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# Distribution of comorbidities in spondyloarthritis with regard to the phenotype and psoriasis: data from the ASAS-COMOSPA study

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***Abstract***

**Introduction:** The aim of the study was to compare the prevalence of comorbidities between patients with axial and peripheral phenotypes and to evaluate the role of psoriasis in such comorbidities.

**Methods:** Patients from the cross-sectional Assessment in SpondyloArthritis Inter-national Society (ASAS)-COMOSPA study were classified as having either the axial (presence of sacroiliitis on X-ray or MRI) or peripheral phenotype (absence of sacroiliitis AND presence of peripheral involvement). Patients with each phenotype were divided into two groups depending on the presence or history of psoriasis. Pair-wise comparisons among the four groups (axial/peripheral phenotype with/without psoriasis) were conducted through univariate logistic regressions and generalized linear mixed models using disease duration and sex as fixed effects and country as random effect.

**Results:** A total of 3291 patients were included in this analysis. The peripheral involvement with psoriasis phenotype showed the highest prevalence of hypertension (44.9%), dyslipidaemia (34%) and diabetes (8.8%), while the axial involvement without psoriasis phenotype exhibited the lowest prevalence of dyslipidaemia (14.2%), diabetes (4.1%) and stroke (0.9%). Among patients with psoriasis, the axial phenotype showed a significantly lower prevalence of hypertension (OR: 0.51, 95% CI: 0.35–0.75) and lower prevalence of Framingham score ⩾15 (OR: 0.57, 95% CI: 0.38–0.85) than patients with peripheral involvement after adjusting for disease duration, sex and country. Among patients with the axial phenotype, patients with psoriasis showed a higher prevalence of hypertension (OR 1.76, 1.40–2.20), dyslipidaemia (OR: 1.99, 95% CI: 1.56–2.53), diabetes (OR: 2.05, 95% CI: 1.39–3.02) and Framingham score ⩾15 (OR: 2.00, 95% CI: 1.57–2.55) than non-psoriatic patients. No differences were found across groups concerning bone metabolism disorders.

**Conclusion:** Both the peripheral phenotype and psoriasis are independently associated with an increased prevalence of cardiovascular risk factors. No differences were found for bone metabolism disorders.

***Keywords:*** comorbidities, phenotype, psoriasis, spondyloarthritis

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## Introduction

Spondyloarthritis (SpA), including psoriatic arthritis (PsA), is a group of interrelated chronic inflammatory diseases that share common clinical, genetic and pathophysiological features, such as involvement of the axial skeleton and peripheral and extra-articular manifestations [uveitis, psoriasis and inflammatory bowel disease (IBD)].[1]

Patients with SpA may suffer from other coexisting disorders, that is, comorbidities.[2] The most

frequent comorbidities observed in SpA patients are osteoporosis (OP), cardiovascular disease (CVD), cancer and infections.[3] The risk of suffering from these disorders has been described to be higher in SpA patients than in the general population, partly because of the treatments used in these patients, systemic inflammation and the presence of psoriasis.[4] Indeed, the immune-mediated chronic inflammatory processes underlying psoriasis may contribute to or even amplify CV comorbidities.[5,6] For example, it has been demonstrated that CV comorbidities are more severe in individuals with exuberant cutaneous involvement than in those with PsA.[5]

OP and low bone mineral density (BMD) were shown to coexist and to represent the most prevalent comorbidity in patients with SpA.[7] This high frequency may be explained by inflammation at the spine, which leads to local bone loss, increasing the risk of fracture (especially at the sites affected by bone marrow oedema),[8,9] but it has also been related to ankylosis and immobilization.[10] Interestingly, the frequency of OP between psoriatic patients and the general population has been described as similar, and differences were only found when PsA and the general population were compared.[11]

All these comorbidities are of particular interest due to their role and their possible involvement in the treatment and prognosis of SpA. An increased risk of mortality has been described in SpA patients in comparison with the general population, partly explained by the increased risk of CVD in these patients.[12] There are several factors that may explain this greater prevalence of CVD, such as the high frequency of traditional CV risk factors, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the presence of a chronic proinflammatory status.[3] In addition, a recent study conducted by our group in the COMOSPA registry[13] suggested that patients with peripheral phenotypes exhibited a higher prevalence of traditional CV risk factors and a higher prevalence of ischaemic heart disease than those with a predominantly axial phenotype. However, these results were focused only on a subgroup of patients, and the role of psoriasis in such differences in comorbidities between phenotypes was not thoroughly investigated.

Many studies have evaluated comorbidities (especially CVD) in PsA and axial spondyloarthritis (axSpA) separately. However, to our knowledge, no studies have evaluated the role of psoriasis (a frequent extra-musculoskeletal manifestation) on comorbidities in the whole spectrum of SpA (including PsA), which could explain the differences in comorbidities between phenotypes. Based on this, we decided to conduct this study in the ASAS-COMOSPA registry, with the aim of determining whether the prevalence of CV comorbidities (CVD and CV risk factors) and OP is different between patients with predominantly axial and predominantly peripheral phenotypes and to evaluate whether the presence of psoriasis influences the prevalence of comorbidities among the different clinical phenotypes of SpA.

