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Title: Cardiovascular risk factors in patients with Spondyloarthritis from Northern European and Mediterranean countries: an ancillary study of the ASAS-COMOSPA project

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1 Cardiovascular risk factors in patients with Spondyloarthritis from Northern European
2 and Mediterranean countries: an ancillary study of the ASAS-COMOSPA project
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11 COMOSPA task force**.
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ABSTRACT

Objectives: The objectives of this study were: 1) To compare the prevalence of cardiovascular disease and cardiovascular risk factors among different phenotypes of Spondyloarthritis (SpA); 2) To assess the differences in cardiovascular disease and cardiovascular risk factors between two geographical areas, i.e. Northern Europe vs. Mediterranean region; 3) To identify potential predictive factors for high Framingham Risk Score regarding disease features in SpA and geographical area.

Methods: Ancillary analysis of the international, multicentric, observational, cross-sectional ASAS-COMOSPA study. Cardiovascular disease and cardiovascular risk factors were compared depending on SpA phenotype and geographical regions. Potential factors associated with higher cardiovascular risk (i.e. Framingham Risk Score) were determined by a multiple logistic regression.

Results: The most frequent cardiovascular risk factor and cardiovascular disease were smoking (31.2%) and ischemic heart disease (3.2%), respectively. Regarding SpA phenotype, axial SpA patients showed significantly lower prevalence ($p < 0.05$) of hypertension (19.2% vs. 33.8% vs. 26.6% for axial, peripheral and mixed phenotypes, respectively), type 2 diabetes mellitus (4.3% vs. 8.5% vs. 7.4%), dyslipidemia (13.9% vs. 28.4% vs. 15.2%) and ischemic heart disease (2.4% vs. 7.0% vs. 3.2%). Regarding geographical area, a higher frequency of hypertension (34.7% vs. 19.4%), dyslipidemia (19.3% vs. 14.4%), obesity (29.3% vs. 20.7%) and ischemic heart disease (6.2% vs. 1.8%) was observed for Northern Europe vs. Mediterranean Region, respectively.

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Conclusions: Our results suggest that SpA phenotype and geographical area are associated with the prevalence of cardiovascular risk factors and the cardiovascular risk itself, observed in patients in the ASAS-COMOSPA cohort.

KEYWORDS: Spondyloarthritis/ Cardiovascular disease/ Cardiovascular risk factors/ Socio-demographic characteristics.

1. Introduction

1 Spondyloarthritis (SpA) is a chronic inflammatory disease that presents under different
2 phenotypes depending on the presence of axial or peripheral manifestations [1]. Patients
3 with SpA can present predominantly with axial symptoms (axial SpA) [2], with
4 peripheral arthritis (peripheral SpA) [3] or both (hereafter called mixed SpA). In
5 addition to articular symptoms, many SpA patients exhibit an array of extra-articular
6 manifestations including psoriasis, anterior uveitis and inflammatory bowel disease
7 (IBD) [4]. This phenotypic presentation generated the division into several subtypes,
8 such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), IBD-associated SpA,
9 reactive arthritis and undifferentiated SpA [5].

10 It has also been reported that patients with SpA present more frequently with
11 comorbidities such as cardiovascular (CV) manifestations, among others [6]. These
12 comorbidities are of particular interest due to their role and their possible involvement
13 in the treatment and prognosis of SpA. An increased mortality has been described in
14 SpA patients compared to the general population, together with a greater risk for CV
15 mortality [7]. Some studies have shown that SpA patients present also an increased risk
16 of cardiovascular disease (CVD) [8,9] compared to the general population. There are
17 several factors that may explain this greater risk, e.g. related to chronic systemic
18 inflammation, to a higher prevalence of classical CV risk factors [10], and to the
19 different treatment modalities depending on the SpA phenotype (i.e. more frequently
20 NSAIDs in axial disease).

