RHEUMATOLOGY

Rheumatology 2022;61:2043–2053
doi:10.1093/rheumatology/keab638
Advance Access publication 13 August 2021

Original article

Individual-level and country-level socio-economic factors and health outcomes in spondyloarthritis: analysis of the ASAS-perSpA study

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Abstract

Objectives. The aim of this study was to investigate the association between individual-level and country-level socio-economic (SE) factors and health outcomes across SpA phenotypes.

Methods. Patients with axial SpA (axSpA), peripheral SpA (pSpA) or PsA from the ASAS-perSpA study (in 23 countries) were included. The effect of individual-level (age, gender, education and marital status) and country-level [e.g. Gross Domestic Product (GDP)] SE factors on health outcomes [Ankylosing Spondylitis Disease Activity Score (ASDAS) $\geq$ 2.1, ASDAS, BASFI, fatigue and the Assessment of SpondyloArthritis international Society Health Index (ASAS-HI)] was assessed in mixed-effects models adjusted for potential confounders. Interactions between SE factors and disease phenotype were tested. A mediation analysis was conducted to explore whether the impact of country-level SE factors on ASDAS was mediated through biologic/targeted synthetic (b/ts) DMARD uptake.

Results. In total, 4185 patients (61% males, mean age 45) were included (65% axSpA, 25% PsA, 10% pSpA). Female gender [β=0.14 (95% CI: 0.06, 0.23)], lower educational level [β = 0.35 (0.25, 0.45)) and single marital status [β = 0.09 (0.01, 0.17)] were associated with higher ASDAS. Living in lower GDP countries was also associated with higher ASDAS [β = 0.39 (0.16, 0.63)], and 7% of this association was mediated by b/tsDMARD uptake. Higher BASFI was similarly associated with female gender, lower education and living alone, without the effect of country-level SE factors. Female gender and lower educational level were associated with worse ASAS-HI, while more fatigue was associated with female gender and higher country-level SE factors [lower GDP, β = −0.46 (−0.89 to −0.04)]. No differences across disease phenotypes were found.

Conclusions. Our study shows country-driven variations in health outcomes in SpA, independently influenced by individual-level and country-level SE factors and without differences across disease phenotypes.

Key words: spondyloarthritis, psoriatic arthritis, peripheral arthritis, disease outcomes, socio-economic factors

Rheumatology key message

- Individual socio-economic factors are independently associated with poorer outcomes in SpA.
- Living in a low-GDP country is independently associated with higher disease activity but lower fatigue levels.
- There are no differences between the effects of socio-economic factors across the various SpA phenotypes.

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Submitted 25 May 2021; accepted 29 July 2021

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CLINICAL SCIENCE

Introduction

Social determinants of health encompass social and economic conditions that influence the health of individuals and communities [1]. These conditions are shaped by an individual's socio-economic (SE) background (e.g. gender, educational level, occupation or income) as well as by country-level SE factors (including government health spending and access to the health system), which vary widely across the world and account for health inequalities and inequities between and within countries [2–5]. Tackling inequities, i.e. inequalities that are unfair and avoidable, can improve health outcomes, especially in chronic conditions, where the gap is wider [6].

Considerable evidence shows that indicators of low SE status (SES) at an individual level are associated with worse self-reported health outcomes and higher disease activity in RA [7, 8]. More recently, multinational studies clarified the independent impact of individual-level and country-level SE factors and their differences across countries; lower-income countries were associated with worse disease activity and functional ability outcomes whereas, paradoxically, higher-income countries showed higher fatigue perception [9, 10].

Beyond RA, recent evidence from the cross-sectional, multinational ASAS-COMOSPA (COMOrbidities in SpA) study largely reported similar findings in axial SpA (axSpA), although (a) effects were smaller and (b) the lack of fatigue data prevented its analysis [11]. Interestingly, although in different proportions, studies in both RA and SpA confirmed that lower access to costly biologic DMARDs (bDMARDs) could be a possible pathway linking lower SES with higher disease activity [12, 13]. However, it was not explored whether the effect of individual SE factors differs depending on the country-level SES, for instance, whether the adverse impact of low education on various health outcomes is even worse when living in a country with a low SES.

axSpA is one of the phenotypes that belong to the SpA spectrum of disease. The term SpA encompasses a heterogeneous group of disorders [14] divided in two major groups: axial SpA [(axSpA), which includes non-radiographic asSpA (nr-axSpA) and radiographic axSpA (r-axSpA)] and peripheral SpA [(pSpA), which includes PsA, reactive arthritis, IBD-associated arthritis and undifferentiated SpA (uSpA)] [14, 15]. Whether the impact of SE factors across the different SpA phenotypes varies, is largely unknown.

In the case of PsA, the wide diversity of domains (back pain, peripheral arthritis or skin disease) might have differential impact on patients depending on the SE context, and thus it would be reasonable to explore the role of SE background across the various phenotypes. It is imperative therefore, to understand whether the effect of individual-level and country-level SE contribute differently to health outcomes, as this might require adjustments in care and healthcare organization. Moreover, SpA is known to impact one's life across many core domains, including disease activity (reflecting inflammation), physical functioning, fatigue, and overall functioning and health. Higher disease activity is known to lead to worse physical functioning [16]; however, it is not known whether this relationship varies across countries and whether this is associated with the SES status of different countries. The multinational Assessment of SpondyloArthritis international Society (ASAS)-peripheral involvement in SpondyloArthritis (ASAS-perSpA) study provides an ideal setting in which to investigate the abovementioned unaddressed questions.

