Increased Risk of Hypertension Associated with Spondyloarthritis Disease Duration: Results from the ASAS-COMOSPA Study

Mohammad H. Derakhshan, Nicola J. Goodson, Jonathan C. Packham, Raj Sengupta, Anna Molto, Helena Marzo-Ortega, and Stefan Siebert, and the BRITSpA and COMOSPA Investigators

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

Methods. Using data from the COMOSPA study, the associations between SpA disease duration and CV-related conditions were evaluated in univariable and multivariable logistic regression models. Each model examined 1 CV-related factor as dependent and "SpA disease duration" as a predictor, adjusted for relevant confounders.

Results. Data from 3923 subjects (median SpA disease duration 5.1 yrs, interquartile range 1.3–11.8 yrs) were available for analysis. The main CV-related conditions were hypertension (HTN; 22.4%), ischemic heart disease (2.6%), stroke (1.3%), and diabetes mellitus (5.5%). HTN was associated with SpA disease duration in both univariable and multivariable analysis, with an 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 HTN were age, male sex, current body mass index, ever steroid therapy, and ever synthetic disease-modifying antirheumatic drug therapy, but not nonsteroidal antiinflammatory drugs (NSAID). In subgroup analysis, the strongest association of HTN and disease duration was seen in subjects with the 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 CV conditions were not associated with SpA disease duration.

Conclusion. Duration of SpA disease in the ASAS-COMOSPA cohort is associated with higher odds of HTN, particularly in those with axial disease, but not with other CV-related conditions. The association with HTN does not appear to be related to NSAID exposure. (J Rheumatol First Release January 15 2019; doi:10.3899/jrheum.180538)

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From the Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow; Academic Rheumatology, Musculoskeletal Biology, Institute of Chronic Disease and Ageing, University of Liverpool, Liverpool; Haywood Rheumatology Centre, Stoke on Trent; Keele University, Keele; Royal National Hospital for Rheumatic Diseases, Bath, UK; Paris Descartes University, Hôpital Cochin, Paris, France; UK National Institute for Health Research (NIHR) Leeds Biomedical Research Centre, Leeds Teaching Hospitals Trust, and Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), University of Leeds, Leeds, UK.

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M.H. Derakhshan, MD, FRCP, Clinical Epidemiologist, Institute of Infection, Immunity and Inflammation, University of Glasgow; N.J. Goodson, MRCP, PhD, Senior Lecturer in Rheumatology, Academic Rheumatology, Musculoskeletal Biology, Institute of Chronic Disease and Ageing, University of Liverpool; J.C. Packham, DM, FRCP, Senior Lecturer in Rheumatology, Haywood Rheumatology Centre, and Keele University; R. Sengupta, MBBS, FRCP, Consultant Rheumatologist, Royal National Hospital for Rheumatic Diseases; A. Molto, MD, PhD, Consultant Rheumatologist, Paris Descartes University, Hôpital Cochin; H. Marzo-Ortega, MRCP, PhD, Consultant Rheumatologist, NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals Trust and LIRMM, University of Leeds; S. Siebert, PhD, FRCP, Senior Lecturer in Rheumatology, Institute of Infection, Immunity and Inflammation, University of Glasgow.

Address correspondence to S. Siebert, Institute of Infection, Immunity and Inflammation, University of Glasgow, Sir Graeme Davis Building, 120 University Place, Glasgow, G12 8TA, UK.
E-mail: Stefan.Siebert@glasgow.ac.uk

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Spondyloarthritis (SpA) encompasses a number of related inflammatory conditions, characterized by considerable overlap in clinical features, reflecting their shared genetic susceptibility and pathophysiology[1,2,3,4,5,6,7]. In common with other chronic inflammatory diseases such as rheumatoid arthritis (RA), SpA is associated with an increased risk of cardiovascular (CV) comorbidity and increased mortality when compared to the general population[8,9,10]. This associ-

ation is incorporated in treatment guidelines, with specific recommendations to monitor and prevent CV disease[11,12,13,14,15]. However, many of these recommendations are adapted from RA, for which this increased risk is better understood[15]. The risk appears to be predominantly related to systemic inflammatory burden, with accumulating evidence for a reduction in CV events in patients whose RA improves with a range of immunomodulatory treatments[16,17,18,19]. By contrast, the inflammatory burden in SpA is significantly lower than in RA, with many patients with SpA having a normal acute phase. Over the past decade, it has been recognized that, in keeping with their pathophysiological differences, there appear to be differences in the prevalence and type of CV-related comorbidities seen in RA and SpA. For example, the prevalence of major adverse cardiac events (MACE) appears to be lower in patients with ankylosing spondylitis (AS; also termed radiographic axial SpA) than in those with RA[20,21]. In turn, AS is associated with an increased risk of hypertension (HTN), while psoriatic arthritis (PsA) is associated with increased diabetes and metabolic syndrome[22,23,24]. These comorbidities have traditionally been studied in patients with distinct SpA subgroups, but in clinical practice, the distinction is often less clear and phenotypes often overlap.

