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Increased risk of hypertension associated with spondyloarthritis disease duration: results from the ASAS-COMOSPA study

Running Title: Hypertension and Spondyloarthritis Duration

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ABSTRACT

Objectives: Spondyloarthritis (SpA) is associated with a number of cardiovascular comorbidities. We examined the association of SpA disease duration and delay in diagnosis with cardiovascular-related conditions.

Methods: Using data from the COMOSPA study, the associations between "SpA disease duration" and cardiovascular-related conditions were evaluated in univariable and multivariable logistic regression models. Each model examined one cardiovascular-related factor as dependent and "SpA disease duration" as predictor, adjusted for relevant confounders.

Results: Data from 3923 subjects (median (IQR) SpA disease duration 5.1 (1.3 – 11.8) years) were available for analysis. The main cardiovascular-related conditions were hypertension (22.4%), ischaemic heart disease (2.6%), stroke (1.3%) and diabetes mellitus (5.5%). Hypertension ("ever diagnosis") was associated with SpA disease duration in both univariable and multivariable analysis, with an odds-ratio (OR) of 1.129 (95% CI: 1.072-1.189; p<0.001) for each 5-year increase in SpA disease duration. Other factors associated with hypertension were age, male gender, current BMI, ever steroid therapy and ever synthetic DMARDs therapy, but not NSAIDs. In subgroup analysis, the strongest association of hypertension and disease duration was seen in subjects with axial-only SpA phenotype (OR=1.202, 95%CI: 1.053-1.372) but not in those with peripheral-only SpA (OR=0.902, 95%CI: 0.760-1.070). The other cardiovascular conditions were not associated with SpA disease duration.

Conclusion: Duration of SpA disease in the ASAS-COMOSPA cohort is associated with higher risk of hypertension, particularly in those with axial disease, but not with other cardiovascular-related conditions. The association with hypertension does not appear to be related to NSAID exposure.

INTRODUCTION

Spondyloarthritis (SpA) encompasses a number of related inflammatory conditions, characterized by considerable overlap in clinical features reflecting their shared genetic susceptibility and pathophysiology (1–7). In common with other chronic inflammatory diseases such as rheumatoid arthritis (RA), SpA is associated with an increased risk of cardiovascular comorbidity and increased mortality when compared to the general population (8–10). This association is incorporated in treatment guidelines, with specific recommendations to monitor and prevent cardiovascular disease (11–15). However, many of these recommendations are adapted from RA where this increased risk is better understood (15) and appears to be predominantly related to systemic inflammatory burden, with accumulating evidence for a reduction in cardiovascular events in patients whose RA improves with a range of immunomodulatory treatments (16–19). By contrast, the inflammatory burden in SpA is significantly lower than in RA, with many SpA patients having a normal acute phase. Over the past decade, it has become recognised that, in keeping with their pathophysiological differences, there appear to be differences in the prevalence and type of cardiovascular-related comorbidities seen in RA and SpA. For example, the prevalence of major cardiac events (MACEs) appears to be lower in patients with ankylosing spondylitis (AS; also termed radiographic axial SpA) than those with RA (20,21). In turn, AS is associated with an increased risk of hypertension, while psoriatic arthritis (PsA) is associated with increased diabetes and metabolic syndrome (22–24). These comorbidities have traditionally been studied in patients with distinct SpA sub-groups, but in clinical practice, the distinction is often less clear and phenotypes often overlap.

The ASAS-COMOSPA study is a large, global study designed to evaluate comorbidities in patients with SpA (27). Initial analysis indicated that the most frequent cardiovascular-related condition observed in this population is hypertension, although there is significant geographic variation in comorbidities (27). However, it is not clear whether this increased risk relates to the disease itself, its treatments (particularly NSAIDs and corticosteroids) or other factors. Although determining causality would require large prospective long-term studies, the ASAS-COMOSPA cohort offers an opportunity to explore some of these associations in more detail. The aim of the current report was to evaluate the association of disease duration and delay in diagnosis with the development of cardiovascular-related comorbidities and risk factors in SpA subjects within the ASAS-COMOSPA cohort.

METHODS & MATERIALS

Study design

The current report is an analysis of data from the COMOSPA multicentre and international cross-sectional study, with 22 participating countries throughout five continents (Africa, Asia, Europe, North and South America) as previously reported (27). Briefly, consecutive adult patients attending participating centres who met the ASAS classification criteria (either axial or peripheral) for SpA according to the treating rheumatologist were included (25,26). All information was obtained at a study visit by the study investigator or research nurse during a face-to-face interview with the participant, combined with review of the medical record. In addition to the study visit date, the date of diagnosis and, where relevant, date(s) of first musculoskeletal symptoms (back pain, peripheral joint symptoms, enthesitis or dactylitis) were captured. The following cardiovascular-related comorbidities and risk factors were recorded: ever diagnosis of hypertension, ischaemic heart disease (IHD), stroke, diabetes mellitus and dyslipidaemia.