21 There are other factors that could contribute to this high CV risk. Several studies have
22 shown that metabolic syndrome and CVD are common in patients with AS and PsA [11-
23 14]. Nevertheless, the comparison among different SpA phenotypes regarding the
24 prevalence of CV risk has not been reported yet. In addition, several factors such as

1 environmental, socio-demographic and behavioural (i.e. smoking, age, socioeconomic
2 status, psychological stress, alcohol or unhealthy diet) may also be key CV risk factors
3 in SpA patients. This constellation of factors may be involved in the impairment of the
4 classical CV risk factors, as well as directly in the CV process. More, it has been noted
5 that these factors are associated with increased CV risk [15] in healthy population, with
6 frequencies depending on each country and geographical area [18-20]. In fact, recent
7 epidemiological studies in general population [19,20] show that CVD and mortality
8 rates are higher in Northern European Countries (eg. UK and Germany) than in some
9 Mediterranean Countries (eg. Spain and Italy). However, these geographical differences
10 have not been studied in SpA patients. Recent data from the ASAS-COMOSPA study
11 [21] illustrate that the worldwide distribution of CVD is strikingly more frequent in
12 Northern Europe and in USA compared to the rest of the population included in the
13 study.

14 The ASAS-COMOSPA is an observational, cross-sectional, multicentre and
15 international study, with 22 participating countries from 4 continents (Africa, America,
16 Asia and Europe), and it was performed under the umbrella of ASAS (Assessment in
17 SpondyloArthritis international Society). The ASAS-COMOSPA study had as objectives
18 to evaluate the prevalence of comorbidities and their risk factors in SpA patients and to
19 evaluate the gap between the available recommendations and their implementation in
20 daily practice.

21 Thus, our aims in the present study were:

- 22 - First, to compare CVD and CV risk factors among different SpA phenotypes.
- 23 - Secondly, to analyze the differences in SpA characteristics and in CVD/ CV risk
24 factors between two geographical areas (Northern European vs. Mediterranean
25 region).

- Finally, to identify potential factors associated with high Framingham Risk Score (FRS) regarding disease features in SpA and geographical area.

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2. Methods

2.1. Study design

This was an ancillary analysis of the ASAS-COMOSPA study, an international, observational, cross-sectional and multicentre study [21]. For the present analysis, only 10 participating countries from two European regions were included: Northern Europe (United Kingdom, Germany, Belgium and Netherlands) and Mediterranean area (Spain, France, Italy, Morocco, Turkey and Egypt). These countries were selected because of dietary similarities (patients from Mediterranean countries consuming the traditional Mediterranean diet, which includes high intake of vegetables, legumes, fruits, nuts and olive oil), genetic, lifestyle and environmental (e.g. hours of sunlight) [22].

2.2. Participants and recruitment

Of the 3984 consecutive adult patients belonging to the paternal study [e.g. at least 18 years old, fulfilling the ASAS criteria (either axial or peripheral) [2,3] and who were able to understand and complete questionnaires included in the original study], we included all participants from the above specified countries selected for the analysis (a total of 2020) [21]; 19 patients were excluded by missing socio-demographic data, resulting in 2001 patients included in this present analysis (1353 participants were from countries of Mediterranean area and 648 from Northern Europe) (Fig. 1). The study was conducted according to guidelines for good clinical practice at the local level. All participants gave written informed consent and underwent a comprehensive medical history, physical examination, and laboratory tests before enrolment. The working protocol was approved by the local ethic committee at each of the intervention centers according to the Helsinki Declaration.

2.3. Data collection

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

A). Demographic and disease characteristics: Demographic characteristics: country of origin, age, gender, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters. Obese subjects were defined as patients with BMI ≥ 30 kg/m²) and smoking status as: a) non-smoker [never or past (>3 years)], b) smoker [present or past (≤ 3 years)]. Disease characteristics: disease duration, presence or absence of HLA-B27 antigen, SpA phenotype (defined as only axial/ axial and peripheral (mixed)/ and only peripheral involvement [3,5]), enthesitis, dactylitis, uveitis, psoriasis, and IBD. Current disease activity was measured by CRP (mg/dL) and ESR (mm/1h) levels, patient and physician global visual analogue scale (VAS; range from 0 to 10), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [23], Ankylosing Spondylitis Disease Activity Score (ASDAS; calculated with the CRP) [24], and the number of swollen and tender joints (44 joint count).