The ASAS-COMOSPA study (Assessment of Spondyloarthritis international Society–COMOrbidities in Spondylo-Arthritis) is a large global study designed to evaluate comorbidities in patients with SpA[25]. Initial analysis indicated that the most frequent CV-related condition observed in this population is HTN, although there is significant geographic variation in comorbidities[25]. However, it is not clear whether this increased risk relates to the disease itself, its treatments [particularly nonsteroidal antiinflammatory drugs (NSAID) and corticosteroids], or other factors. Although determining causality would require large prospective longterm studies, the ASAS-COMOSPA cohort offers an opportunity to examine some of these associations in more detail. The aim of our current report was to evaluate the association of disease duration and delay in diagnosis with the development of CV-related comorbidities and risk factors in SpA subjects within the ASAS-COMOSPA cohort.

MATERIALS AND METHODS

Study design. The current report is an analysis of data from the COMOSPA multicenter and international cross-sectional study, with 22 participating countries throughout 5 continents (Africa, Asia, Europe, North and South America) as previously reported[25]. Briefly, consecutive adult patients attending participating centers who met the ASAS classification criteria (either axial or peripheral) for SpA according to the treating rheumatologist were included[26,27]. 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 recorded. The following CV-related comorbidities and risk factors were recorded and confirmed in the medical records: ever diagnosis of HTN, ischemic heart disease (IHD), stroke, diabetes mellitus, and dyslipidemia.

As described in the original COMOSPA paper[25], in each participating 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 subjects before enrollment.

Data analysis. Central tendencies in each group are presented by median and interquartile range (IQR), unless otherwise stated based on results of normality tests conducted for each group of data. Where necessary, the differences between independent groups were examined using Mann-Whitney U test. To study the association between SpA chronology and CV-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. Second, 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 (Supplementary Figure 1, available with the online version of this article).

The association between SpA disease duration (defined in 5-yr blocks) and CV-related conditions was examined using univariable and multivariable binary logistic regression. Each model comprised 1 CV-related condition as dependent and SpA disease duration as predictor adjusted for relevant confounders in 2 stages of adjustments. In the first stage (partial adjustment), confounders were age (continuous), sex (reference: females), current body mass index (BMI; continuous), history of smoking (pack-year), alcohol (reference: non-drinker), ever use of NSAID (reference: none), ever use of steroids (reference: none), ever use of synthetic disease-modifying antirheumatic drugs (DMARD; reference: none), ever use of biological DMARD (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 because of 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, OR, and relevant 95% CI. Potential collinearity was tested using correlation matrix, tolerance, and variation inflation factors in a linear regression model. All significance levels were set to a p value < 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 clinician 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

Demographic and disease characteristics. A total of 3923 participants had suitable data for analysis. A small proportion (1.5%) were excluded because of age < 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). The number of participants from each country is shown in Supplementary Table 1, available with the online version of this article.

Baseline demographics showed an age range of 18 to 100 years, with a median (IQR) of 42 (32–53) years; 64.9% (n = 2547) 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), more than 33.4% were overweight (BMI 25–29.9), and 19.5% were obese (BMI ≥ 30). 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 < 3 units/day, and only 6.7% currently drink 3 units or more/day.

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

CV-related conditions. The prevalence of the main CV-related conditions assessed were ever diagnosis of HTN 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 dyslipidemia in 643 (16.6%).

Association of SpA disease duration with HTN. An association between the HTN 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 HTN (OR 1.11, 95% CI 1.06–1.16; Supplementary Table 2, available with the online version of this article). The full adjustment model included a further adjustment for delay in SpA diagnosis (Table 1) and indicated that the odds of having a diagnosis of HTN 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 HTN 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 sex (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 DMARD (OR 1.34, 95% CI 1.09–1.66; p = 0.006), but not ever use of NSAID or biologic DMARD (Table 1).

Association of SpA disease duration with HTN in SpA subgroups. To evaluate whether the association was generalized 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, available with the online version of this article). 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 = 0.007) 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 the "any peripheral" subgroup showed slightly higher odds of HTN in the former group. The results in the "mixed" axial and peripheral subgroup were comparable to that of the 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.

Association of delay in SpA diagnosis with HTN. There was a weak but marginally significant association between HTN 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 odds of HTN 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).