The aims of this study were (1) to investigate the association between individual-level and country-level SE factors and various core outcomes in SpA and to determine differences across the disease phenotypes; (2) to explore whether individual SE factors have a different impact on health outcomes according to country-level SE factors; (3) to investigate whether any effect of these SE factors is mediated by the use of biologic or targeted synthetic DMARD (b/tsDMARD) therapy; and (4) to investigate whether the impact of disease activity on functional ability varies according to country-level SE factors.

Methods

Study design and data collection

Data from the ASAS-perSpA study were used [17]. Briefly, the ASAS-perSpA study is an international, multicentre and cross-sectional study with 24 participating countries (23 actively involved). Patients aged 18 or older with a diagnosis of axSpA, PsA or pSpA according to their rheumatologist were recruited and data was collected between July 2018 and February 2020. Written informed consent was obtained from all patients before enrolment and Ethics Committees from the individual participating centres approved the study.

Outcome variables

The following health outcomes were investigated:

Disease activity

Disease activity was assessed using the Ankylosing Spondylitis Disease Activity Score (ASDAS). This measure combines patient-reported overall back pain, overall peripheral pain/swelling, duration of morning stiffness, global assessment of disease activity, ranging from 0–10 in a Numeric Rating Scale (NRS), and one acute phase reactant (CRP or ESR) as a measure of inflammation. ASDAS was calculated with CRP and explored both as a continuous and a dichotomized variable [inactive disease (ASDAS < 2.1) or active disease (ASDAS ≥ 2.1)] [18, 19].

Physical function

Physical function was assessed using the self-reported BASFI, which assesses difficulties in performing 10 activities in everyday life. The total score ranges between 0 and 10, with 10 indicating worse functional capacity [20].

Fatigue and overall functioning and health

Fatigue was evaluated using the first item of the BASDAI [21] in a 0–10 NRS; and overall functioning and health through the ASAS Health Index (ASAS-HI), a Patient-Reported Outcomes (PROs) questionnaire containing 17 dichotomous items addressing categories of pain, emotional functions, sleep, sexual functions, mobility, self-care, community life and employment, ranging from 0–17, with lower scores indicating a better health status [22].

Individual-level and country-level socio-economic factors

Individual SE factors were age, gender, educational level (highest level of educational attainment, distinguishing primary school or less, secondary school, and university degree as the reference category) and marital status (married or not living alone as the reference category, single and divorced or widowed).

Country-level SE factors were Gross Domestic Product (GDP) and Current Health Care Expenditure (HCE) per capita in international dollars [adjusted for purchasing power parity (PPP)], Human Development Index (HDI, range from 0 to 1) and the Gini Index of income inequality, [range from 0 (absolute equality) to 100 (absolute inequality)]. Latest values available for GDP, HCE and Gini Index were collected from the World Development Indicators database from the World Bank (2019, 2018 and 2012–2018, respectively) [23]. HDI was recorded from the 2019 Global Human Development Reports published by the United Nations Development Programme (UNDP) with data from 2018 [24]. For better interpretation of the results, each indicator was dichotomized into lower and higher, based on the median value. The lower category of each of them was used as the reference, except for the Gini Index, where higher values (corresponding to higher inequities) were chosen as the reference.

Covariates

The following lifestyle and clinical information was collected and tested as potential confounders: disease duration (since diagnosis, in years), smoking status (past or current *vs* never smoker), BMI, presence of HLA-B27 (positive, negative or missing), history of axial involvement, history of peripheral arthritis, enthesitis or dactylitis, extra musculoskeletal manifestations (EMMs) including uveitis, psoriasis and IBD and the presence of concomitant FM diagnosed by the rheumatologist (yes/no). Lastly, NSAIDs use during last month, history of conventional synthetic DMARD (csDMARD) and b/tsDMARD therapy since diagnosis, and current steroids intake were also recorded. Finally, disease activity assessed by ASDAS and functional ability assessed by BASFI were included in some models, as appropriate.

Statistical analysis

The association between individual SE factors and each health outcome was analysed using mixed-effects logistic and linear regression models, as appropriate. The mixed-effects structure allowed us to account simultaneously for the within-country and between-country variances, by including country of residence as a random intercept [25].

Covariates associated with the outcomes in the univariable analysis ($P < 0.20$) were sequentially added into the multivariable model and retained if significantly contributing to explain the outcome ($P < 0.05$) or if a relevant confounder of the main relationships of interest. Of note, as disease activity is an important determinant of physical function, fatigue, health and functioning, ASDAS was added as a covariate in the models of the remaining outcomes. Next, to investigate the macroeconomic influence on the outcomes, country-level SE factors were each entered separately into the final models: GDP (lower *vs* higher); HCE (lower *vs* higher); HDI (lower *vs* higher); and Gini Index (higher *vs* lower). The likelihood ratio test was used to compare the importance of the random intercept and random slope in the model (*vs* logistic or linear regression).

Potential interactions between SE factors and disease phenotype as well as country characteristics were tested in the final models. If statistically ($P < 0.10$) and clinically relevant, analyses were stratified for the disease phenotype or for the country-level SE factors, respectively. Additionally, in order to assess whether the relationship between disease activity and functional ability varied according to country-level SE, interaction models were also performed between disease activity and country-level SE, following the same procedure.

Lastly, mediation analysis was conducted to explore whether the impact of country-level SE factors on ASDAS was mediated through b/tsDMARDs uptake. Briefly, through the Baron and Kenny procedure, we decomposed the effect of each SE factor on disease activity into natural direct effects (NDEs; e.g. the effect of GDP on disease activity) and natural indirect effects (NIEs; e.g. the effect of GDP on disease activity through its effect on treatment exposure), with b/tsDMARD uptake as the mediator. Proportion of b/tsDMARD uptake mediation (PMed) was computed as: PMed = NIEs/(NIEs + NDEs). Mediation analyses were only performed for SE factors that were significant in the multivariable model and adjusted for the same covariates from the mixed-effect model. CIs were derived using the delta method [26]. Analyses were performed using Stata SE V.14.