B). CVD and CV risk factors: CVD: history of ischaemic heart disease (IHD) or stroke; risk factors for CVD: hypertension [defined as history of hypertension or antihypertensive therapy or blood pressure (BP) > 140/90 mm Hg (>130/80 mm Hg in case of history of diabetes or renal insufficiency) at the study visit], type 2 diabetes mellitus (T2DM) [defined as history of diabetes or glycaemia >7.0 mmol/L], dyslipidemia (defined as history of hypercholesterolaemia or cholesterol-lowering therapy or an low-density lipoprotein (LDL) cholesterol above target according to the French recommendations [25], chronic renal failure (CRF) [defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m² for 3 months or more], and family history of myocardial infarction (MI). Furthermore, the Framingham Risk Score (FRS) [26], was used to estimate the 10-year risk for a CV event of an individual [range

1 from <5 % (low risk) to $\geq 15\%$ (high risk)]. All these variables were collected during a
2 one-to-one study visit for the parent study including the review of the medical charts.
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7 **2.4. Statistical analysis**

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9 All data presented in the Figure and Tables are expressed as mean and Standard
10 Deviation (SD) for continuous variables, and as number and/or percentage of patients
11 for categorical variables. Chi-square test (categorical variables) and Independent-
12 Samples t test (continuous variables) were used to evaluate the association between CV
13 risk factors and SpA phenotype, and to compare the prevalence of SpA clinical
14 characteristics and CV risk in Northern European vs. Mediterranean countries.
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24 A multiple logistic regression was performed to assess the variables potentially
25 associated with high FRS ($FRS \geq 15$) by including in the model the most important
26 phenotypes and disease activity covariates. Those covariates which reflect CV risk were
27 excluded from the model, with the aim to avoid the presence of similar components on
28 both sides of the equation. Interactions, confounding factors and collinearity were
29 tested, and all comparisons were bilateral considering $p \leq 0.05$ as a significant result.
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39 SPSS 17.0 for Windows was used for the statistical analysis.
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44 **2.5. Founding source**

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46 The ASAS-COMOSPA parent study was conducted thanks to an unrestricted grant from
47 Abbvie, Pfizer and UCB. This ancillary study has not any funding source.
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3. Results

Demographics and disease characteristics of the 2001 patients included are summarized in Table 1. Participants were predominantly males (1202, 60.1%), had an average age of 46.1 ± 13.3 years and a disease duration of 9.5 ± 10.4 years. A half of patients exhibited mixed involvement (50.1%), whereas 39.8% and 10.1% of patients presented only axial and only peripheral phenotype, respectively.

In the entire population, the most prevalent CV risk factor was smoking (n=625, 31.2%), followed by hypertension (n=488, 24.4%) and obesity (n=468, 23.4%). Prevalence of T2DM, dyslipidemia, family history of MI and CRF were 6.2%, 15.9%, 18.0% and 2.2%, respectively. Regarding CVD, the estimated prevalence for IHD in our study was 3.2% whereas for stroke was 1.6% (Fig. 2).

The analysis of the association between CV risk and SpA phenotype is shown in Table 2. Several CV risk factors were noted to be less frequent in axial SpA patients compared to patients with peripheral and/or mixed involvement. Particularly, axial SpA patients exhibited lower prevalence of hypertension (19.2% vs. 33.8% vs. 26.6%, for axial, peripheral and mixed phenotypes, respectively) ($p < 0.001$) and T2DM (4.3% vs. 8.5% vs. 7.4%, for axial, peripheral and mixed phenotypes, respectively) ($p = 0.010$) than peripheral and mixed SpA patients. Obesity (19.0% vs. 24.9% vs. 26.8%, for axial, peripheral and mixed phenotypes, respectively) ($p = 0.001$) and family history of MI (15.3% vs. 15.6% vs. 21.1%, for axial, peripheral and mixed phenotypes, respectively) ($p = 0.007$) were less frequently detected in axial SpA compared to mixed SpA. Furthermore, dyslipidemia was less prevalent (13.9% vs. 28.4% vs. 15.2%, for axial, peripheral and mixed phenotypes, respectively), and FRS was lower (8.0 vs. 9.4 vs. 8.7, for axial, peripheral and mixed phenotypes, respectively) in axial and mixed SpA patients as compared to peripheral SpA ($p < 0.001$). Regarding tobacco, a higher

1 prevalence of smoking was observed in axial SpA patients compared to peripheral and
2 mixed SpA patients (38.1% vs. 27.4% vs. 26.5%, for axial, peripheral and mixed
3 phenotypes, respectively) ($p<0.001$). Concerning CVD, there were no significant
4 differences for stroke among SpA phenotypes; however, IHD was less frequent in axial
5 and mixed SpA patients compared to peripheral SpA patients (2.4% vs. 7.0% vs. 3.2%,
6 for axial, peripheral and mixed phenotypes, respectively) ($p<0.05$).