## Patients and methods

### *Patients*

This is an ancillary analysis of the cross-sectional, multicentric and international ASAS-COMOSPA study with 22 participating countries from four continents (Africa, America, Asia and Europe). A total of 3984 patients with a diagnosis of SpA were included. The inclusion criteria were adult patients (⩾18 years old) fulfilling the ASAS criteria (either axial or peripheral) and who were able to understand and complete questionnaires.[3]

The study was conducted according to guidelines for good clinical practice at the local level, and each of the participants signed an informed consent form to be part of the study. All the participating centres were expert in SpA, and all local ethics committees (North East-Newcastle/North Tyneside 2 Research Ethics committee 12/Ne/0417 on 14 December 2012) approved the ASAS-COMOSPA study protocol.

### *Collected variables*

A case report form was used to collect the following data:

A. Sociodemographic data: sex, age, country, smoking (ever), alcohol intake (ever), university education and current marital status.
B. Clinical characteristics and SpA features: Details on disease duration (years), diagnosis delay (years), inflammatory back pain, sacroiliitis on X-ray (evaluated by the local reader), sacroiliitis on magnetic resonance

imaging (MRI), peripheral joint disease, enthesitis, dactylitis, uveitis, psoriasis and IBD were collected. The C-reactive protein (CRP, mg/dl) level and HLA-B27 antigen status were also collected.

C. Patient-reported outcomes (PROs): The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[14] the Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP)[15] and the Bath Ankylosing Spondylitis Functional Index (BASFI)[16] were collected.
D. Past and current medications: Information on the use of NSAIDs, and synthetic and biological disease-modifying antirheumatic drugs (DMARDs) and treatment of OP was collected, and the total intake of corticosteroids was estimated.
E. Comorbidities: (a) CV risk factors: information concerning body mass index (BMI, kg/m$^2$), waist circumference (cm), family history of myocardial infarction, hypertension (defined as a previous diagnosis of hypertension or antihypertensive therapy), dyslipidaemia (defined as a previous diagnosis of dyslipidaemia or anti-cholesterol therapy), diabetes (defined as a previous diagnosis of diabetes), renal deficiency (defined as a previous diagnosis of renal deficiency) and a Framingham score $\geqslant$15 (representing a high risk of development of CV event)[17] was obtained; (b) CV disease: ischaemic heart disease (IHD) and stroke; (c) bone metabolism: history of secondary OP, spinal (vertebral or transdiscal) fracture and peripheral nontraumatic fracture was collected. OP was defined as a BMD *T*-score $<-2.5$ standard deviations (SDs) in the total hip, lumbar spine or femoral neck. Finally, a composite index was calculated using *T*-score $<-2.5$ SDs at any location or osteoporotic fracture or previous treatment for OP.

All the clinical manifestations and comorbidities were collected during a face-to-face consultation and confirmed in the clinical records.

### *Definition of axial and peripheral phenotypes*

First, patients were classified as having either an axial phenotype (defined as the presence of radiographic sacroiliitis OR sacroiliitis on MRI) or a peripheral phenotype [defined as the absence of radiographic sacroiliitis AND absence of sacroiliitis on MRI AND the presence of peripheral involvement ever (arthritis, enthesitis or dactylitis)]. Since the psoriasis may be related to both the phenotype and the comorbidities, we decided to stratify the phenotypes depending on the presence of this cutaneous involvement. Thus, each phenotype was split into two groups depending on the presence or history of psoriasis (defined as current psoriasis on physical examination or current psoriatic nail dystrophy or personal history of psoriasis diagnosed by a physician). Using this stratification, we obtained four groups of patients depending on the phenotype and the presence of psoriasis: axial involvement with psoriasis, axial involvement without psoriasis, peripheral involvement with psoriasis and peripheral involvement without psoriasis.

Patients who could not be classified into any of these groups because of missing data were excluded from the analysis.

### *Statistical analysis*

First, the prevalence of sociodemographic and clinical characteristics and comorbidities was described and compared across the four groups (axial involvement with psoriasis, axial involvement without psoriasis, peripheral involvement with psoriasis and peripheral involvement without psoriasis) using one-way analysis of variance (ANOVA) and Chi-square tests for qualitative and quantitative variables, respectively.

Comorbidities were compared between axial involvement with psoriasis *versus* peripheral involvement with psoriasis and between axial involvement without psoriasis *versus* peripheral involvement without psoriasis groups to evaluate whether the phenotype is associated with the prevalence of comorbidities. First, a simple logistic regression was conducted to estimate the odds ratio [95% confidence interval (CI)] for each comorbidity. Then, generalized linear mixed models adjusted by disease duration and sex and using country as a random effect were conducted, with the aim being to take into account disease duration and sex (which may be associated with the development of comorbidities) and country (which could also be associated with the development of comorbidities due to the different country-level socioeconomic factors).

The same analysis was conducted to compare comorbidities between axial involvement with psoriasis *versus* axial involvement without

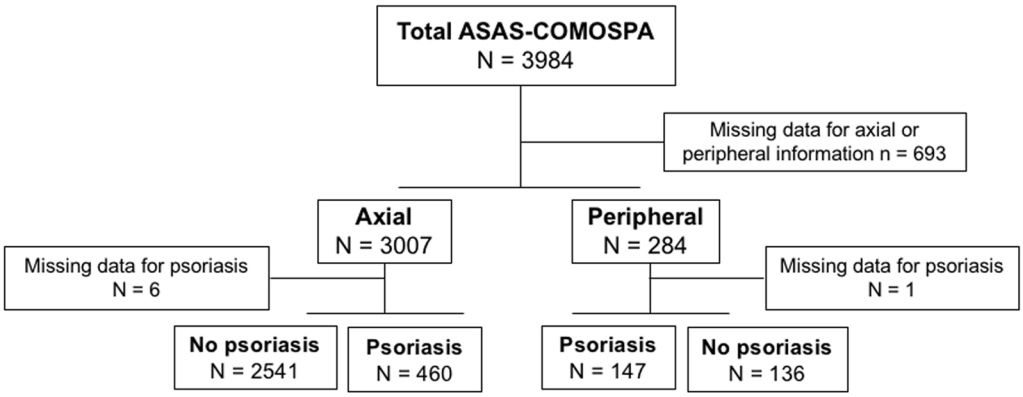


**Figure 1.** Flowchart of the patients included in the analysis.

psoriasis and between peripheral involvement with psoriasis *versus* peripheral involvement without psoriasis to evaluate whether psoriasis is associated with the prevalence of comorbidities.