As described in the original COMOSPA study (27), in each participant country, consecutive adult patients who were able to understand and complete questionnaires were included. The study was conducted according to guidelines for good clinical practice in all countries. Written informed consent was obtained from all sub-jects before enrolment.

Data analysis

Central tendencies in each group are presented by median and interquartile range, unless otherwise stated. Where necessary, the differences between independent groups were examined using Mann Whitney U test. In order to explore the association between SpA chronology and cardiovascular-related conditions, a number of new time variables were created: first, "*SpA Disease Duration"* was defined as the period between age at diagnosis of SpA and the date of completing the survey. Secondly, the "*Delay in SpA Diagnosis"* was defined as the time gap between the first musculoskeletal symptoms of SpA (i.e. the earliest report of back pain, peripheral joint pain, enthesitis or dactylitis) and the diagnosis of SpA (See Supplementary Figure 1).

The association between *SpA disease duration* (defined in 5-year blocks) and cardiovascular-related conditions was examined using univariable and multivariable binary logistic regression. Each model comprised one cardiovascular-related condition as dependent and *SpA disease duration* as predictor adjusted for relevant co-founders in two stages of adjustments. In the first stage (partial adjustment),

confounders were age (continuous), sex (reference: females), current BMI (continuous), history of smoking (pack-year), alcohol (reference: non-drinker), ever use of NSAIDs (reference: none), ever use of steroids (reference: none), ever use of synthetic DMARDs (reference: none), ever use of biological DMARDs (reference: none), other relevant factors and interaction terms, if necessary. Thereafter (full adjustment), the model also included the *delay in SpA diagnosis* (defined in single years due to the shorter duration than SpA disease duration) in addition to all the factors used earlier. The magnitude of the associations is presented using Wald statistics, odds ratios and relevant 95% confidence intervals. Potential collinearity was tested using correlation matrix, tolerance and variation inflation factors (VIF) in a linear regression model. All significance levels set to a *p* value less than 0.05.

Where positive associations were identified, patients were stratified depending on whether their joint involvement was axial, peripheral or mixed. Axial involvement was defined as the clinicians' report in the dataset of "ever suffered from inflammatory chronic (at least 3 months) back pain starting before the age of 45 years", while peripheral involvement was defined as the presence of "ever suffered from peripheral joint disease/symptoms suggestive of enthesitis/dactylitis".

RESULTS

A) Demographic and disease characteristics

A total of 3,923 participants had suitable data for analysis. A small proportion (1.5%) were excluded due to age less than 18 years (n=41), missing date of visit (n=15), missing date of birth (n=4) and missing date of birth and date of visit (n=1).

Baseline demographics showed an age range of 18 to 100, with a median (IQR) of 42 (32-53) years; 64.9% (n=2,547) were male. Female patients were significantly older than males [median (IQR): 44.0 (19.0) vs 41.0 (21.0), p<0.001]. Median BMI was 25.3 (IQR: 6.2). Almost a quarter (23.0%) of the patients were current smokers, 23.4% were ex-smokers and 53.6% had never smoked. Regarding alcohol consumption, 47.8% of patients reported drinking no alcohol, 7.5% were ex-drinkers, 37.5% currently drink less than 3 units/day, and only 6.7% currently drink 3 units or more /day.

The median (IQR) age at SpA diagnosis was 33 (25.0 – 43.0) years while the median (IQR) age at which the first musculoskeletal symptom(s) of SpA appeared was 29.4 (21.9 – 39.9) for the entire group (Figure 1). The estimated median (IQR) SpA disease duration was 5.1 (1.3 – 11.8) years and the estimated median (IQR) delay in SpA diagnosis was 1.1 (0.0 – 5.9) years.

B) Cardiovascular-related conditions

The prevalence of the main cardiovascular-related conditions assessed were: ever diagnosis of hypertension in 872 (22.4%), ever diagnosis of IHD in 102 (2.6%), ever diagnosis of stroke in 50 (1.3%), ever diagnosis of diabetes in 215 (5.5%) and ever diagnosis of dyslipidaemia in 643 (16.6%).

C) Association of *SpA Disease Duration* with Hypertension

An association between the risk of hypertension and SpA disease duration was found in both univariable, and multivariable models (Table 1), the latter conducted with partial and full adjustment. In the partial adjustment model, the risk was calculated taking into account the possible effects and interactions of all main confounders, but without considering the effect of delay in SpA diagnosis. This model showed a statistically significant association between SpA disease duration and hypertension (OR= 1.11, 95% CI: 1.06 – 1.16) (Supplementary Table 1). The full adjustment model included a further adjustment for delay in SpA diagnosis (Table 1 lower rows) and indicated that the risk of having a diagnosis of hypertension increased by 13% per each 5-year increase in the duration of SpA (OR= 1.13, 95% CI: 1.07 – 1.19; p<0.001) (Figure 1).