Results

From a total of 4185 patients with SpA across 23 countries, 2719 (65%) were diagnosed by the rheumatologist as axSpA, 1033 (25%) PsA and 433 (10%) pSpA. The mean age was 45 years (S.D. 14), and 2562 (61%) were male. Only 17% of the patients did not achieve an educational degree beyond primary school, while 43% and

Table 1 Patient characteristics according to SpA phenotype

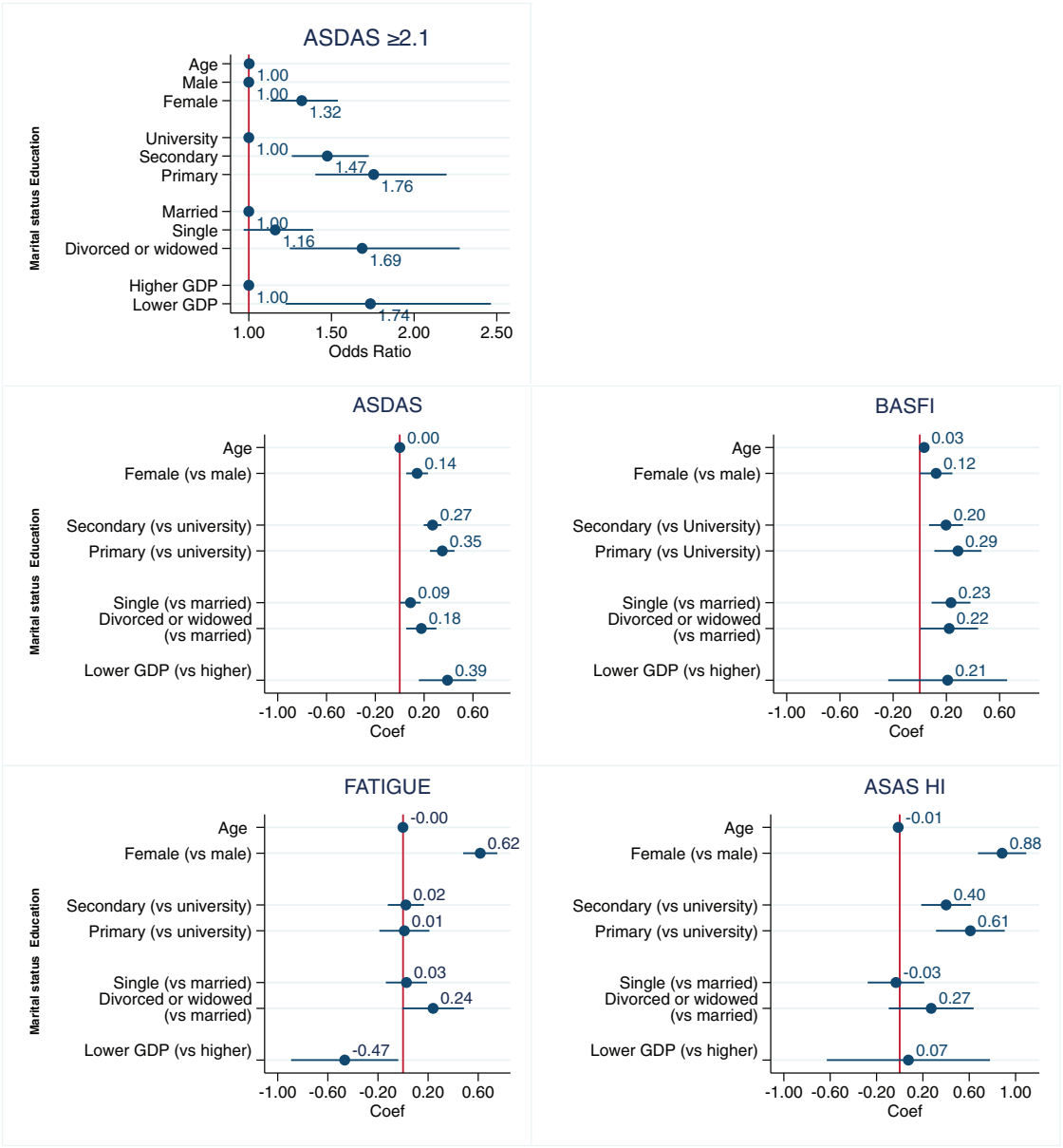
	axSpA	PsA	pSpA	*p*
n (%)	2719 (65)	1033 (25)	433 (10)	
Age (years)	42 (13)	52 (13)	44 (14)	<0.001
Disease duration (years)	14.4 (11.1)	16.8 (12.3)	10.1 (9.4)	<0.001
Diagnosis delay (years)	5.8 (7.7)	9.1 (11.1)	4.2 (6.6)	<0.001
Male gender	1858 (68)	501 (48)	203 (47)	<0.001
Educational level				<0.001
University	1178 (43)	320 (31)	197 (46)	
Secondary school	1140 (42)	472 (46)	180 (42)	
Primary school	399 (15)	239 (23)	56 (13)	
Current marital status				<0.001
Married or living together	1735 (64)	748 (73)	267 (62)	
Single	815 (30)	158 (15)	141 (32)	
Divorced or widowed	168 (6)	124 (12)	25 (6)	
Employed (<65 years)	1652 (64)	512 (59)	224 (56)	<0.001
BMI (kg/m^2)	25.9 (5.1)	28.0 (5.9)	26.3 (5.4)	<0.001
Smoking status				<0.001
Never smoker	1532 (56)	538 (52)	304 (70)	
Current or past smoker	1185 (44)	494 (48)	128 (30)	
HLA-B27 positive	1709 (63)	86 (8)	197 (46)	<0.001
Axial involvement[a]	2651 (98)	367 (36)	238 (55)	<0.001
Peripheral arthritis[a]	978 (36)	938 (91)	410 (95)	<0.001
Dactylitis[a]	164 (6)	382 (37)	100 (23)	<0.000
Enthesitis[a]	1113 (41)	473 (46)	248 (57)	<0.001
Uveitis[a]	588 (22)	27 (3)	75 (10)	<0.001
IBD[a]	132 (5)	6 (1)	25 (6)	<0.001
Psoriasis[a]	187 (7)	946 (92)	64 (15)	<0.001
FM	212 (8)	120 (12)	48 (11)	<0.001
CRP (mg/l)	11.7 (26.6)	11.4 (28.6)	13.9 (25.4)	0.012
ASDAS (CRP)	2.5 (1.1)	2.6 (1.1)	2.6 (1.2)	0.02
ASDAS (CRP) ≥2.1	1594 (59.4)	636 (62.7)	275 (64.2)	0.058
BASFI (0–10)	3.0 (2.6)	3.1 (2.7)	2.8 (2.6)	0.054
Fatigue (BASDAI Q1, 0–10)	4.5 (2.8)	4.9 (2.8)	4.6 (2.8)	<0.001
ASAS-HI (0–17)	6.3 (4.5)	7.2 (4.7)	6.6 (4.4)	<0.001
EQ-5D (0–1)	0.7 (0.3)	0.6 (0.3)	0.66 (0.3)	<0.001
NSAIDs intake[b]	1931 (71)	614 (59)	311 (72)	<0.001
Current Steroids	202 (7)	200 (19)	89 (21)	<0.001
csDMARDs (since diagnosis)	628 (23)	616 (60)	230 (53)	<0.001
b/tsDMARDs (since diagnosis)	1289 (47)	522 (50)	158 (36)	<0.001