All contrasts were bilateral and considered significant when the $p$ value was $<0.05$. Data were processed and analysed using SPSS software version 25.0 (SPSS, Inc., Chicago, IL, USA) and R-Studio version 1.3.1073 (Boston), and the reporting of this study conforms to the STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) statement.[18]

## Results

### *Overall population*

A total of 3984 patients were included in the COMOSPA study. In this ancillary analysis, 693 patients were excluded because of missing data for axial or peripheral information, and 7 patients were excluded because of missing information about psoriasis (Figure 1). Thus, a total of 3291 patients were selected for this analysis (2541 axial involvement without psoriasis, 460 axial involvement with psoriasis, 147 peripheral involvement with psoriasis and 136 peripheral involvement without psoriasis).

Descriptions of clinical characteristics and disease activity across the four groups are presented in Table 1. Overall, the axial involvement without psoriasis phenotype showed the highest prevalence of men (68.9%) and was the youngest group (mean age of 41 years), while the oldest group was that of peripheral involvement with psoriasis patients (mean age of 52.4 years). The distribution of smoking was similar across phenotypes, ranging between 43.4% and 49.8%, without significant differences between groups. Patients from the peripheral involvement without psoriasis group showed a shorter disease duration (mean of 6 years) and the lowest use of tumour necrosis factor (TNF) blockers (36.8%), while the largest disease duration (mean of 10.2 years) and the greater use of TNF blockers (57.6%) were found in the axial involvement with psoriasis group.

Descriptions of comorbidities across the four groups are presented in Table 2. The peripheral involvement with psoriasis showed the highest prevalence of hypertension (44.9%), dyslipidaemia (34%) and diabetes (8.8%), as well as the highest prevalence of a Framingham score $\geqslant 15$ (35.4%) in comparison with the other groups. On the contrary, the axial involvement without psoriasis phenotype exhibited the lowest mean BMI (25.5 kg/m$^2$) and the lowest prevalence of dyslipidaemia (14.2%), diabetes (4.1%) and stroke (0.9%) compared with the other three groups.

No differences were found across groups concerning bone metabolism variables.

### *Comorbidities among patients with psoriasis: axial involvement with psoriasis versus peripheral involvement with psoriasis*

The comparison of comorbidities between axial involvement with psoriasis and peripheral involvement with psoriasis groups to evaluate the role of phenotype is represented in Tables 2 and 3.

**Table 1.** Description of clinical characteristics and disease activity across the four groups: axial involvement with psoriasis, axial involvement without psoriasis, peripheral involvement with psoriasis and peripheral involvement without psoriasis.

| | **Axial involvement with psoriasis** ***N*** **= 460** ***n*** **(%)** | **Axial involvement without psoriasis** ***N*** **= 2541** ***n*** **(%)** | **Peripheral involvement with psoriasis** ***N*** **= 147** ***n*** **(%)** | **Peripheral involvement without psoriasis** ***N*** **= 136** ***n*** **(%)** | ***p*** **value*** |
|---|---|---|---|---|---|
| Age, mean (SD) | 48.3 (13.1) | 41.0 (13.3) | 52.4 (13.3) | 42.5 (12.1) | <**0.001** |
| Sex (male) | 60.9 | 68.9 | 52.4 | 52.2 | <**0.001** |
| Smoking (ever) | 228/458 (49.8) | 1159/2538 (45.7) | 49.7 | 43.4 | 0.287 |
| Alcohol (ever) | 247/456 (54.2) | 1230/2535 (48.5) | 57.1 | 54.4 | **0.024** |
| University studies | 169/459 (36.8) | 1121/2536 (44.2) | 30.6 | 47.1 | <**0.001** |
| Married | 69.3 | 1636/2539 (64.4) | 70.1 | 66.9 | 0.124 |
| Europe | 53.0 | 38.1 | 32.7 | 31.6 | <**0.001** |
| South America | 9.8 | 7.5 | 22.4 | 28.7 | <**0.001** |
| Disease duration, mean (SD) | 10.2 (10.2) | 8.1 (9.4) | 7.6 (8.4) | 6 (7.2) | <**0.001** |
| Diagnosis delay, mean (SD) | 11.0 (10.9) | 5.9 (7.5) | 10.8 (12.1) | 5.5 (7.4) | <**0.001** |
| Family history of SpA | 222/443 (50.1) | 880/2489 (35.4) | 67/145 (46.2) | 52/133 (39.1) | <**0.001** |
| HLA-B27 | 181/327 (55.4) | 1697/2167 (78.3) | 25/101 (24.8) | 91/122 (74.6) | <**0.001** |
| Inflammatory back pain | 90.2 | 2422/2539 (95.4) | 56 (30.1) | 98 (72.1) | <**0.001** |
| Radiographic sacroiliitis | 383/452 (87.7) | 2150/2501 (86.0) | 0 | 0 | <**0.001** |
| Sacroiliitis on MRI | 187/250 (74.8) | 1138/1424 (79.9) | 0 | 0 | <**0.001** |
| Peripheral joint disease | 73.7 | 1231/2539 (48.5) | 97.3 | 92.6 | <**0.001** |
| Enthesitis | 217/459 (47.3) | 846/2539 (33.3) | 52.4 | 70.6 | <**0.001** |
| Dactylitis | 27.0 | 188/2539 (7.4) | 36.7 | 30.9 | <**0.001** |
| Uveitis | 98/456 (21.5) | 588/2532 (23.2) | 8.8 | 33/135 (24.4) | **0.001** |
| IBD | 9.6 | 5.5 | 4.8 | 12.5 | <**0.001** |
| DMARDs (csDMARDs or bDMARDs) | 61.7 | 71.1 | 89.1 | 87.5 | <**0.001** |
| TNF blockers (ever) | 57.6 | 41.6 | 44.2 | 36.8 | <**0.001** |
| NSAID intake ever | 402/458 (87.8) | 2295/2537 (90.5) | 83.7 | 88.2 | **0.023** |
| Estimated total intake of corticosteroids, mean (SD) | 2936.7 (8405.5) | 1485.4 (6662.1) | 2510.5 (9470.4) | 1838.5 (8061.6) | **0.001** |
| CRP, mg/dl, mean (SD) | 0.5 (0.9) | 0.5 (1.1) | 0.4 (0.7) | 0.5 (1) | 0.393 |
| ASDAS-CRP, mean (SD) | 2.1 (1) | 2 (1) | 1.8 (1) | 1.9 (1.1) | **0.008** |
| BASDAI, mean (SD) | 4 (2.4) | 3.7 (2.3) | 3.4 (2.4) | 3.6 (2.5) | **0.010** |
| BASFI, mean (SD) | 36.1 (27.6) | 30.2 (26.5) | 26 (25.5) | 26.7 (27.2) | <**0.001** |

ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; SpA, spondyloarthritis; TNF blockers, tumour necrosis factor blockers.
*Analysis of variance or Chi-square test for continuous and qualitative variables, respectively.
Bold values are statistically significant.

**Table 2.** Description of comorbidities across the four groups: axial involvement with psoriasis, axial involvement without psoriasis, peripheral involvement with psoriasis and peripheral involvement without psoriasis.

| | Axial involvement with psoriasis *N* = 460 *n* (%) | Axial involvement without psoriasis *N* = 2541 *n* (%) | Peripheral involvement with psoriasis *N* = 147 *n* (%) | Peripheral involvement without psoriasis *N* = 136 *n* (%) | *p* value* |
|---|---|---|---|---|---|
| CV risk and CV risk factors | | | | | |
| BMI, mean (SD) | 27.4 (5.5) | 25.5 (5.5) | 27.3 (5.7) | 26.6 (5.3) | <**0.001** |
| Anti-hypertensive therapy or hypertension | 135/458 (29.5) | 487/2533 (19.2) | 66 (44.9) | 25 (18.4) | <**0.001** |
| Anti-cholesterol therapy or dyslipidaemia | 113/456 (24.8) | 359/2526 (14.2) | 50 (34) | 23/135 (17) | <**0.001** |
| Diabetes | 37/459 (8.1) | 104/2535 (4.1) | 13 (8.8) | 7/134 (5.2) | <**0.001** |
| Renal deficiency | 14/459 (3.1) | 49/2535 (1.9) | 2 (1.3) | 3/135 (2.2) | 0.426 |
| Ischaemic heart disease | 16/459 (3.5) | 51/2534 (2) | 5/145 (3.4) | 2 (1.5) | 0.162 |
| Stroke | 11/458 (2.4) | 22/2532 (0.9) | 3 (2) | 2 (1.5) | **0.028** |
| Family history of myocardial infraction | 79/441 (17.9) | 346/2477 (14) | 20/144 (13.9) | 22/134 (16.4) | 0.166 |
| Waist circumference, mean (SD) | 95.2 (15.5) | 88.3 (15.1) | 92.6 (13.6) | 90.1 (16.2) | <**0.001** |
| Framingham score ⩾15 | 109 (23.7) | 341 (13.4) | 52 (35.4) | 11 (8.1) | <**0.001** |
| Bone metabolism disorders | | | | | |
| Spinal fracture (vertebral or transdiscal) | 16/459 (3.5) | 62/2527 (2.5) | 5/146 (3.4) | 0/135 (0) | 0.126 |
| Peripheral non-traumatic fracture | 17/459 (3.7) | 66/2531 (2.6) | 4 (2.7) | 5 (3.7) | 0.552 |
| Secondary osteoporosis | 10/459 (2.2) | 36/2519 (1.4) | 2/146 (1.4) | 4/134 (3) | 0.372 |
| OP total hip | 5/104 (4.8) | 36/666 (5.4) | 2/34 (5.9) | 1/24 (4.2) | 0.985 |
| OP neck hip | 6/107 (5.6) | 41/665 (6.2) | 3/35 (8.6) | 4/24 (16.7) | 0.204 |
| OP lumbar | 14/107 (13.1) | 82/677 (12.1) | 4/37 (10.8) | 1/26 (3.8) | 0.611 |
| *T*-score <−2.5 or osteoporotic fracture or previous treatment for OP | 70/459 (15.3) | 341/2537 (13.4) | 23 (15.6) | 17 (12.5) | 0.637 |

BMI, body mass index; CV, cardiovascular; OP, osteoporosis; SD, standard deviation.
*Analysis of variance or Chi-square test for continuous and qualitative variables, respectively.