Associations of SpA disease duration with other CV-related

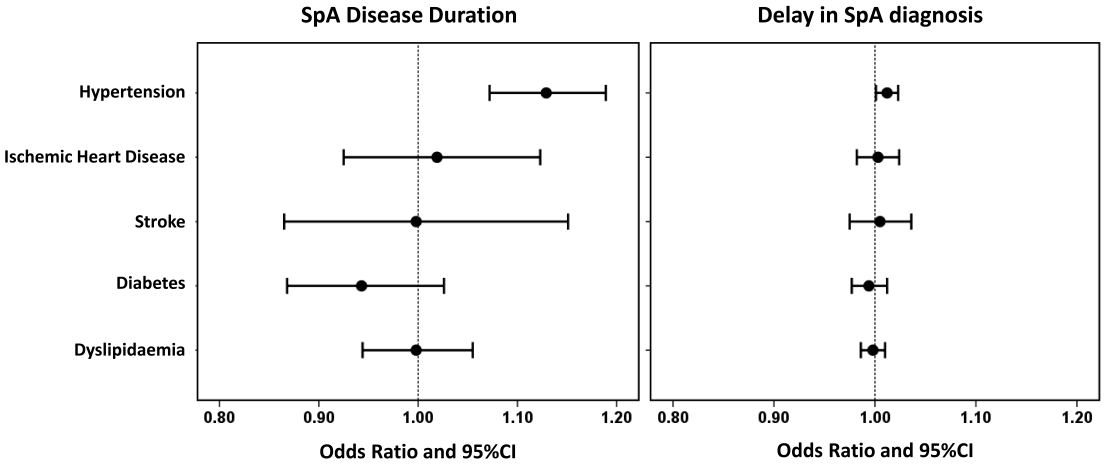

Figure 1. Summary results of logistic regression showing OR (black circles) and 95% CI (lines) for the associations of SpA disease duration and delay in diagnosis with the various cardiovascular-related conditions. SpA: spondyloarthritis.

Table 1. Association between SpA disease duration and hypertension, adjusted for all relevant confounders including delay in SpA diagnosis; entire cohort.

All	Wald Test	p	OR	95% CI for OR
Univariable				
SpA disease duration, 5-yr blocks	253.050	< 0.001	1.387	1.332–1.444
Multivariable				
SpA disease duration, 5-yr 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, yrs	360.371	< 0.001	1.089	1.080–1.099
Sex (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-yr	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/day	2.848	0.092	0.835	0.678–1.029
Current, ≥ 3 units/day	1.353	0.245	0.794	0.539–1.171
Ever use of NSAID	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 DMARD	7.451	0.006	1.341	1.086–1.655
Ever use of biologic DMARD	0.244	0.622	1.050	0.866–1.272

SpA: spondyloarthritis; BMI: body mass index; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.

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 Test	p	OR	95% CI
SpA disease duration (5-yr 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 and 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 and peripheral	2254	9.420	0.002	1.020	1.007–1.033

[1] The model adjusted to potential confounders including age, sex, BMI, smoking, alcohol consumption, ever use of NSAID, ever use of steroids, ever use of synthetic DMARD, ever use of biologic DMARD, and delay in SpA diagnosis. [2] Adjusted to all above factors, including SpA disease duration but not delay in SpA diagnosis. SpA: spondyloarthritis; BMI: body mass index; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs.

conditions. Other CV-related conditions including IHD, stroke, diabetes mellitus (Tables 3–5, and summarized in Figure 1), and dyslipidemia (Supplementary Table 3, available with the online version of this article) were incorporated into logistic regression models, adjusting for relevant confounders 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.

DISCUSSION

The large COMOSPA cohort has allowed for the evaluation of the association of a number of CV-related conditions with disease duration across the spectrum of SpA. In this analysis, we found that HTN 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 dyslipidemia.

The association of CV comorbidities with inflammatory rheumatic conditions is well recognized and widely quoted[11,12,13,14,15]. However, most of the data come from RA, with fewer, smaller studies with significant heterogeneity in

Table 3. Association between SpA disease duration and ischemic heart disease, adjusted for all relevant confounders including delay in SpA diagnosis; entire cohort.