[a]Results reflect mean (S.D.) or *n* (%). Disease phenotype and FM were defined by the physician. Comparisons by Chi^2 and *t* test. Data were incomplete for: education/marital status ($n=4$), employment status ($n=8$), BMI ($n=15$), HLA-B27 ($n=1227$), fatigue ($n=11$), ASDAS ($n=60$), CRP ($n=29$), BASFI ($n=6$), FM ($n=2$). Manifestation ever present. [b]During last month. axSpA: axial SpA; pSpA: peripheral spondyloarthritis; ASDAS: AS DAS; ASAS-HI: Assessment of SpondyloArthritis international Society Health Index Health Index; EQ-5D: Euro Quality of life 5 Dimensions; cs/b/tsDMARDs: conventional synthetic/biologic/targeted synthetic DMARDs.

40% achieved secondary and university degrees, respectively. Sixty-five percent of patients were married or living with a partner, 27% single and 8% divorced or widowed. PsA patients were older, with a slight female predominance, lower educational level and higher cDMARDs and b/tsDMARDs intake (Table 1). Country-specific descriptions can be found in Supplementary Tables S1 and S2, available at *Rheumatology* online.

Across all countries, 61% patients had active disease (ASDAS ≥ 2.1), with the lowest frequency reported in Japan (44%), and the highest in Egypt (90%). Overall mean (S.D.) ASDAS was 2.5 (1.1) and mean BASFI 3.0 (2.6), with Japan showing the lowest scores for both [ASDAS 2.1 (0.9) and BASFI 1.6 (2.3)], and Chile the highest scores [ASDAS 3.3 (1.2) and BASFI 5.6 (2.9)]. Mean fatigue was 4.6 (2.8), with the lowest values in Morocco [3.5 (2.5)] and the highest reports in Chile [6.4 (2.8)]; and the mean overall ASAS HI was 6.6 (4.6), ranging from 4.7 (3.5) in China to 9.8 (4.4) in Chile. Lastly, looking for an objective measure, the mean CRP value was 11.9 (26.7), with a very wide range of values, from 4.3 mg/l (10.6) in Italy to 34.5 mg/l (69) in Argentina (see Supplementary Fig. S1, available at *Rheumatology* online). b/tsDMARDS were used by 46% of the patients across countries, with a marked variance in frequency, from 14% in India to 77% in Italy and 92% in Canada.

Fig. 1 Association between individual-level and country-level socio-economic factors and health outcomes in SpA



Effect of individual-level and country-level socio-economic factors on ASDAS ≥ 2.1, continuous ASDAS, BASFI, fatigue and Assessment of SpondyloArthritis international Society Health Index (ASAS-HI), derived from multivariable mixed-effects models adjusted by clinical confounders. (ASDAS ≥ 2.1 model: BMI, axial involvement, peripheral arthritis, enthesitis, FM and NSAIDs; ASDAS model: BMI, smoking status, axial involvement, peripheral arthritis, enthesitis, FM and NSAIDs; BASFI model: BMI, ASDAS, axial involvement, FM and conventional DMARDs; fatigue model: ASDAS, uveitis and FM; ASAS HI model: smoking status, ASDAS, BASFI, peripheral arthritis and FM) (full model coefficients in Supplementary Table S3, available at *Rheumatology* online).