Axial involvement with psoriasis patients exhibited a lower prevalence of hypertension (29.5% *versus* 44.9%) (OR: 0.51, 95% CI: 0.35–0.75), a lower prevalence of dyslipidaemia (24.8% *versus* 34%) (OR: 0.64, 95% CI: 0.43–0.96) and a lower prevalence of Framingham score ⩾15 (23.7% *versus* 35.4%) (OR: 0.57, 95% CI: 0.38–0.85) than peripheral involvement with psoriasis. Differences in dyslipidaemia disappeared after adjusting for disease duration, sex and country, but hypertension and Framingham score remained significant. No differences were found between these two groups in CVD (i.e. IHD and stroke) or bone metabolism disorders.

**Table 3.** Role of phenotype: comparison of comorbidities between axial and peripheral phenotypes in patients with and without psoriasis.

| | **Patients with psoriasis** | | | **Patients without psoriasis** | | |
|---|---|---|---|---|---|---|
| | **Axial involvement with psoriasis (reference) *versus* peripheral involvement with psoriasis** | | | **Axial involvement without psoriasis (reference) *versus* peripheral involvement without psoriasis** | | |
| | **OR (95% CI) crude model** | ***p* value crude model[a]** | ***p* value disease duration, sex and country adjusted model[b]** | **OR (95% CI) crude model** | ***p* value crude model[a]** | ***p* value disease duration, sex and country adjusted model[b]** |
| CV risk factors and CV disease | | | | | | |
| BMI, mean (SD) | 1.00 (0.97–1.04) | 0.939 | 0.774 | **0.97 (0.94–0.99)** | **0.025** | 0.343 |
| Anti-hypertensive therapy or hypertension | **0.51 (0.35–0.75)** | **0.001** | **<0.001** | 0.95 (0.61–1.48) | 0.808 | 0.813 |
| Anti-cholesterol therapy or dyslipidaemia | **0.64 (0.43–0.96)** | **0.029** | 0.076 | 0.81 (0.51–1.28) | 0.363 | 0.544 |
| Diabetes | 0.90 (0.47–1.75) | 0.764 | 0.351 | 0.78 (0.35–1.70) | 0.527 | 0.458 |
| Renal deficiency | 2.28 (0.51–10.16) | 0.279 | 0.220 | 0.87 (0.27–2.82) | 0.813 | 0.750 |
| Ischaemic heart disease | 1.01 (0.36–2.81) | 0.983 | 0.469 | 1.38 (0.33–5.71) | 0.660 | 0.902 |
| Stroke | 1.18 (0.32–4.29) | 0.800 | 0.621 | 0.59 (0.14–2.52) | 0.474 | 0.313 |
| Family history of myocardial infraction | 1.35 (0.80–2.30) | 0.265 | 0.515 | 0.83 (0.52–1.32) | 0.428 | 0.579 |
| Waist circumference | 1.01 (0.99–1.03) | 0.141 | 0.756 | 0.99 (0.98–1.01) | 0.230 | 0.432 |
| Framingham score ⩾15 | **0.57 (0.38–0.85)** | **0.006** | **0.003** | 1.76 (0.98–3.49) | 0.077 | 0.315 |
| Bone metabolism disorders | | | | | | |
| Spinal fracture (vertebral or transdiscal) | 1.02 (0.37–2.83) | 0.972 | 0.853 | – | – | – |
| Peripheral non-traumatic fracture | 1.38 (0.46–4.15) | 0.572 | 0.663 | 0.70 (0.28–1.77) | 0.453 | 0.181 |
| Secondary osteoporosis | 1.60 (0.35–7.40) | 0.545 | 0.225 | 0.47 (0.17–1.34) | 0.159 | 0.488 |
| OP total hip | 0.81 (0.15–4.37) | 0.805 | 0.434 | 1.31 (0.17–10.01) | 0.792 | 0.766 |
| OP neck hip | 0.63 (0.15–2.68) | 0.535 | 0.385 | 0.33 (0.11–1.01) | 0.051 | **0.040** |
| OP lumbar | 1.24 (0.38–4.04) | 0.719 | 0.907 | 3.45 (0.46–25.77) | 0.228 | 0.907 |
| *T*-score <–2.5 or osteoporotic fracture or previous treatment for OP | 0.97 (0.58–1.62) | 0.908 | 0.854 | 1.09 (0.65–1.83) | 0.754 | 0.625 |

BMI, body mass index; CI, confidence interval; CV, cardiovascular; OP, osteoporosis; OR, odds ratio; SD, standard deviation.
[a]Simple logistic regression.
[b]Generalized linear mixed models disease duration, sex and country adjusted.

### *Comorbidities among patients without psoriasis: axial involvement without psoriasis versus peripheral involvement without psoriasis*

Among patients without psoriasis (Tables 2 and 3), the axial group showed a lower BMI than the peripheral group (25.5 *versus* 26.6) (OR: 0.97, 95% CI: 0.94–0.99), although these differences disappeared after adjusting for disease duration, sex and country. No differences were found between the two groups in either CV risk factors or CVD.

No differences concerning bone metabolism variables were found between these two groups.

### *Comorbidities among patients with the axial phenotype: axial involvement with psoriasis versus axial involvement without psoriasis*

Among patients with the axial phenotype, we compared comorbidities between patients with and without psoriasis to evaluate the role of psoriasis (Tables 2 and 4).