Confounding variables with significant association with hypertension were: delay in SpA diagnosis (OR=1.01, 95%CI: 1.00 – 1.02; p=0.033), current age (OR=1.09, 95% CI: 1.08 - 1.10; p<0.001), male gender (OR=1.44, 95%CI: 1.17 - 1.77; p<0.001), current BMI (OR=1.09, 95% CI: 1.07 - 1.11; p<0.001), ever use of steroids (OR=1.23, 95% CI: 1.01 - 1.50; p=0.038) and ever use of synthetic DMARDs (OR=1.34, 95% CI: 1.09 - 1.66; p=0.006), but not ever use of NSAIDs or biologic DMARDs (Table 1).

D) Association of *SpA Disease Duration* with Hypertension in SpA subgroups

In order to evaluate whether the association was generalised for SpA or related to joint distribution, participants were stratified into those with axial disease only, peripheral disease only, mixed axial and peripheral disease, any axial disease (axial only plus mixed) and any peripheral (peripheral disease only plus mixed) (Supplementary Figure 2). Stratification by SpA subgroup indicated a stronger association was found in the “axial only” subgroup (OR=1.20, 95% CI: 1.05 - 1.37, p<0.001) compared to “peripheral only” subgroup (OR=0.90, 95% CI: 0.76 - 1.07, p=0.237) (Table 2). Similarly, comparing the “any axial” subgroup to “any peripheral” subgroup showed a slightly stronger risk of hypertension

in the former group. The results in "mixed" axial and peripheral subgroup were comparable to that of entire cohort (Table 2).

Analyses of associations with partial adjustments (all confounders excluding delay in SpA diagnosis) produced similar estimates to those for the full adjustment models.

E) Association of *Delay in SpA Diagnosis* with Hypertension

There was a weak but marginally significant association between hypertension and the *delay in SpA diagnosis* (OR=1.01, 95% CI: 1.00 - 1.02; *p*=0.033) in the entire cohort, indicating a 1% increase in the risk of hypertension for each year of delay in SpA diagnosis (Table 1; Figure 1). Stratifying the results by SpA subgroups revealed that the association was largest in the "any axial" (OR=1.02, 95% CI: 1.01 - 1.03; p=0.004) and "mixed axial and peripheral" subgroups (OR=1.02, 95% CI: 1.01 - 1.03; *p*=0.002) (Table 2).

F) Associations of *SpA Disease Duration* with Other Cardiovascular-related Conditions

Other cardiovascular-related conditions including IHD, stroke, diabetes mellitus and dyslipidaemia were incorporated to logistic regression models, adjusting for relevant confounders (Tables 3 to 6 and summarised in Figure 1) with no associations found with *SpA disease duration*, in either univariable or multivariable models. Similarly, *delay in SpA diagnosis* was not associated with any of these conditions (Tables 3-5, Suppl.Table 2 and Figure 1).

DISCUSSION

The large COMOSPA cohort has allowed for the evaluation of the association of a number of cardiovascular-related conditions with disease duration across the spectrum of SpA. In this analysis, we found that hypertension was associated with increased SpA disease duration and delay in SpA diagnosis, even when adjusted for other confounding factors. This association was stronger in patients with axial disease than in those with peripheral disease. There was no association of SpA disease duration with IHD, stroke, diabetes mellitus or dyslipidaemia.

The association of cardiovascular comorbidities with inflammatory rheumatic conditions is well recognised and widely quoted (11,12,14,15,28). However, most of the data come from RA, which is characterised by high levels of systemic inflammation and where successful reduction in inflammation through treatment with biologics and methotrexate, but not corticosteroids or NSAIDs, is associated with reduced cardiovascular risk (16–19). By contrast, this association is not as clear in SpA, where there are fewer, smaller studies with significant heterogeneity in results (20,29). Several reports have suggested that, when appropriately adjusted for age and gender, the risk of MACEs in PsA and AS may

be less than in RA (20,30,31). In fact, in several AS studies, the lower limit of the 95% confidence interval for the risk of IHD was 1.0 or less (20,21,32), whereas others report IHD rates similar to RA (33–35).

The differences in reported rates of MACEs associated with PsA and AS relate to a number of factors, including cohort size, the definition of disease used and adjustment for confounding factors. Age and gender are particularly important as patients with AS are more likely to be male (therefore already at increased risk for cardiovascular disease) and develop disease at a younger age, so will have had a longer duration of disease by a specified age than patients with RA. Almost two-thirds (65%) of the COMOSPA participants were male, with a median age at SpA diagnosis of 33 years and estimated median SpA disease duration of 5.1 years.