7 SpA clinical characteristics and the prevalence of CV risk and CVD in patients from
8 Northern European vs. Mediterranean countries was compared (Table 3).
9 Geographically, 1353 patients (67.6%) belonged to Mediterranean area countries and
10 648 (32.4%) to Northern European countries, with an average disease duration of $7.9 \pm$
11 12.0 and 12.8 ± 12.3 years, respectively. A higher mean age (49.9 ± 13.5 vs 44.28 ± 12.7
12 years, $p<0.001$) and longer disease duration (12.8 ± 12.3 vs 7.9 ± 12.0 years, $p<0.001$),
13 was noted in north Europeans. These patients also have significantly higher frequency
14 of HLA-B27 antigen (72.6% vs 56.6%, $p<0.001$), dactylitis (18.7% vs 13.2%, $p<0.001$),
15 uveitis (26.4% vs 17.4%, $p<0.001$), psoriasis (35.8% vs 20.3%, $p<0.001$) and IBD
16 (11.1% vs 7.0%, $p=0.002$). Regarding CV risk, higher prevalence of hypertension
17 (34.7% vs 19.4%, $p<0.001$), dyslipidemia (19.3% vs 14.4%, $p=0.005$), obesity (29.3%
18 vs 20.7%, $p<0.001$) and CRF (3.9% vs 1.5%, $p=0.001$) was observed in patients from
19 countries of Northern European region vs. Mediterranean region. Further, a higher
20 prevalence of IHD (6.2% vs 1.8%, $p<0.001$), was detected in patients from Northern
21 European vs. Mediterranean countries. Detailed prevalence for CVD and CV risk
22 factors per sex, age interval and country are summarised in an additional file [Appendix
23 A, Tables S1-S10; See the supplementary material associated with this article online].

24 Finally, a multiple logistic regression model was used to identify potential predictors
25 of high FRS (Table 4). A higher FRS was present in SpA patients from Northern
26 European vs. Mediterranean countries.

1 European vs. Mediterranean region (OR 1.69; $p < 0.001$). Furthermore, elevated FRS was
2 observed in patients with a longer disease duration (OR 1.09; $p < 0.001$), peripheral
3 involvement (OR 1.62; $p = 0.025$), psoriasis (OR 1.83; $p < 0.001$), presence of tender
4 joints (OR 1.03; $p = 0.004$) and elevated ESR levels (OR 1.01; $p = 0.040$).
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4. Discussion