A higher prevalence of hypertension (29.5% *versus* 19.2%) (OR: 1.76, 95% CI: 1.40–2.20), dyslipidaemia (24.8% *versus* 14.2%) (OR: 1.99, 95% CI: 1.56–2.53), diabetes (8.1% *versus* 4.1%) (OR: 2.05, 95% CI: 1.39–3.02), family history of myocardial infarction (17.9% *versus* 13.9%) (OR: 1.34, 95% CI: 1.03–1.76) and Framingham score ⩾15 (23.7% *versus* 13.4%) (OR: 2.00, 95% CI: 1.57–2.55) was observed in the axial involvement with psoriasis group than in the axial involvement without psoriasis group. Moreover, these patients exhibited a higher BMI (27.4 *versus* 25.5) (OR: 1.05, 95% CI: 1.04–1.07) and waist circumference (95.2 *versus* 88.3) (OR: 1.03, 95% CI: 1.02–1.04) than axial involvement without psoriasis. The prevalence of stroke was also higher in the group with psoriasis than in axial involvement without psoriasis group (2.4% *versus* 0.9%) (OR: 2.81, 95% CI: 1.35–5.83). After adjusting for disease duration, sex and country, BMI, hypertension, dyslipidaemia, diabetes, waist circumference and Framingham score remained significantly different, while stroke and family history of myocardial infarction did not.

Variables concerning bone metabolism did not show significant differences between axial involvement with or without psoriasis patients.

### *Comorbidities among patients with the peripheral phenotype: peripheral with psoriasis versus peripheral without psoriasis*

Finally, when we compared peripheral involvement with psoriasis *versus* peripheral involvement without psoriasis (Tables 2 and 4), we found that a higher prevalence of hypertension (44.9% *versus* 18.4%) (OR: 3.62, 95% CI: 2.10–6.22), dyslipidaemia (34% *versus* 17%) (OR 2.51, 95% CI: 1.43–4.41) and Framingham score ⩾15 (35.4% *versus* 8.1%) (OR 6.22, 95% CI: 3.19–13.16) was noted in the peripheral involvement with psoriasis group than in the peripheral involvement without psoriasis group. In addition, differences in these three variables remained significant after adjusting for disease duration, sex and country.

Patients with peripheral involvement with psoriasis and peripheral involvement without psoriasis did not show significant differences concerning bone metabolism disorders.

## Discussion

In this study, we evaluated whether phenotype and the presence of psoriasis are associated with the prevalence of comorbidities in the whole spectrum of SpA (including PsA). Several studies have evaluated comorbidities (especially CVD) in PsA and axSpA separately, but to our knowledge, this is one of the first studies to evaluate the effect of psoriasis on comorbidities among the different clinical phenotypes of SpA. These results suggest that two factors associated with a higher prevalence of CV risk are the presence of psoriasis and the peripheral phenotype.

We found that the highest prevalence of hypertension, dyslipidaemia, diabetes and a Framingham score ⩾15 was found among patients with peripheral involvement with psoriasis, while the lowest prevalence of such manifestations was found among patients with axial involvement without psoriasis. Many studies conducted in various countries have demonstrated that psoriasis is associated with an increased prevalence of CV risk factors, including hypertension, diabetes mellitus, dyslipidaemia, obesity and metabolic syndrome.[19,20] Our results showed a strong association between CV risk factors and psoriasis irrespective of the phenotype, since patients with this cutaneous involvement showed a greater prevalence of hypertension and dyslipidaemia and a higher Framingham score than patients without psoriasis in both the axial and peripheral groups, confirming the role of psoriasis

**Table 4.** Role of psoriasis: comparison of comorbidities between patients with and without psoriasis in peripheral and axial phenotypes.

| | **Patients with axial involvement** | | | **Patients with peripheral involvement** | | |
|---|---|---|---|---|---|---|
| | **Axial involvement with psoriasis (reference) *versus* axial involvement without psoriasis** | | | **Peripheral involvement with psoriasis (reference) *versus* peripheral involvement without psoriasis** | | |
| | **OR (95% CI) crude model** | ***p* value crude model[a]** | ***p* value disease duration, sex and country adjusted model[b]** | **OR (95% CI) crude model** | ***p* value crude model[a]** | ***p* value disease duration, sex and country adjusted model[b]** |
| CV risk factors and CV disease | | | | | | |
| BMI, mean (SD) | **1.05 (1.04–1.07)** | **<0.001** | **<0.001** | 1.02 (0.98–1.07) | 0.299 | 0.203 |
| Anti-hypertensive therapy or hypertension | **1.76 (1.40–2.20)** | **<0.001** | **0.001** | **3.62 (2.10–6.22)** | **<0.001** | **<0.001** |
| Anti-cholesterol therapy or dyslipidaemia | **1.99 (1.56–2.53)** | **<0.001** | **<0.001** | **2.51 (1.43–4.41)** | **0.001** | **0.003** |
| Diabetes | **2.05 (1.39–3.02)** | **0.001** | **0.005** | 1.76 (0.68–4.55) | 0.244 | 0.102 |
| Renal deficiency | 1.60 (0.87–2.92) | 0.128 | 0.344 | 0.61 (0.10–3.69) | 0.588 | 0.724 |
| Ischaemic heart disease | 1.76 (0.99–3.11) | 0.053 | 0.381 | 2.39 (0.46–12.54) | 0.302 | 0.606 |
| Stroke | **2.81 (1.35–5.83)** | **0.006** | 0.073 | 1.40 (0.23–8.48) | 0.717 | 0.987 |
| Family history of myocardial infraction | **1.34 (1.03–1.76)** | **0.031** | 0.709 | 0.82 (0.43–1.58) | 0.557 | 0.543 |
| Waist circumference | **1.03 (1.02–1.04)** | **<0.001** | **<0.001** | 1.01 (0.99–1.03) | 0.221 | 0.146 |
| Framingham score ⩾15 | **2.00 (1.57–2.55)** | **<0.001** | **<0.001** | **6.22 (3.19–13.16)** | **<0.001** | **<0.001** |
| Bone metabolism disorders | | | | | | |
| Spinal fracture (vertebral or transdiscal) | 1.44 (0.82–2.51) | 0.204 | 0.718 | – | – | – |
| Peripheral non-traumatic fracture | 1.44 (0.84–2.47) | 0.191 | 0.267 | 0.73 (0.19–2.79) | 0.648 | 0.399 |
| Secondary osteoporosis | 1.54 (0.76–3.12) | 0.235 | 0.884 | 0.45 (0.08–2.51) | 0.363 | 0.336 |
| OP total hip | 0.88 (0.34–2.31) | 0.801 | 0.895 | 1.44 (0.12–16.82) | 0.772 | 0.673 |
| OP neck hip | 0.90 (0.37–2.18) | 0.823 | 0.901 | 0.47 (0.09–2.32) | 0.353 | 0.416 |
| OP lumbar | 1.09 (0.60–2.01) | 0.776 | 0.860 | 3.03 (0.32–28.81) | 0.335 | 0.359 |
| *T*-score <−2.5 or osteoporotic fracture or previous treatment for OP | 1.16 (0.88–1.53) | 0.300 | 0.478 | 1.30 (0.66–2.55) | 0.449 | 0.892 |