Cross sectional studies can only indicate association and do not imply causality. Attempts have been made to evaluate a possible dose-response relationship between the rheumatic inflammatory burden and the risk of cardiovascular disease. Although there is some evidence to suggest this may also be the case in SpA (38–40), this association is difficult to assess as many of the disease activity measures (eg BASDAI) are subjective and acute phase reactants often do not reflect disease activity.

Cardiovascular-related conditions generally take many years or decades to develop and become evident, so the duration of the underlying SpA disease offers an alternative way to further evaluate the association of these conditions as it represents the cumulative amount of time the patient has had the disease, and any therapies for this, and therefore represents a surrogate of the SpA disease burden. The delay from symptom onset to SpA diagnosis represents the period without diagnosis or specific therapy. In this study, we found that neither the length of SpA disease duration nor the delay in diagnosis were associated with the risk of developing IHD, stroke, diabetes mellitus or dyslipidaemia.

In contrast, we found that the longer the SpA disease duration, the higher the risk of developing hypertension (OR 1.13 for every 5 years of SpA disease duration). Furthermore, delay in SpA diagnosis was associated with a small increase in hypertension (OR 1.01 for every year of delay in SpA diagnosis; 5% increased risk for every 5 years of delay). This increased risk was highest in those patients with axial disease and remained significant, even when corrected for age, gender and other confounding factors. Previous publications have suggested that SpA conditions, particularly AS, are associated with an increased risk of hypertension (20,21,41–43). The mechanism for this association is currently unclear. NSAIDs are known to increase blood pressure (44,45) and remain the mainstay of treatment in axSpA (28), while patients with PsA have an increased risk of metabolic syndrome (22–24).

Interestingly, NSAIDs were not associated with an increased risk of hypertension in this cohort. This may be because almost 90% of participants received NSAIDs at some stage for their symptoms, with no adjustment possible for cumulative dose. Two-thirds (67.8%) of participants had taken NSAIDs within the three months prior to the study assessment. It is also likely that in clinical practice, NSAIDs were avoided or stopped in patients with existing hypertension. Our data therefore suggest that longer SpA disease duration is associated with an increased risk of developing hypertension, but not IHD or stroke.

The study results must be interpreted in the context of the study limitations. COMOSPA is a cross-sectional study and included self-reported data, which may incur recall bias. However, the clinical staff corroborated the information using the participant's medical records. The prevalence of hypertension in this paper (22.4%) cannot be compared to the prevalence reported in the earlier COMOSPA paper (33.5%) as a different definition of hypertension were used (27). We defined hypertension as "ever diagnosis of hypertension", as we wanted to only include participants with confirmed hypertension, whereas the previous paper used a broader definition, which included the current blood pressure reading and history of any antihypertensive medication (27). Similarly, for diabetes mellitus and dyslipidaemia, we also used only "ever diagnosis of" and not the current glucose or lipid levels, respectively, as these were not fasting, and these data fields contained significant missing data, although sensitivity analysis did not reveal any significant difference (data not shown). The study format did not capture the date of onset of hypertension, so it is not possible to comment on the timing relative to the SpA disease course. The study design did not rigorously capture cumulative dose or duration of NSAIDs, so this could not be assessed in the analysis and we were limited to using "ever use of NSAIDs". Patients with IHD or stroke may have been unable to attend clinics or have died, so would not be captured in study selection, leading to underestimation of these comorbidities. The participants were recruited from secondary care clinics, so may not be representative of the wider population of patients with SpA. The impact of this is likely to vary between countries, with global variation in comorbidities evaluated in other COMOSPA-related analyses.

In summary, this study suggests an increased risk of hypertension with longer SpA disease duration, particularly in patients with axial disease, which is not related to NSAID use. Interestingly, disease duration was not associated with an increased risk of the other cardiovascular-related conditions in this cohort, adding further support to the growing literature suggesting there are differences in cardiovascular-related comorbidities between RA and SpA. Blood pressure measurement is a simple, feasible procedure which should be regularly checked in patients with SpA in the clinical setting, particularly in those with longer disease duration.

Contributors

NJG, JCP, RS, HMO, AM and SS contributed to recruitment and data collection. MD and SS analysed the data. MD wrote the first draft of the manuscript. All authors reviewed the data analysis and interpretation, contributed to writing, revising and approving the manuscript.

Competing interests

None declared.