All	Wald Test	p	OR	95% CI
Univariable				
SpA disease duration, 5-yr blocks	55.447	< 0.001	1.333	1.236–1.438
Multivariable				
SpA disease duration, 5-yr 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, yrs	50.129	< 0.001	1.079	1.056–1.101
Sex (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-yr	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/day	0.478	0.489	0.835	0.500–1.393
Current, ≥ 3 units/day	0.546	0.460	0.713	0.291–1.747
Ever use of NSAID	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 DMARD	2.675	0.102	1.564	0.915–2.673
Ever use of biologic DMARD	0.108	0.742	1.081	0.679–1.722
Ever diagnosis of HTN	25.855	< 0.001	4.436	2.498–7.877
Ever diagnosis of diabetes	13.868	< 0.001	2.774	1.621–4.745

SpA: spondyloarthritis; BMI: body mass index; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; HTN: hypertension.

Table 4. Association between SpA disease duration and stroke, adjusted for all relevant confounders including delay in SpA diagnosis; entire cohort.

All	Wald Test	p	OR	95% CI
Univariable				
SpA disease duration, 5-yr blocks	20.107	< 0.001	1.287	1.153–1.437
Multivariable				
SpA disease duration, 5-yr 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, yrs	6.969	0.008	1.042	1.011–1.074
Sex (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-yr	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/day	0.268	0.605	1.202	0.598–2.417
Current, ≥ 3 units/day	0.551	0.458	0.561	0.122–2.578
Ever use of NSAID	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 DMARD	2.222	0.136	0.593	0.298–1.179
Ever use of biologic DMARD	0.019	0.891	1.046	0.546–2.006
Ever diagnosis of HTN	21.433	< 0.001	8.843	3.514–22.252
Ever diagnosis 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

SpA: spondyloarthritis; BMI: body mass index; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; HTN: hypertension; FHx: family history; MI: myocardial infarction.

results in SpA[20,28]. Several reports have suggested that, when appropriately adjusted for age and sex, the risk of MACE in PsA and AS may be less than in RA[20,29,30]. In fact, in several AS studies, the lower limit of the 95% CI for the odds of IHD was 1.0 or less[20,21,31], whereas others report IHD rates similar to RA[32,33,34]. The prospective CARdiovascular in rheuMAtology (CARMA) project reported higher prevalence of CV disease in RA than in AS and PsA, with disease duration associated with increased risk of CV risk factors in all groups[35].

Table 5. Association between SpA disease duration and diabetes, adjusted for all relevant confounders including delay in SpA diagnosis; entire cohort.

All	Wald Test	p	OR	95% CI
Univariable				
SpA disease duration, 5-yr blocks	27.441	< 0.001	1.184	1.112–1.262
Multivariable				
SpA disease duration, 5-yr 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, yrs	41.189	< 0.001	1.050	1.035–1.066
Sex (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-yr	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/day	12.746	< 0.001	0.492	0.333–0.726
Current, ≥ 3 units/day	0.729	0.393	0.750	0.388–1.450
Ever use of NSAID	0.170	0.680	0.897	0.534–1.506
Ever use of steroid	0.369	0.544	1.111	0.791–1.561
Ever use of synthetic DMARD	0.521	0.471	1.149	0.788–1.677
Ever use of biologic DMARD	1.862	0.172	1.263	0.903–1.768
Ever diagnosis of HTN	52.893	< 0.001	4.067	2.787–5.936
Ever diagnosis 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

SpA: spondyloarthritis; BMI: body mass index; NSAID: nonsteroidal antiinflammatory drugs; DMARD: disease-modifying antirheumatic drugs; HTN: hypertension; FHx: family history; MI: myocardial infarction.

The differences in reported rates of MACE associated with PsA and AS relate to several factors, including cohort size, the definition of disease used, and adjustment for confounding factors. Age and sex are particularly important because patients with AS are more likely to be male (therefore already at increased risk for CV disease) and to develop disease at a younger age, and 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 CV disease. Although there is some evidence to suggest this may also be the case in SpA[36,37,38], this association is difficult to assess in SpA because many of the disease activity measures [e.g., Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)] are subjective, and acute-phase reactants often do not reflect disease activity.

CV-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. The duration of the SpA disease 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 our study, we found that neither the length of SpA disease duration nor the delay in diagnosis were associated with development of IHD, stroke, diabetes mellitus, or dyslipidemia.

In contrast, we found that the longer the SpA disease duration, the higher the odds of developing HTN (OR 1.13 for every 5 yrs of SpA disease duration). Further, delay in SpA diagnosis was associated with a small increase in HTN (OR 1.01 for every year of delay in SpA diagnosis; 5% increased risk for every 5 yrs of delay). Previous publications have suggested that SpA conditions, particularly AS, are associated with an increased risk of HTN[20,21,39,40,41]. The mechanism for this association is currently unclear. NSAID are known to increase blood pressure[42,43] and remain the mainstay of treatment in axial SpA (axSpA)[13], while patients with PsA have an increased risk of metabolic syndrome[22,23,24]. Interestingly, NSAID were not associated with HTN in this cohort. This may be because almost 90% of participants received NSAID at some stage for their symptoms, with no adjustment possible for cumulative dose. Two-thirds (67.8%) of participants had taken NSAID within the 3 months prior to the study assessment. It is also likely that in clinical practice, NSAID were avoided or stopped in patients with existing HTN.