BMI, body mass index; CI, confidence interval; OP, osteoporosis; OR, odds ratio; SD, standard deviation.
[a]Simple logistic regression.

in the development of CV risk factors. The increased risk of metabolic syndrome among patients with psoriasis is well known, which is explained by the proinflammatory status. High serum levels of proinflammatory cytokines such as interferon-alpha and TNF initiate and accelerate the progression of atherosclerosis, promoting vasoconstriction and endothelial dysfunction.[21] This higher risk of metabolic syndrome and CV events has been described as even more important among PsA than among patients with psoriasis alone.[22]

The peripheral involvement with psoriasis group showed, in comparison with the peripheral involvement without psoriasis group, a greater prevalence of hypertension and dyslipidaemia and a higher Framingham score, confirming the association between psoriasis and increased CV risk. In addition, this peripheral involvement with psoriasis group showed, in comparison with the axial involvement with psoriasis group, a greater prevalence of these three CV risk factors, confirming that phenotype may also influence the development of certain CV risk factors. These results are in line with a previous study conducted by our group describing a greater prevalence of traditional CV risk factors among peripheral phenotypes; however, we did not deeply investigate the role of psoriasis in such an association.[13] With these results, we can state that CV risk is associated not only with the presence of psoriasis but also with the phenotype of the patient.

Interestingly, we found that axial involvement without psoriasis patients seem to be the 'milder' group in terms of CV risk factors, although this was the group with the greatest use of NSAIDs, whose effects on hypertension and renal deficiency are well known. The reduced prevalence of CV risk factors in this group could be explained by differences in disease activity across groups, leading to a reduced proinflammatory status, as well as by tobacco. Nevertheless, our results did not show significant differences in inflammatory markers such as CRP or smoking status. It should also be noted that the estimated total intake of corticosteroids was lower among patients with axial involvement without psoriasis than among patients in the other three groups, which may also influence the lower prevalence of CV risk factors in these patients.

Classically, OP has been described to be more frequent in patients with SpA than in the general population. Systemic inflammation evaluated by an MRI and by CRP levels or the erythrocyte sedimentation rate are factors associated with a decrease in BMD in these patients. Previous studies also showed a possible association between psoriatic disease and a reduction in BMD due to an increase in TNF and interleukin 6 concentrations.[23] In addition, patients with a peripheral phenotype may have a higher risk of OP due to the higher consumption of corticosteroids. However, in our study, we did not find differences either between phenotypes or with regard to the presence of psoriasis.

This study has some limitations in addition to its strengths. A limitation was the cross-sectional nature of the study, which hampers us from determining whether the presence of psoriasis is the major cause of these comorbidities. However, a strong association between psoriasis and different comorbidities can be established. Another limitation is that we did not take into account the use of TNF inhibitors during the analysis, since we were not able to determine whether the patients developed comorbidities before, during or after the use of these drugs. Finally, the recruitment strategy for the participating centres could have influenced the higher prevalence of axial phenotypes in comparison with the peripheral phenotypes, since the participating investigators were ASAS members, who are specially interested in axSpA. The main strengths of our study are the large sample of SpA patients covering the whole spectrum of SpA (including PsA), which allows us to split the sample into four groups to evaluate the association of comorbidities not only with psoriasis but also with the axial or peripheral phenotype. In addition, we did not classify patients according to the presence of ASAS criteria or ClASsificationcriteria for Psoriatic ARthritis (CASPAR) criteria[24,25] to avoid an artificial classification of patients who may have fulfilled both sets of criteria, which would have occurred in many cases (as was demonstrated in some previous studies).[26] For this reason, we decided to not consider these classification criteria and to group patients as having the axial or peripheral phenotype using their clinical findings, which allows for a better evaluation of how psoriasis and phenotype are associated with comorbidities in the full spectrum of SpA. Another strength is that all the analyses were adjusted for disease duration, sex and country. We consider that disease duration in these patients may be one of the most important factors associated with the development of comorbidities, since the maintained inflammatory status may play a key role in such events. For this reason, we decided to adjust by disease duration and to use the country as a random effect to control the potential variability in socioeconomic and environmental factors that could have an influence on the development of these comorbidities.