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LIST OF FIGURES AND TABLES:

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Table 1: Association between *SpA Disease Duration* and Hypertension, adjusted for all relevant confounders including *Delay in SpA Diagnosis*; entire cohort

All	Wald	*p* value	OR	95% CI for OR
Univariable				
SpA Disease duration (5y blocks)	253.050	<0.001	1.387	1.332 - 1.444
Multivariable				
SpA Disease duration (5y blocks)	**21.031**	**<0.001**	**1.129**	**1.072 - 1.189**
Delay in SpA Diagnosis	**4.521**	**0.033**	**1.012**	**1.001 - 1.023**
Age (year)	360.371	<0.001	1.089	1.080 - 1.099
Gender (ref: Female)	12.196	<0.001	1.442	1.174 - 1.771
Current BMI	108.154	<0.001	1.089	1.072 - 1.107
Smoking (pack-year)	0.017	0.895	1.000	0.993 - 1.006
Alcohol (ref: Never)	5.613	0.132		
Ex-drinker	0.838	0.360	1.185	0.824 - 1.706
Current, <3 Units	2.848	0.092	0.835	0.678 - 1.029
Current, >=3 Units	1.353	0.245	0.794	0.539 - 1.171
Ever use of NSAIDs	0.514	0.473	1.125	0.816 - 1.551
Ever use of Steroids	4.308	0.038	1.231	1.012 - 1.497
Ever use of Synthetic DMARDs	7.451	0.006	1.341	1.086 - 1.655
Ever use of Biologic DMARDs	0.244	0.622	1.050	0.866 - 1.272

Table 2: Association between hypertension and *SpA Disease Duration* or *Delay in SpA Diagnosis* in entire group and subgroups of SpA (Multivariable)

	Group N		Wald	*p* value	OR	95% CI for OR
SpA Disease Duration (5-year blocks)[1]						
Entire group	3923		21.031	<0.001	1.129	1.072 - 1.189
Any Axial	3393		29.471	<0.001	1.170	1.106 - 1.239
Any Peripheral	2688		12.591	<0.001	1.109	1.047 - 1.174
Axial only	1138		7.393	0.007	1.202	1.053 - 1.372
Peripheral only	434		1.397	0.237	0.902	0.760 - 1.070
Mixed Axial & Peripheral	2254		20.240	<0.001	1.158	1.086 - 1.234
Delay in SpA Diagnosis[2]						
Entire group	3923		4.521	0.033	1.012	1.001 - 1.023
Any Axial	3393		8.397	0.004	1.017	1.006 - 1.029
Any Peripheral	2688		5.019	0.025	1.013	1.002 - 1.025
Axial only	1138		0.321	0.571	1.008	0.980 - 1.038
Peripheral only	434		1.026	0.311	0.978	0.936 - 1.021
Mixed Axial & Peripheral	2254		9.420	0.002	1.020	1.007 - 1.033

Note: 1: The model adjusted to potential confounders including age, gender, BMI, smoking, alcohol consumption, ever use of NASIDs, ever use of steroids, ever used of synthetic DMARDs, ever use of biologic DMARDs, and *Delay in SpA diagnosis*; **2:** adjusted to all above factors, including *SpA disease duration* but not *Delay in SpA diagnosis*.

Table 3: Association between *SpA Disease Duration* and Ischaemic Heart Disease, adjusted for all relevant confounders including *Delay in SpA Diagnosis*; entire cohort

All	Wald	*p* value	OR	95% CI for OR
Univariable				
SpA Disease Duration (5y blocks)	55.447	<0.001	1.333	1.236 - 1.438
Multivariable				
SpA Disease Duration (5y blocks)	**0.142**	**0.706**	**1.019**	**0.925 - 1.123**
Delay in SpA Diagnosis	**0.059**	**0.808**	**1.003**	**0.982 - 1.024**
Age (year)	50.129	<0.001	1.079	1.056 - 1.101
Gender (ref: Female)	6.710	0.010	2.100	1.198 - 3.681
Current BMI	1.430	0.232	1.023	0.986 - 1.062
Smoking (pack-year)	4.540	0.033	1.013	1.001 - 1.024
Alcohol (ref: Never)	1.201	0.753		
Ex-drinker	0.104	0.747	1.140	0.515 - 2.524
Current, <3 Units	0.478	0.489	0.835	0.500 - 1.393
Current, >=3 Units	0.546	0.460	0.713	0.291 - 1.747
Ever use of NSAIDs	0.450	0.502	1.301	0.603 - 2.807
Ever use of Steroids	1.597	0.206	1.353	0.847 - 2.161
Ever use of Synthetic DMARDs	2.675	0.102	1.564	0.915 - 2.673
Ever use of Biologic DMARDs	0.108	0.742	1.081	0.679 - 1.722
Ever Dx of HTN	25.855	<0.001	4.436	2.498 - 7.877
Ever Dx of Diabetes	13.868	<0.001	2.774	1.621 - 4.745