Relationship between individual SE factors and health outcomes

Female gender, lower educational level and not being married or living with a partner were associated with higher ASDAS in multivariable models. Furthermore, these factors discriminated between active (ASDAS ≥ 2.1) and low disease activity: female gender (OR = 1.32; 95% CI: 1.13, 1.54), educational level (primary *vs* university OR = 1.76; 95% CI: 1.40, 2.20) and being divorced or widowed (OR = 1.68; 95% CI: 1.25, 2.28) (Fig. 1).

Female gender was likewise associated with worse PROs: 0.12 points higher BASFI (95% CI: 0.01, 0.24), 0.88 points higher ASAS-HI (95% CI: 0.68, 1.09) and 0.62 points higher fatigue (95% CI: 0.48, 0.75). Lower

TABLE 2 Effect of country-level socio-economic factors on disease activity (ASDAS), physical function (BASFI), fatigue and ASAS-HI

Assessment	ASDAS ≥2.1 Odds ratio (95% CI)	ASDASβ (95% CI)	BASFIβ (95% CI)	Fatigue β (95% CI)	ASAS-HIβ (95% CI)
GDP (lower *vs* high)	**1.74 (1.22, 2.46)**	**0.39 (0.16, 0.63)**	0.21 (−0.24, 0.66)	**−0.46 (−0.89, −0.04)**	0.07 (−0.63, 0.78)
HCE (lower *vs* high)	1.37 (0.92, 2.02)	**0.28 (0.01, 0.54)**	−0.04 (−0.49, 0.40)	**−0.64 (−1.02, −0.26)**	0.12 (−0.57, 0.82)
HDI (lower *vs* high)	1.37 (0.92, 2.04)	**0.28 (0.01, 0.55)**	0.01 (−0.44, 0.46)	**−0.49 (−0.92, −0.07)**	0.25 (−0.44, 0.95)
Gini index (higher *vs* lower)	1.08 (0.71, 1.64)	0.07 (−0.21, 0.36)	0.09 (−0.36, 0.54)	**−0.55 (−0.95, −0.14)**	0.02 (−0.68, 0.71)

*Results from multilevel multivariable linear and logistic regression analyses. Values from 2019 (GDP), 2018 (HCE, HDI), and the last available (Gini index). HCE, Gini index estimates are derived from three separate models (due to collinearity), by replacing GDP in the final multivariable mixed-effects models shown in Fig. 1 and Supplementary Table S3, available at *Rheumatology* online. Estimates with $P < 0.05$ are highlighted in bold. ASAS-HI: Assessment of SpondyloArthritis international Society Health Index Health Index; GDP: gross domestic product; HCE: healthcare expenditure; HDI: Human Development Index.

education was also associated with higher BASFI and ASAS-HI, 0.29 and 0.61 points, respectively, but not with fatigue. Patients living alone (single and divorced or widowed) reported worse functional ability (∼0.22 higher BASFI). Lastly, age had a significant but smaller effect on functional impairment (0.03 higher units of BASFI for each year of age), and ASAS-HI score (−0.01 units). Full model coefficients are shown in Supplementary Table S3, available at *Rheumatology* online. No significant differences were found across disease phenotypes (axSpA, pSpA and PsA) for any of the outcomes.

Relationship between country-level SE factors and health outcomes

Living in lower-GDP countries was associated with higher ASDAS (lower GDP *vs* higher $\beta = 0.39$; 95% CI: 0.16, 0.63), and higher odds of active disease (OR = 1.74; 95% CI: 1.22, 2.46). Similar results were found for HCE and HDI (Table 2). Conversely, lower fatigue score was associated with lower GDP countries [compared with higher-GDP countries ($\beta = -0.46$; 95% CI: −0.89, −0.04)]. Comparable patterns were seen for fatigue for the remaining of the country-level SE factors. Physical function and ASAS-HI were not associated with country-level SE factors. These results were not modified by disease phenotype.

Individual-level and country-level SE factors across countries

Exploring potential differential effects of individual level SE factors across countries revealed a difference in variance for the association between gender and ASDAS. By adding a random slope to the model, it was demonstrated that even though females had higher mean ASDAS than males, their variance across countries was lower (female variance: 0.94 *vs* male variance: 1.07), suggestive of an interaction. When further cross-level interactions were tested (i.e. between gender and countries' GDP), the effect of gender across different country-level SE factors was not relevant (data not shown). Furthermore, the remaining interactions between individual-level and country-level SE factors were not statistically significant or clinically relevant. In other words, the effect of the individual SE factors on the various outcomes was not associated with the country-level SE factors.Finally, the relationship between disease activity and functional ability did not vary across countries with different SES; that is, when taking BASFI as the outcome, associations between disease activity and country-level SE factors were not statistically significant (data not shown).

Mediation analysis

Use of b/tsDMARDs had a small but statistically significant mediation effect on the relationship between lower-income countries and higher disease activity. Patients in countries with lower GDP (*vs* those with higher GDP) had 0.34 (95% CI: 0.27, 0.41) higher ASDAS units, and 0.02 (95% CI: 0.01, 0.03) of those units (7%; 95% CI: 0, 10) was due to lower uptake of b/tsDMARDs. This mediated effect was consistent when assessing the other SE factors: 11% (95% CI: 5.2, 16.8) for HCE and 14.3% (95% CI: 6.4, 22.2) for HDI mediated effect through b/tsDMARDs.

Discussion

This worldwide study of patients across the SpA spectrum demonstrates associations between individual-level and country-level SE factors and various health outcomes. Female gender, lower educational level and single marital status were associated with higher disease activity and higher odds of active disease, as well as worse physical function; female gender and lower educational level were the SE factors associated with worse overall functioning and health (ASAS-HI); and female gender was also associated with more fatigue. Interestingly, living in wealthier countries was related to lower disease activity but to higher reports of fatigue.