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2 To our knowledge, this is the first study that has assessed the prevalence of CVD and
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4 its classical risk factors in patients with different SpA phenotypes together with the
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6 influence of the geographical area (Northern Europe vs. Mediterranean) in the
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8 prevalence of CV risk and SpA clinical characteristics.
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11 Several studies have suggested an increased risk of hypertension, T2DM, obesity and
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13 dyslipemia in the two most common subtypes of SpA, PsA [11,13,27] and AS
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15 [10,11,28], compared to the general population. However, studies evaluating the CV
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17 risk profile between both diseases have provided contradictory results [11,14,29],
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19 showing a similar or lower prevalence of CV risk in AS than PsA patients. The observed
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21 discrepancies may be due to the fact that these studies do not compared all clinical
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23 phenotypes present in SpA. The present analysis, conducted in the ASAS-COMOSPA
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25 database, is the first one that took into account the phenotypes of the disease. Our
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27 results demonstrated that axial SpA patients exhibited a lower prevalence of traditional
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29 CV risk factors than patients with peripheral and/or mixed phenotypes, and this could be
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31 associated to a lower development of CV events. Consistent with our results, previous
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33 data showed that predominantly axial SpA is related with a lower frequency of
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35 hypertension, dyslipidemia, T2DM and obesity [14,30] than PsA (a mainly peripheral
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37 disease). However, an increased prevalence of family history of MI was observed in
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39 patients with axial SpA, an independent risk factor that may contribute to a higher
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41 prevalence of CVD [30]. Finally, a higher prevalence of smoking was observed in
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43 patients with axial phenotype than in those with peripheral and mixed phenotype, as
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45 previously reported in AS patients [14,29].
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56 Regarding CV comorbidities, previous studies have demonstrated an increased risk
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58 of CV mortality in AS and PsA patients [31], with a prevalence of CV events similar for
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1 both diseases [11,29]. However, as mentioned above, these studies did not consider the
2 clinical phenotype of the disease. Our present study is the first one, to our knowledge,
3 which showed that IHD has a lower prevalence in axial SpA patients than those with
4 peripheral phenotype. Moreover, the decreased prevalence of CVD in axial SpA is
5 consistent with our results demonstrating that these patients exhibit less classical CV
6 risk factors (i.e. hypertension, obesity, T2DM, dyslipidemia and family history of MI)
7 than peripheral and/or mixed SpA patients.
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17 The reason for the reduced prevalence of CVD and its traditional risk factors in axial
18 SpA patients could be due to the low disease activity in these patients, which results in a
19 decrease of pro-inflammatory state and, consequently, in a reduction in classical CV
20 risk factors (i.e. dyslipidemia, T2DM, obesity). Nevertheless, in our present study, there
21 are non-significant differences in disease activity between axial and peripheral
22 phenotypes; although, mixed SpA patients exhibited higher levels of disease activity
23 markers than axial and peripheral SpA patients. An additional file shows this in more
24 detail (Appendix A, Table S11). Our findings are indicative of an inflammatory status at
25 the recruitment moment and only a history of low activity during disease progression
26 might explain the reduced CV events observed in axial SpA patients. Additional factors
27 should be taken into account for the difference in CV risk between phenotypes. Perhaps
28 one of the causes of the increased prevalence of vascular risk in peripheral SpA patient
29 is the physical inactivity as a result of progressive joint damage. On the same note, PsA
30 patients showed low levels of physical exercise [32] and in rheumatoid arthritis (a
31 predominantly peripheral form) an association of physical inactivity with increased CV
32 risk [33] has been demonstrated. Likewise, a higher prevalence of metabolic syndrome,
33 an independent predictor of CV events, has been noted in patients with PsA, but not AS,
34 compared to the general population [14].
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The comparison of the two population groups suggested that SpA patients from the two geographical regions displayed differences in phenotype, CV comorbidities and in classical CV risk factors. Specifically, SpA patients from Northern European countries showed a lower prevalence of axial involvement, as well as a higher mean age, longer disease duration, an elevated prevalence of HLA-B27 antigen and extra-articular manifestations than countries from Mediterranean region. In relation to CV risk, SpA patients from Northern European area showed a higher prevalence of traditional CV risk factors (i.e. obesity, hypertension, dyslipidemia, and CRF) and CV comorbidities (i.e. IHD) than those from Mediterranean countries. The increased CV events in Northern European region could be explained by the older age of the patients and longer mean disease duration, both factors related to the development of CVD [34,35]. Likewise, an HLA-B27-associated cardiac syndrome consisting of aortic insufficiency and atrial ventricular block has been described [36], demonstrating the implication of this antigen in CV pathogenesis. Nevertheless, the higher prevalence of peripheral involvement observed in this geographical area might also contribute to increased development of CV risk factors observed in these patients (Appendix A, Table S12).

The prevalence of CV risk profile was different than what has been reported in healthy individuals from each geographical area. Specifically, in Northern Europe the prevalence of obesity was estimated at 11.8% in healthy individual (reference data from Netherlands) [37,38] whereas in our SpA patients it was 29.30%. However, global prevalence of dyslipidemia, hypertension and T2DM was similar in healthy individuals (23.2%, 31.4% and 7.9% respectively) and SpA patients (19.3%, 34.7% and 6.0% respectively). Regarding countries from Mediterranean region, we noted that the estimated prevalence of hypertension, dyslipidemia and T2DM was 42.6 %, 49.5 % and 13.6 % in healthy individual (reference data from Spain) [39,40] and 19.4 %, 14.4 %