Table 4: Association between *SpA Disease Duration* and Stroke, adjusted for all relevant confounders including *Delay in SpA Diagnosis*; entire cohort

All	Wald	*p* value	OR	95% CI for OR
Univariable				
SpA Disease Duration (5y blocks)	20.107	<0.001	1.287	1.153 - 1.437
Multivariable				
SpA Disease Duration (5y blocks)	**0.001**	**0.979**	**0.998**	**0.865 - 1.151**
Delay in SpA Diagnosis	**0.102**	**0.749**	**1.005**	**0.975 - 1.036**
Age (year)	6.969	0.008	1.042	1.011 - 1.074
Gender (ref: Female)	0.004	0.952	0.978	0.472 - 2.025
Current BMI	0.495	0.482	0.980	0.925 - 1.037
Smoking (pack-year)	5.121	0.024	1.017	1.002 - 1.033
Alcohol (ref: Never)	1.405	0.704		
Ex-drinker	0.184	0.668	0.750	0.201 - 2.796
Current, <3 Units	0.268	0.605	1.202	0.598 - 2.417
Current, >=3 Units	0.551	0.458	0.561	0.122 - 2.578
Ever use of NSAIDs	0.126	0.723	1.219	0.408 - 3.644
Ever use of Steroids	0.396	0.529	0.804	0.408 - 1.586
Ever use of Synthetic DMARDs	2.222	0.136	0.593	0.298 - 1.179
Ever use of Biologic DMARDs	0.019	0.891	1.046	0.546 - 2.006
Ever Dx of HTN	21.433	<0.001	8.843	3.514 - 22.252
Ever Dx of Diabetes	2.173	0.140	1.843	0.817 - 4.156
FHx of MI	6.436	0.011	0.423	0.217 - 0.822

Table 4: Association between *SpA Disease Duration* and Stroke, adjusted for all relevant confounders including *Delay in SpA Diagnosis*; entire cohort

All	Wald	*p* value	OR	95% CI for OR
Univariable				
SpA Disease Duration (5y blocks)	20.107	<0.001	1.287	1.153 - 1.437
Multivariable				
SpA Disease Duration (5y blocks)	**0.001**	**0.979**	**0.998**	**0.865 - 1.151**
Delay in SpA Diagnosis	**0.102**	**0.749**	**1.005**	**0.975 - 1.036**
Age (year)	6.969	0.008	1.042	1.011 - 1.074
Gender (ref: Female)	0.004	0.952	0.978	0.472 - 2.025
Current BMI	0.495	0.482	0.980	0.925 - 1.037
Smoking (pack-year)	5.121	0.024	1.017	1.002 - 1.033
Alcohol (ref: Never)	1.405	0.704		
Ex-drinker	0.184	0.668	0.750	0.201 - 2.796
Current, <3 Units	0.268	0.605	1.202	0.598 - 2.417
Current, >=3 Units	0.551	0.458	0.561	0.122 - 2.578
Ever use of NSAIDs	0.126	0.723	1.219	0.408 - 3.644
Ever use of Steroids	0.396	0.529	0.804	0.408 - 1.586
Ever use of Synthetic DMARDs	2.222	0.136	0.593	0.298 - 1.179
Ever use of Biologic DMARDs	0.019	0.891	1.046	0.546 - 2.006
Ever Dx of HTN	21.433	<0.001	8.843	3.514 - 22.252
Ever Dx of Diabetes	2.173	0.140	1.843	0.817 - 4.156
FHx of MI	6.436	0.011	0.423	0.217 - 0.822

Table 5: Association between *SpA Disease Duration* and Diabetes, adjusted for all relevant confounders including *Delay in SpA Diagnosis*; entire cohort