To the best of our knowledge, this is the first study in SpA patients evaluating the effect of SE factors not only on traditionally studied outcomes i.e. disease activity and function, but also on multifaceted outcomes that matter most to patients, namely fatigue and overall functioning and health status; in addition, we understand it is the first study in SpA patients to study the relationship between individual-level and country-level SE factors and the different disease phenotypes.

Our findings are in line with the recent ASAS-COMOSPA study, in which female gender and lower educational level were found to be associated with higher disease activity, functional disability and higher odds of an ASDAS score $\geq$2.1 [11]. The present study included marital status, which permitted us to show that living alone (being whether single, divorced or widowed) was similarly related (although in a minor magnitude) to worse outcomes. Furthermore, we found no proof for differences in effects varying across disease phenotype.

Regarding the country-level SE factors, unlike the COMOSPA study [11], we found that not only living in less developed countries (lower HDI), but also in economies with lower income and healthcare spending (represented by lower GDP and HCE), is associated with higher disease activity, even after adjusting for individual SE and clinical variables. As has been found in other disease areas, our study adds to the literature suggesting superior health outcomes in higher-income countries (and likely better health systems and treatment access) [3, 10, 27].

Only a very small part of the effect of these country-level SE factors can be explained by inequities in b/tsDMARDs uptake, meaning that differences may be caused not only by the lack of access to more effective though expensive treatments, but also by lower access to rheumatologists, and differences in knowledge and medical decision-making, medical and patient beliefs, preferences, and cultural background [28]. Our study indicates that the effect of gender on disease activity (although with differences in magnitude) did not differ between countries but appeared to be universal.

Disease activity and female gender have proven in several publications to be important determinants of fatigue [29–31]; however, in this analysis, we could also demonstrate, by the inclusion of confounders like FM diagnosis, that female gender is consistently and independently associated with higher reports of fatigue. In addition to variations in fatigue levels across countries, our study demonstrated significant associations with country-level SE factors: patients living in higher-GDP countries were more likely to have higher levels of fatigue than those living in lower-GDP countries; the same results were found with HCE and HDI, and also with the Gini index: countries with greater income inequality showed higher fatigue scores. Previous reports in RA speculated on this paradoxical effect of country-level SES on disease activity opposed to fatigue, and referred to the role of stressors and higher personal and environmental expectations for patients to fully participate in all aspects of life [9]. Sociocultural factors and personal beliefs likely play a role in explaining this phenomenon, which are not easy to measure, and therefore there is no straightforward explanation of this paradox. In line with this, a different longitudinal study, again in RA, demonstrated that due to its multidimensional origin, fatigue is a persistent problem despite treatment [32]. Also in axSpA, there is evidence that fatigue remains unresponsive to bDMARDs in nearly 80% of patients, independently of disease activity improvement [33].

Higher ASAS-HI was found in lower-educated patients. Although these factors were previously reported in r-axSpA cohorts [34, 35], in the current study we could also corroborate the same behavior in PsA and pSpA.

We found no reinforcement between the two levels of SE factors (cross-level interaction). This means that individual characteristics did not impact in a different magnitude or direction in higher- or lower-income countries or vice versa. Similarly, no evidence was found of a different impact of disease activity on functional ability across countries. This means that the relationship between both outcomes does not seem to vary depending on the SES of the countries.

Our study had general limitations: although we could compare national income and healthcare spending by the inclusion of national macroeconomic indicators, they do not provide information on use of the health system, insurance schemes, accessibility of rheumatology services or cost of health and social services, which may represent more reliable national determinants of health outcomes [27]. A clear example is the USA: in spite of being the highest-income country (although among the countries with a higher GINI index), it consistently remains one of the countries with poorer outcomes. A second limitation is that macro-economic indicators do not tell the whole story about access, as level of co-payment, type of services reimbursed, number of rheumatologists and access to specialists would play a major role in further explaining country-level SE variation in disease activity; these data were, unfortunately, not available for exploration. Furthermore, we appreciate that the country-level factors assessed in our study do not capture all aspects of socio-cultural background. While a previous study did not show a relationship between language and latitude (as a potential surrogate for climate/lifestyle) and health outcomes, many potentially relevant socio-cultural aspects are yet not measurable [9]. In addition, we did not include some well-known determinants of fatigue, like comorbidities (anaemia, hypothyroidism, etc.) and sleep disturbance, as these data were not collected [36].

Another limitation was the fact that the participating centres of each country were specialized tertiary institutions, with ASAS members, which may have contributed to some selection bias; not to mention that the number of patients included by each country varied considerably. Thus, our results may not be generalizable to all SpA patients (e.g. those who are managed by primary

care only) or fully represent SpA patients from countries that contributed small patient numbers.

Lastly, some of the tools used for health outcomes were validated in axSpA, but not directly in PsA or pSpA. However, since there is a known overlap between the disease phenotypes [37], which was precisely the rational for comparing them, we decided to apply the same outcomes in all of them to enable comparison.

In conclusion, we found that individual SE factors, mainly female gender, low educational level and living alone are associated with poorer outcomes in SpA, with no differences across SpA phenotypes. Even though the four outcomes varied across the world, association with country-level SE factors could only be found with disease activity (higher ASDAS in lower income countries) and fatigue (higher fatigue in higher income countries, and those with higher inequities). The use of b/tsDMARDS could only marginally explain the relationship between poorer countries and worse outcomes; further analysis should thus focus on sociocultural aspects to better understand and manage diseases. These are findings that pose a great challenge not only to public health policies about the necessity of improvement in educational and social strategies and policies, but when improving standards of rheumatological care, physicians should be more perceptive regarding the needs of socio-economically vulnerable patients in order to obtain better outcomes.

