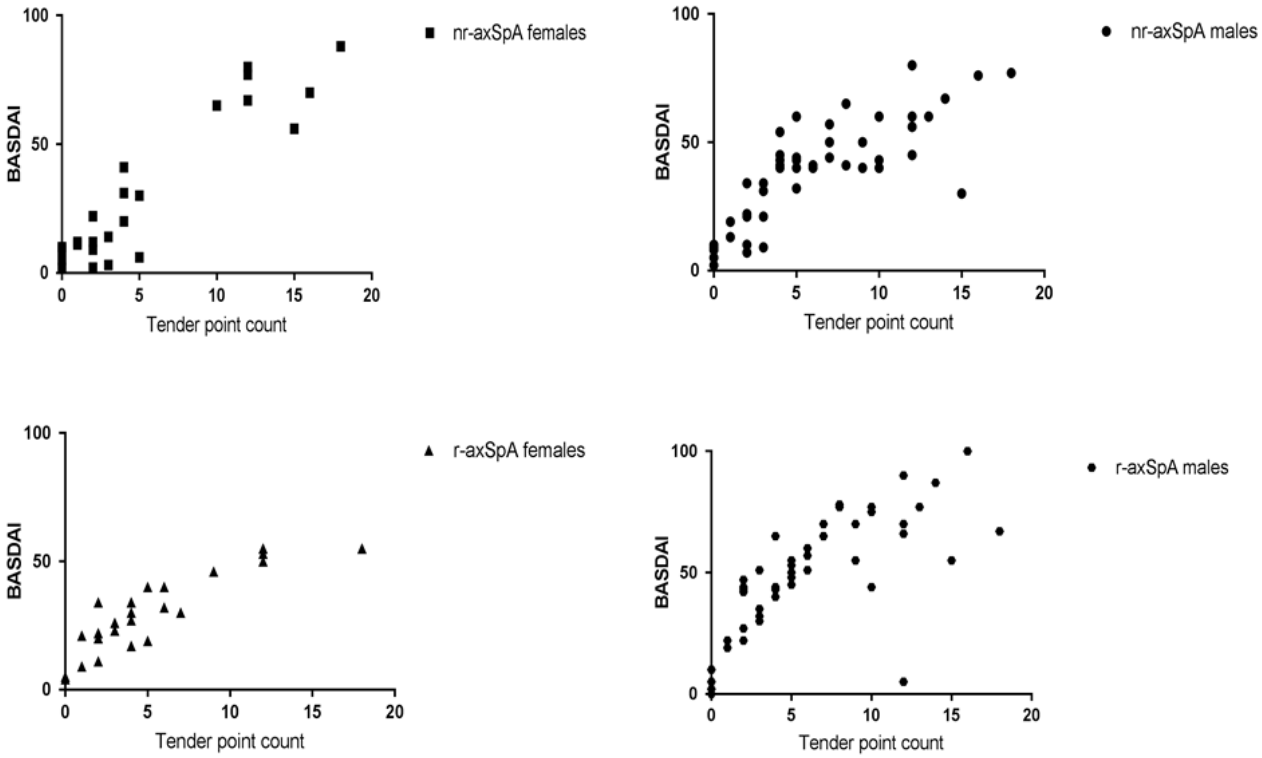
**Appendix A**




**Appendix A.** (Data are simulated for visual illustration) Correlation between tender point count and BASDAI stratified on gender and axSpA classification.