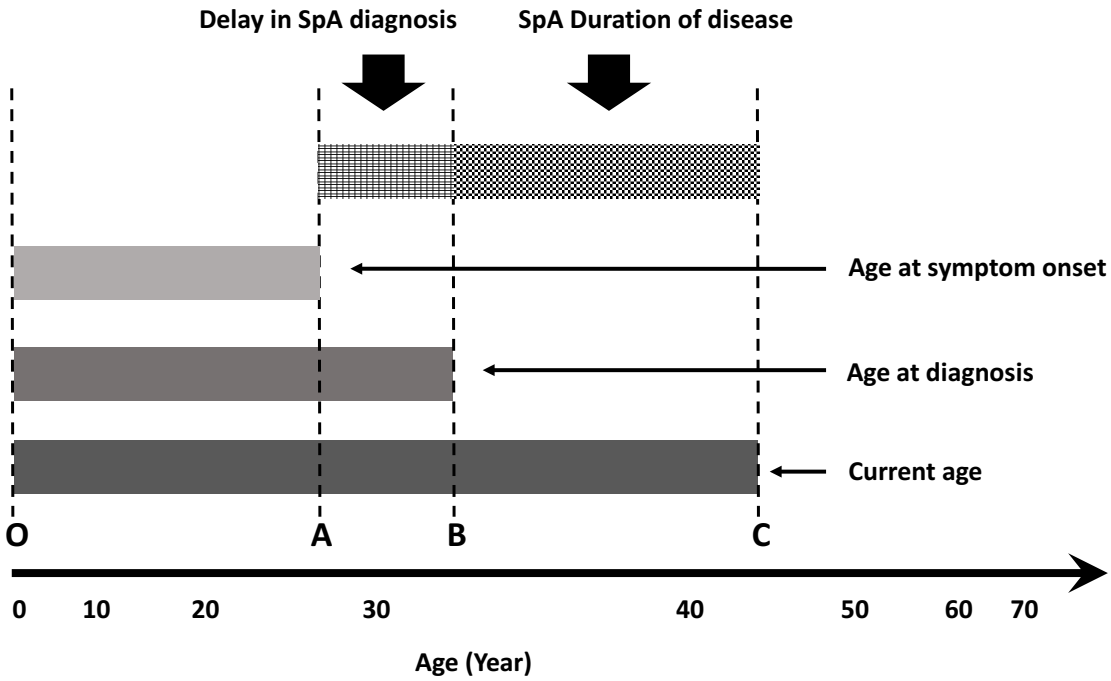
All	Wald	*p* value	OR	95% CI for OR
Univariable				
SpA Disease Duration (5y blocks)	27.441	<0.001	1.184	1.112 - 1.262
Multivariable				
SpA Disease Duration (5y blocks)	**1.867**	**0.172**	**0.943**	**0.868 - 1.026**
Delay in SpA Diagnosis	**0.440**	**0.507**	**0.994**	**0.977 - 1.012**
Age (year)	41.189	<0.001	1.050	1.035 - 1.066
Gender (ref: Female)	5.254	0.022	1.543	1.065 - 2.235
Current BMI	63.528	<0.001	1.095	1.071 - 1.120
Smoking (pack-year)	0.095	0.757	1.002	0.991 - 1.012
Alcohol (ref: Never)	14.507	0.002		
Ex-drinker	0.109	0.742	1.100	0.625 - 1.935
Current, <3 Units	12.746	<0.001	0.492	0.333 - 0.726
Current, >=3 Units	0.729	0.393	0.750	0.388 - 1.450
Ever use of NSAIDs	0.170	0.680	0.897	0.534 - 1.506
Ever use of Steroids	0.369	0.544	1.111	0.791 - 1.561
Ever use of Synthetic DMARDs	0.521	0.471	1.149	0.788 - 1.677
Ever use of Biologic DMARDs	1.862	0.172	1.263	0.903 - 1.768
Ever Dx of HTN	52.893	<0.001	4.067	2.787 - 5.936
Ever Dx of Stroke	1.944	0.163	1.757	0.796 - 3.881
FHx of MI	3.712	0.054	0.695	0.480 - 1.006

Supplementary Figures and Tables:

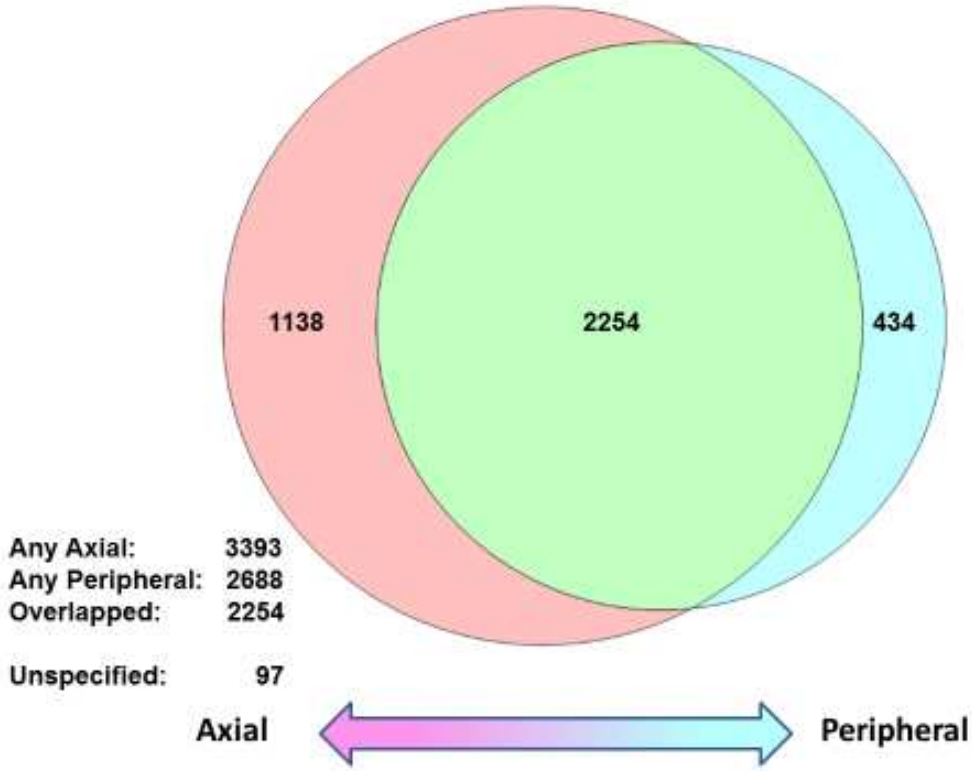
Supplementary Figure 1: Definition of "SpA Duration of Disease" and "Delay in SpA Diagnosis" terms used in the study