Acknowledgements

We would like to thank all the collaborators who participated in the study: José Maldonado-Cocco (Buenos Aires University School of Medicine, Buenos Aires, Argentina), Hernán Maldonado Ficco (Hospital San Antonio de Padua, Rio Cuarto, Argentina), Rodolfo Pérez Alamino (Hospital Dr Nicolás Avellaneda, Tucumán, Argentina), Emilio Buschiazzo (Hospital Señor del Milagro, Salta, Argentina), Romina Calvo (Hospital Provincial Dr José M. Cullen, Santa Fé, Aregntina), Vanesa Duarte (Clínica Monte Grande, Buenos Aires, Argentina), Maria Victoria Martire (Instituto Médico Platense, La Plata, Argentina), Diego Baenas (Hospital Privado de Córdoba, Córdoba, Argentina), Dora Pereira (Hospital Ricardo Gutiérrez, La Plata, Argentina), Adrian Salas (Consultorio Reumatológico, La Plata, Argentina), Juan Manuel Bande (Hospital General de Agudos Dr E Tornú, Buenos Aires, Argentina), Alberto Berman (Centro Médico Privado de Tucumán, Tucumán, Argentina), Walter P Maksymowych (University of Alberta, Canada), Stephanie Belton (University of Alberta, Canada), Sebastián Ibáñez (Facultad de Medicina Clínica Alemana—Universdidad del Desarrollo, Santiago de Chile, Chile), María Paz Poblete (Facultad de Medicina Clínica Alemana—Universidad del Desarrollo, Santiago de Chile, Chile), Francisca Valenzuela (Facultad de Medicina Clínica Alemana—Universidad del Desarrollo, Santiago de Chile, Chile), Wilson Bautista-Molano (University Hospital Fundación Santa Fé de Bogotá, Bogotá, Colombia), Jieruo Gu (Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China), Min Xiao (Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China), CS Lau (Hong-Kong University, China), Ho Yin Chung (Hong-Kong University, China), Bassel Elzorkany (Cairo University, Cairo, Egypt), Sherif Gamal (Cairo University, Cairo, Egypt), Catherine Lebourlout (Cochin Hospital, Paris, France), Daniel Wendling (CHU Besançon, Besançon, France), Clément Prati (CHU Besançon, Besançon, France), Frank Verhoeven (CHU Besançon, Besançon, France), Martin Soubrier (CHU Clermont-Ferrand, Clermont-Ferrand, France), Carine Savel (CHU Clermont-Ferrand, Clermont-Ferrand, France), Trigui Alia (CHU Clermont-Ferrand, Clermont-Ferrand, France), Fan Angélique (CHU Clermont-Ferrand, Clermont-Ferrand, France), Pascal Claudepierre (Henri Mondor Hospital, Créteil, France), Valerie Farrenq (Henri Mondor Hospital, Créteil, France), Kamelia Faramarz (Henri Mondor Hospital, Créteil, France), Uta Kiltz (Rheumazentrum Ruhrgebiet, Herne, Germany), Isabella Sieber (Rheumazentrum Ruhrgebiet, Herne, Germany), Dories Morzeck (Rheumazentrum Ruhrgebiet, Herne, Germany), Fabian Proft (Charité University, Berlin, Germany), Pál Geher (Semmelweis University, Budapest, Hungary), Edit Toth (Flór Ferenc Hospital, Kistarcsa, Hungary), Katalin Nagy (Markhot Ferenc Hospital, Eger, Hungary), Attila Kovacs (MÁV Hospital, Szolnok, Hungary), Meghna Gavali (Nizam's Institute of Medical Sciences, Hyderabad, India), Liza Rajasekhar (Nizam's Institute of Medical Sciences, Hyderabad, India), Sapan Pandya (Smt NHL Medical College and Sardar Vallabhbhai Patel Hospital and Vedanta Institute of Medical Sciences, Ahmedabad, India), Bhowmik Meghnathi (Sri Sai Siri Hospital and Prathima Institue of Medical Sciences, Karimnagar, India), Carlomaurizio Montecucco (Fondazione IRCCS Policlinico San Matteo, Pavia, Italia), Sara Monti (Fondazione IRCCS Policlinico San Matteo, Pavia, Italia), Alessandro Biglia (Fondazione IRCCS Policlinico San Matteo, Pavia, Italia), Mitsumasa Kishimoto (Kyorin University School of Medicine, Tokyo, Japan), Akihiko Asahina (The Jikei University School of Medicine, Japan), Masato Okada (St Luke's International University and Hospital, Japan), Tadashi Okano (Osaka City University, Japan), Yuko Kaneko (Keio University School of Medicine, Japan), Hideto Kameda (Toho University, Japan), Yoshinori Taniguchi (Kochi University, Japan), Naoto Tamura (Juntendo University School of Medicine, Japan), Shigeyoshi Tsuji (National Hospital Organization Osaka Minami Medical Center, Japan), Hiroaki Dobashi (Kagawa University Faculty of Medicine, Japan), Yoichiro Haji (Daido Hospital, Japan), Akimichi Morita (Nagoya City University, Japan), Nelly Salloum (Saint-Joseph University, Beirut, Lebanon), Rubén Burgos-Vargas (Hospital General de México Eduardo Liceaga, Mexico City, Mexico), Graciela Meza (CLIDITER), Julio Casasola-Vargas (Hospital General de Mexico, Mexico), César Pacheco-Tena (Hospital General Dr Salvador Zubirán, Chihuahua, Mexico), Greta Reyes-Cordero (Hospital General Dr Salvador Zubirán, Chihuahua,