1 and 6.4 % in our SpA patients. In relation to obesity, we observed that the global
2 prevalence was estimated at 29.7 % in healthy individuals and 20.7 % in SpA patients.
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4 Thus, our data suggest that disease phenotype may be involved in the development of
5
6 CV comorbidities in SpA patients.
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9 This study presents some limitations. First, the study was performed in 2001 of the
10 3984 patients who form the COMOSPA database, which can hamper the external
11 validity of the study. Secondly, the prevalence of CVD might have been underestimated
12 as a result of the inability of patients to participate or even died at a premature age,
13 preventing them to collaborate in the study. Finally, the prevalence of CV comorbidities
14 in these patients was variable across countries. This finding can be explained by the
15 socioeconomic differences, which has an effect on health systems, and differences in
16 diet, genetic and environment; however, it is possible that this may be also influenced
17 by the selection type used in each country.
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31 Overall, our results seem to indicate that SpA phenotype and socio-demographic
32 characteristics are associated with the CV risk observed in the two geographical areas.
33 A better knowledge of the association between SpA and CV comorbidities is useful for
34 the development of a comprehensive and integrated intervention in the prevention of
35 CVD, for minimizing the impact of the CV risk, and for improving patients' long-term
36 outcome.
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40 Appendix A. Supplementary data

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42 Supplementary data (Table S1-S12) associated with this article can be found in the
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1 **Figure legend section**
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6 Figure 1. Distribution of the 2001 patients selected from the parent COMOSPA study.
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10 Figure 2. Prevalence of Cardiovascular risk factors and Cardiovascular Disease in the
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12 entire population.
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15 T2DM: type 2 diabetes mellitus. CRF: Chronic renal failure. MI: myocardial infarction
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Table 1. Demographic data and disease characteristics of the 2001 patients from the ASAS-COMOSPA study.

	Global results (%)	Axial involvement (%)	Axial and peripheral involvement (%)	Peripheral involvement (%)
Number of patients	2001	797 (39.8)	1003 (50.1)	201 (10.1)
Age (years), Mean (SD)	46.1 (13.3)	43.9 (12.6)	46.5 (13.3)	53.1(13.1)
Gender (males)	1202 (60.1)	536 (67.3)	543 (54.1)	123 (61.2)
Disease duration (years), Mean (SD)	9.5 (10.4)	9.2 (10.5)	10.0 (10.7)	8.3 (8.1)
HLA-B27 ¹	967 (62.67)	471 (59.2)	454 (45.7)	42 (21.0)
Enthesitis	805 (40.2)	208 (26.1)	526 (52.4)	71 (35.3)
Dactylitis	299 (14.9)	0 (0)	212 (21.1)	87 (43.3)
Uveitis	406 (20.3)	164 (20.6)	224 (22.3)	18 (9.0)
Psoriasis	506 (25.3)	81 (10.2)	285 (28.4)	140 (69.7)
IBD	167 (8.3)	56 (7.0)	106 (10.6)	5 (2.5)

All results are presented as mean and Standard Deviation (SD), and as percentages for continuous and categorical variables, respectively.

Percentages indicate number of patients with the covariate from the total number of patients in each category.

HLA: Human leukocyte antigen; IBD: Inflammatory Bowel Disease.

¹HLA-B27: percentage from the total of available data (n=1543).

Table 2. Comparison of the prevalence for CVD and CV risk factors among disease clinical forms.

	Axial involvement	Axial and peripheral involvement	Peripheral involvement	p-value¹
	n=797	n=1003	n=201	
	(%)	(%)	(%)	
Hypertension	153 (19.2)	267 (26.6) ^a	68 (33.8) ^a	<0.001
T2DM	34 (4.3)	74 (7.4) ^a	17 (8.5) ^a	0.010
Dislipidemia	111 (13.9)	152 (15.2)	57 (28.4) ^{a,b}	<0.001
Obesity	151 (19.0)	267 (26.8) ^a	50 (24.9)	0.001
CRF	15 (1.9)	25 (2.5)	5 (2.5)	n.s.
Tobacco	304 (38.1)	266 (26.5) ^a	55 (27.4) ^a	<0.001
Family history MI	122 (15.3)	206 (21.1) ^a	31 (15.6)	0.007
IHD	19 (2.4)	32 (3.2)	14 (7.0) ^{a,b}	0.005
Stroke	12 (1.5)	16 (1.6)	5 (2.5)	n.s.
FRS, Mean (SD)	8.0 (8.1)	8.7 (8.7)	12.2 (9.4) ^{a,b}	<0.001

All results are presented as percentages for categorical variables, and as mean and Standard Deviation (SD) for continuous variables. Percentages indicate number of patients with the covariate from the total number of patients in each disease clinical form.