Supplementary Figure 2: Subgroups of SpA based on joint distribution

Supplementary. Table 1: Association between *SpA Disease Duration* and Hypertension, partially-adjusted for all relevant confounders; entire cohort



Supplementary Figure 1: Definition of "SpA Duration of Disease" and "Delay in SpA Diagnosis" terms used in the study



Supplementary Figure 2: Subgroups of SpA based on joint distribution

Supplementary Table 1: Association between SpA Disease Duration and Hypertension, partially-adjusted for all relevant confounders; entire cohort

All	Wald	*p* value	OR	95% CI for OR
Univariable				
Disease duration (5y blocks)	267.839	<0.001	1.392	1.338 - 1.448
Multivariable				
Disease duration (5y blocks)	**17.785**	**<0.001**	**1.109**	**1.057 - 1.164**
Age (year)	432.227	<0.001	1.093	1.084 - 1.102
Gender (ref: Female)	13.591	<0.001	1.462	1.195 - 1.790
Current BMI	112.437	<0.001	1.090	1.072 - 1.107
Smoking (pack-year)	0.000	1.000	1.000	0.994 - 1.007
Alcohol (ref: Never)	3.715	0.294		
Ex-drinker	1.094	0.296	1.206	0.849 - 1.712
Current, <3 Units	1.408	0.235	0.884	0.720 - 1.084
Current, >=3 Units	0.464	0.496	0.879	0.605 - 1.275
Ever use of NSAIDs	1.001	0.317	1.173	0.858 - 1.602
Ever use of Steroids	4.790	0.029	1.239	1.023 - 1.500
Ever use of Synthetic DMARDs	5.849	0.016	1.284	1.049 - 1.573
Ever use of Biologic DMARDs	0.532	0.466	1.072	0.889 - 1.293

Supplementary Table 2: Association between *SpA Disease Duration* and Dyslipidaemia, adjusted for all relevant confounders including *Delay in SpA Diagnosis*; entire cohort

All	Wald	*p* value	OR	95% CI for OR
Univariable				
SpA Disease Duration (5y blocks)	102.593	<0.001	1.242	1.191 - 1.295
Multivariable				
SpA Disease Duration (5y blocks)	**0.006**	**0.938**	**0.998**	**0.944 - 1.055**
Delay in SpA Diagnosis	**0.090**	**0.764**	**0.998**	**0.986 - 1.010**
Age (year)	82.217	<0.001	1.044	1.035 - 1.054
Gender (ref: Female)	3.555	0.059	1.243	0.991 - 1.559
Current BMI	14.153	<0.001	1.034	1.016 - 1.052
Smoking (pack-year)	1.387	0.239	1.004	0.997 - 1.011
Alcohol (ref: Never)	1.210	0.751		
Ex-drinker	0.514	0.473	1.157	0.777 - 1.722
Current, <3 Units	0.841	0.359	1.113	0.885 - 1.401
Current, >=3 Units	0.003	0.956	0.988	0.645 - 1.513
Ever use of NSAIDs	8.701	0.003	1.764	1.210 - 2.572
Ever use of Steroids	0.716	0.397	1.097	0.886 - 1.358
Ever use of Synthetic DMARDs	17.278	<0.001	1.653	1.304 - 2.096
Ever use of Biologic DMARDs	2.770	0.096	1.195	0.969 - 1.474
Ever Dx of HTN	81.697	<0.001	2.893	2.298 - 3.642
Ever Dx of Stroke	43.131	<0.001	3.319	2.320 - 4.748
FHx of MI	4.408	0.036	2.132	1.052 - 4.324
Ever Dx of Diabetes	7.695	0.006	1.428	1.110 - 1.837