The association of increased odds of HTN with SpA disease duration was strongest in those patients with axial disease and remained significant, even when corrected for age, sex, and other confounding factors. Because people with

AS have longer disease duration, are more likely to be male, and have been shown to be more likely to have subclinical atherosclerosis than those with nonradiographic axSpA[44], it is possible that the association with HTN would be even more evident in the AS subgroup. However, the available data in this study do not allow us to confidently distinguish AS from nonradiographic axSpA.

Our data therefore suggest that longer SpA disease duration is associated with increased odds of developing HTN, but not IHD or stroke. It should be noted that the cross-sectional nature of this study in a selected group of patients with SpA means that no comment can be made regarding the overall prevalence in comparison to the general population. The reasons for the observed differences in HTN and the other CV-related comorbidities in the literature and our study are unclear. It is possible that older age and longer disease duration may have unveiled other CV-related associations. However, from the available literature, it does appear that the prevalence of MACE is higher in RA than in AS and PsA[20,29,30], suggesting that SpA conditions may have less effect on MACE, possibly owing to the lower inflammatory burden. In contrast, metabolic syndrome, which includes HTN, appears to be higher in PsA[22,23,24]. The reason for the increased association of HTN with AS, reported in the literature[20,21,41] and observed with prolonged disease duration in our study, remains unexplained. While our study did not indicate this was related to NSAID use, these agents are a mainstay of treatment for this condition, and for a long time were the only effective therapy, so it is still possible there is an effect of prolonged use of high-dose NSAID that cannot be detected in our study owing to the limitations related to the NSAID data collection (highlighted elsewhere). This is worthy of further study, including whether the association with HTN is altered by reduced use of NSAID since the introduction of biologic therapies.

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 participants' medical records. The prevalence of HTN in this paper (22.4%) cannot be compared to the prevalence reported in the earlier COMOSPA paper (33.5%) because a different definition of HTN was used[27]. We defined HTN as "ever diagnosis of HTN," because we wanted to include only participants with confirmed HTN, whereas the previous paper used a broader definition, which included the current blood pressure reading and history of any antihypertensive medication[27]. Participants with undiagnosed HTN would not be identified in our analysis, but because of the cross-sectional nature of the study with a single study timepoint, we did not wish to incorrectly attribute a diagnosis of HTN on the basis of a single blood pressure reading. Similarly, for diabetes mellitus and dyslipidemia, we also used only "ever diagnosis of" and not the current glucose or lipid levels, respectively, because these were not fasting, and these data fields had significant missing data, although sensitivity analysis did not reveal any significant difference (data not shown). The study format did not record the date of onset of HTN, so it is not possible to comment on the timing relative to the SpA disease course. The study design did not rigorously determine cumulative dose or duration of NSAID, so this could not be assessed in the analysis and we were limited to using "ever use of NSAID." We were also unable to analyze the effect of cumulative dose or duration of synthetic or biologic DMARD for the same reasons. There were no measures of physical activity available in the study, so we were not able to incorporate this into our analysis. Patients with IHD or stroke may have been unable to attend clinics or have died, so would not be identified in study selection, leading to underestimation of these comorbidities. While the broad definition of SpA, large numbers, and global distribution in COMOSPA are strengths, they result in significant heterogeneity, and there are likely to be regional variations in diagnostic definitions and management. The broad definition of SpA used in our study also means that no single measure of disease activity is applicable to the entire cohort (e.g., BASDAI not applicable to those with only peripheral disease), so we were unable to examine the effect of current (or previous) disease activity on these comorbidities. The participants were recruited from secondary care clinics, and so may not be representative of the wider population of patients with SpA. The effect of this is likely to vary among countries, with global variation in comorbidities evaluated in other COMOSPA-related analyses. Prospective and longitudinal studies, ideally with record linkage, are required to investigate the observed associations of this and other cross-sectional studies.

Our study suggests increased odds of HTN with longer SpA disease duration, particularly in patients with axial disease. Interestingly, disease duration was not associated with the other CV-related conditions in this cohort, adding further support to the growing literature suggesting there are differences in CV-related comorbidities between RA and SpA. Blood pressure measurement is a simple, feasible procedure that should be regularly checked in patients with SpA in the clinical setting, particularly in those with longer disease duration.

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