¹ Calculated using ANOVA for the covariate FRS with Post-hoc analysis using Sidak test, and a chi-square test for the rest of covariates.

^a significant differences ($p \leq 0.05$) regarding Axial involvement.

^b significant differences ($p \leq 0.05$) regarding Axial and Peripheral involvement.

CRF: Chronic Renal Failure; IHD: Ischemic heart disease; FRS: Framingham Risk Score. MI: Miocardial infarction. T2DM: Type 2 diabetes mellitus.

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Table 3. Comparison of the prevalence of disease characteristics, CV risk factors and CVD in Northern European countries vs. Mediterranean countries.

	Global results	Mediterranean	Northern		
		countries	European	OR (95% CI)	p-value ¹
	n=2001	n=1353	n=648		
	(%)	(%)	(%)		
Age (years), Mean (SD)	46.1 (13.3)	44.28 (12.7)	49.95 (13.5)	1.03 (1.02-1.04)	<0.001
Sex (male)	1202 (60.1)	804 (59.4)	398 (61.4)	1.09 (0.90-1.32)	n.s.
Disease d (years), Mean (SD)	9.5 (10.4)	7.9 (12.0)	12.8 (12.3)	1.04 (1.03-1.05)	<0.001
HLA- B27 ²	967 (62.67)	604 (56.6)	363 (76.2)	2.46 (1.93-3.14)	<0.001
Clinical form					
- Axial (ref.)	797 (39.8)	585 (43.2)	212 (32.7)	Reference	
- Axial and peripheral	1003 (50.1)	671 (49.6)	332 (51.2)	1.36 (1.11-1.67)	0.003
- Peripheral	201 (10.1)	97 (7.17)	104 (16.05)	2.96 (2.15-4.07)	<0.001
Enthesitis	805 (14.9)	547 (40.4)	258 (39.8)	0.97 (0.80-1.18)	n.s.
Dactylitis	299 (40.2)	178 (13.2)	121 (18.7)	1.52 (1.18-1.95)	0.001
Uveitis	406 (20.3)	235 (17.4)	171 (26.4)	1.71 (1.37-2.14)	<0.001
Psoriasis	506 (23.3)	274 (20.3)	232 (35.8)	2.19 (1.78-2.70)	<0.001
IBD	167 (8.3)	95 (7.0)	72 (11.1)	1.65 (1.2-2.28)	0.002
Hypertension	488 (24.4)	263 (19.4)	255 (34.7)	2.20 (1.78-2.72)	<0.001
T2DM	125 (6.2)	86 (6.4)	39 (6.0)	0.94 (0.64-1.39)	n.s.
Dyslipidemia	320 (15.9)	195 (14.4)	125 (19.3)	1.42 (1.11-1.81)	0.005
Obesity	468 (23.4)	280 (20.7)	188 (29.3)	1.59 (1.28-1.96)	<0.001
CRF	45 (2.2)	20 (1.5)	25 (3.9)	2.67 (1.47-4.85)	0.001
Smoking status	625 (31.2)	406 (30.0)	219 (33.8)	1.19 (0.97-1.45)	n.s.
Family history of MI	359 (18.0)	232 (17.1)	127 (19.6)	1.16 (0.92-1.48)	n.s.
IHD	65 (3.2)	25 (1.8)	40 (6.2)	3.49 (2.10-5.81)	<0.001
Stroke	33 (1.6)	17 (1.3)	16 (2.5)	1.99 (0.99-3.96)	n.s.
FRS, Mean (SD)	8.8 (8.6)	7.49 (7.8)	11.42 (9.6)	1.05 (1.04-1.06)	<0.001

All results are presented as mean and Standard Deviation (SD), and number of patients (%) for continuous and categorical variables, respectively. Percentages indicate number of patients with the covariate from the total number of patients in each category.

¹ Calculated using a univariate logistic regression. Mediterranean countries were used as the reference category. The OR represents Northern European countries vs. Mediterranean countries.

² Number of HLA-B27 positive patients from the total of available data (n=1532).