In summary, this study suggests that across the whole group of SpA, both the peripheral phenotype and the presence of psoriasis are independently associated with a higher prevalence of CV risk factors. These results have implications in

daily clinical practice since they reveal the importance of closely monitoring such comorbidities specially in patients with psoriasis and peripheral phenotypes. Finally, evidence for an association between bone metabolism disorders and phenotype or the presence of cutaneous involvement was not found. Further prospective studies are needed to better elucidate the role of psoriasis and phenotype in comorbidities.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Data sharing statement

Researchers willing to use data collected during the study should contact the first author of the main ASAS-COMOSPA manuscript, who will send a study proposal template to be completed by the applicant. Thereafter, the steering committee of the ASAS-COMOSPA study will approve (or not) the proposal and proceed to the data sharing.

## References

1. Dougados M and Baeten D. Spondyloarthritis. *Lancet* 2011; 377: 2127–2137.
2. López Medina C and Molto A. Comorbidity management in spondyloarthritis. *RMD Open* 2020; 6: e001135.
3. Moltó A, Etcheto A, van der Heijde D, *et al.* Prevalence of comorbidities and evaluation of their screening in spondyloarthritis: results of the international cross-sectional ASAS-COMOSPA study. *Ann Rheum Dis* 2016; 75: 1016–1023.
4. Exarchou S, Lie E, Lindström U, *et al.* Mortality in ankylosing spondylitis: results from a nationwide population-based study. *Ann Rheum Dis* 2016; 75: 1466–1472.
5. Oliveira Mde F, Rocha Bde O and Duarte GV. Psoriasis: classical and emerging comorbidities. *An Bras Dermatol* 2015; 90: 9–20.
6. Gottlieb AB and Dann F. Comorbidities in patients with psoriasis. *Am J Med* 2009; 122: 1150–1150.
7. Adami G, Fassio A, Rossini M, *et al.* Osteoporosis in rheumatic diseases. *Int J Mol Sci* 2019; 20: 5867.
8. Maas F, Spoorenberg A, van der Slik BPG, *et al.* Clinical risk factors for the presence and development of vertebral fractures in patients with ankylosing spondylitis. *Arthritis Care Res* 2017; 69: 694–702.
9. Briot K, Durnez A, Paternotte S, *et al.* Bone oedema on MRI is highly associated with low bone mineral density in patients with early inflammatory back pain: results from the DESIR cohort. *Ann Rheum Dis* 2013; 72: 1914–1919.
10. Ghozlani I, Ghazi M, Nouijai A, *et al.* Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. *Bone* 2009; 44: 772–776.
11. Millard TP, Antoniades L, Evans AV, *et al.* Bone mineral density of patients with chronic plaque of psoriasis. *Clin Exp Dermatol* 2001; 26: 446–448.
12. Bremander A, Petersson IF, Bergman S, *et al.* Population-based estimates of common comorbidities and cardiovascular disease in ankylosing spondylitis. *Arthritis Care Res* 2011; 63: 550–556.
13. López-Medina C, Jiménez-Gómez Y, Moltó A, *et al.* Cardiovascular risk factors in patients with spondyloarthritis from Northern European and Mediterranean countries: an ancillary study of the ASASCOMOSPA project. *Joint Bone Spine* 2018; 85: 447–453.

14. Garrett S, Jenkinson T, Kennedy LG, *et al*. A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index. *J Rheumatol* 1994; 21: 2286–2291.

15. Lukas C, Landewé R, Sieper J, *et al*. Assessment of SpondyloArthritis International SOCIETY. Development of an ASAS-endorsed Disease Activity Score (ASDAS) in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 18–24.

16. Calin A, Garrett S, Whitelock H, *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: 2281–2285.

17. Berry JD, Lloyd-Jones DM, Garside DB, *et al*. Framingham risk score and prediction of coronary heart disease death in young men. *Am Heart J* 2007; 154: 80–86.

18. von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453–1457.

19. Hu SC and Lan CE. Psoriasis and cardiovascular comorbidities: focusing on severe vascular events, cardiovascular risk factors and implications for treatment. *Int J Mol Sci* 2017; 18: E2211.

20. Jensen P and Skov L. Psoriasis and obesity. *Dermatology* 2016; 232: 633–639.

21. Perez-Chada LM and Merola JF. Comorbidities associated with psoriatic arthritis: review and update. *Clin Immunol* 2020; 214: 108397.

22. Lin YC, Dalal D, Churton S, *et al*. Relationship between metabolic syndrome and carotid intima media thickness: cross-sectional comparison between psoriasis and psoriatic arthritis. *Arthritis Care Res* 2014; 66: 97–103.

23. Kastelan D, Kastelan M, Massari LP, *et al*. Possible association of psoriasis and reduced bone mineral density due to increased TNF-alpha and IL-6 concentrations. *Med Hypotheses* 2006; 67: 1403–1405.

24. Taylor W. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665–2673.

25. Rudwaleit M, van der Heijde D, Landewé R, *et al*. The development and assessment of spondyloarthritis international society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 677–683.

26. López-Medina C, Moltó A and Dougados M. Peripheral manifestations in spondyloarthritis and their effect: an ancillary analysis of the ASAS-COMOSPA study. *J Rheumatol* 2020; 47: 211–217.