Disease d: disease duration. HLA: Human leukocyte antigen; CI: Confidence interval; CRF: Chronic Renal Failure; FRS: Framingham Risk score; IBD: Inflammatory bowel disease; IHD: Ischemic heart disease; MI: Myocardial Infarction; OR: Odds Ratio; SD: Standard deviation; T2DM: Type 2 diabetes mellitus. Ref.: Reference.

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Table 4. Identification of potential predictors of high Framingham index score¹.

	OR (95% CI)	p-value
North Europe (ref. Mediterranean patients)	1.68 (1.28 – 2.21)	<0.001
Disease duration (years)	1.09 (1.08 – 1.11)	<0.001
Clinical form:		
-Mixed involvement (ref. axial)	1.02 (0.76 – 1.37)	0.877
-Peripheral involvement (ref. axial)	1.85 (1.25 – 2.75)	0.002
Psoriasis	1.99 (1.47 – 2.69)	<0.001
Dactylitis	0.65 (0.45 – 0.95)	0.024
Number of tender joints	1.03 (1.01 – 1.05)	0.003
ESR	1.01 (1.00 – 1.01)	0.042

Hosmer-Lemeshow test: χ^2 square = 8.916, p=0.349

¹ Calculated using a multiple logistic regression. Primary outcome: Framingham risk score ≥ 15 .

Variables included in the model: Disease duration, geographical area, HLA-B27, clinical form, dactylitis, enthesitis, uveitis, psoriasis, inflammatory bowel disease, number of tender joints, number of swollen joints, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score-CRP), CPR (C Reactive Protein), ESR (Erythrocyte Sedimentation Rate) and PGVAS (Patient Global Visual Analogue Scale).

Ref.: Reference.

Fig. 1. Distribution of the 2001 patients selected from the parent COMOSPA study.

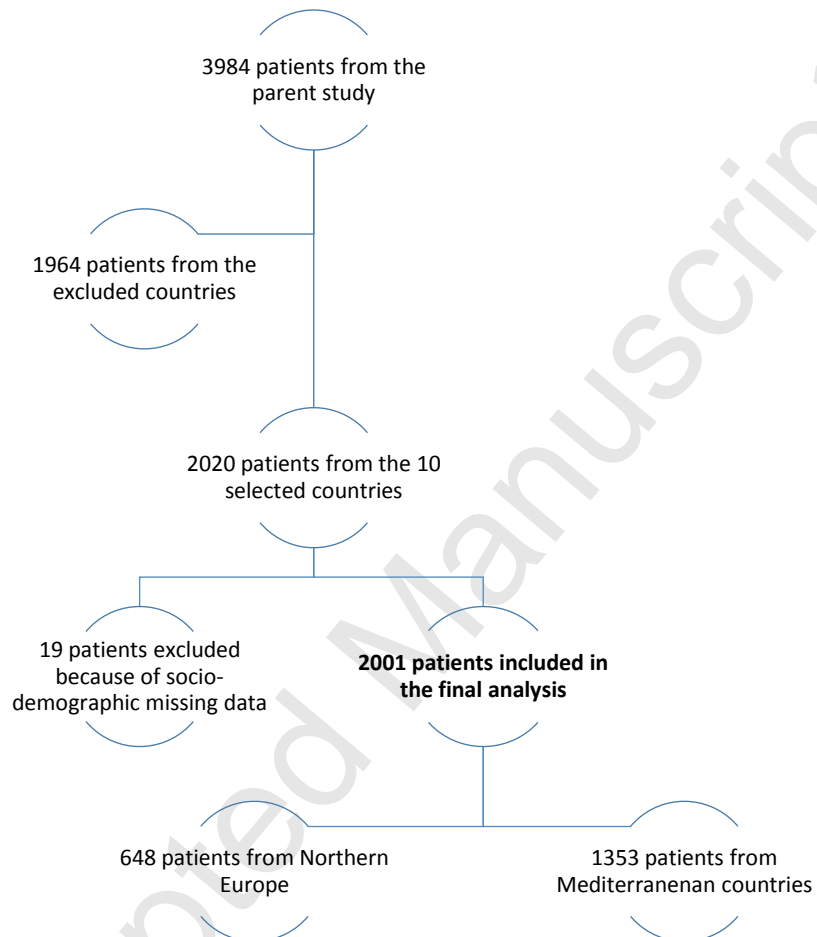


Fig. 2. Prevalence of Cardiovascular risk factors and Cardiovascular Disease in the entire population.