Mexico), César Ramos-Remus (Unidad de Investigación de Enfermedades Crónico Degenerativas, Jalisco, Mexico), J Dionisio Castillo (Unidad de Investigación de Enfermedades Crónico Degenerativas, Jalisco, Mexico), Laura González-López (Universidad de Guadalajara, Jalisco, Mexico), Iván Gámez-Nava (Unidad de Investigación Biomédica 02, Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS Guadalajara, Jalisco, Mexico), Najia Hajjaj-Hassouni [International University of Rabat (UIR), Rabat, Morocco], Fadoua Allali (University Mohammed V, CHU Ibn Sina, Rabat, Morocco), Hanan Rkain (University Mohammed V, CHU Ibn Sina, Rabat, Morocco), Lahcen Achemlal (University Mohammed V, CHU Ibn Sina, Rabat, Morocco), Taoufik Harzy (University Sidi Mohammed Benabdellah, CHU Hassan II, Fès, Morocco), Fernando M Pimentel-Santos (Universidade NOVA de Lisboa, Lisboa, Portugal), Santiago Rodrigues-Manica (Universidade NOVA de Lisboa, Portugal), Agna Neto (Universidade NOVA de Lisboa, Portugal), Jose Marona (Universidade NOVA de Lisboa, Portugal), M[a] Joao Gonçalves (Universidade NOVA de Lisboa, Portugal), Ana Filipa Mourao (Universidade NOVA de Lisboa, Portugal), Rita Pinheiro Torres (Universidade NOVA de Lisboa, Portugal), Ruxandra Schiotis (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Simona Rednic (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Siao-Pin Simon (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Laura Muntean (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Ileana Filipescu (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Maria Tamas (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Laura Damian (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Ioana Felea (Iuliu Hatieganu University of Medicine, Cluj-Napoca, Romania), Dana Fodor (Second Medical Clinic, Emergency Conty Hospital, Cluj-Napoca, Romania), Tae-Jong Kim (Chonnam National University Medical School and Hospital, South Korea), Hyun-Yi Kook (Chonnam National University Medical School and Hospital, South Korea), Hyun-Ju Jung (Chonnam National University Medical School and Hospital, South Korea), Tae-Hwan Kim (Hanyang University Hospital for Rheumatic Diseases, South Korea), Victoria Navarro-Compan (University Hospital La Paz, Madrid, Spain), Mireia Moreno (Hospital Parc Taulí, Barcelona, Spain), Eduardo Collantes-Estévez (Hospital Universitario Reina Sofía de Córdoba, Spain), M. Carmen Castro-Villegas (Hospital Universitario Reina Sofía, Córdoba, Spain), Cristina Fernández-Carballido (Hospital Universitario San Juan de Alicante, Alicante, Spain), Elizabeth Fernández (Hospital Universtario La Paz, Madrid, Spain), Marta Arévalo (Hospital Parc Taulí, Barcelona, Spain), Shue-Fen Luo (Chang Gung Memorial Hospital-Linkou, Taoyuan, Taiwan), Yeong-Jian Jan Wu (Chang Gung Memorial Hospital at Kee-Lung, Taiwan), Tian-Tsai Cheng (Chang Gung Memorial Hospital at Kao-Hsiung, Taiwan), Cheng-Chung Wei (Chung Sun Medical University, Taiwan), Tuncay Duruöz (Marmara University School of Medicine, Istanbul, Turkey), Servet Akar (Izmir Katip Çelebi University School of Medicine, Turkey), Ilhan Sezer (Akdeniz University School of Medicine), Umut Kalyoncu (Hacettepe University School of Medicine, Turkey), Sebnem Ataman (Ankara University School of Medicine, Turkey), Meltem Alkan Melikoglu (Erzurum Atatürk University School of Medicine, Turkey), Sami Hizmetli (Sivas Cumhuriyet University School of Medine, Turkey), Ozgur Akgul (Manisa Celal Bayar University School of Medicine, Turkey), Nilay Sahin (Balikesir University School of Medicine, Turkey), Erhan Capkin (Karadeniz Teknik University School of Medicine, Turkey), Fatima Gluçin Ural (Ankara Yildirim Beyazit University School of Medicine, Turkey), Figen Yilmaz (Istanbul Sisli Etfal Training and Research Hospital), Ilknur Aktas (Istanbul Fatih Sultan Mehmet Training and Research Hospital, Turkey), Floris van Gaalen (Leiden University Medical Center, The Netherlands), Anne Boel (Leiden University Medical Center, The Netherlands), Mirian Starmans-Kool (Zuyderland Medical Center, The Netherlands), Femke Hoekstra-Drost (Zuyderland Medical Center, The Netherlands), Maha Abdelkadir (Maasstad Hospital in Rotterdam, The Netherlands), Angelique Weel (Maasstad Hospital in Rotterdam, The Netherlands), Pedro M. Machado (University College of London, London, UK), Marina Magrey (Cases Western Reserve University School of Medicine, Cleveland, Ohio, United States), Darerian Schueller (Cases Western Reserve University School of Medicine, Cleveland, Ohio, United States). S.R., E.N. and A.B. designed the study. D.C. analysed the data, and all authors were involved in the interpretation and discussion of the results. D.C. wrote the manuscript, with significant input from all co-authors. The steering committee included Joaquim Sieper (Charité University, Berlin, Germany), Desirée van der Heijde (Leiden University Medical Center, The Netherlands), Robert Landewé (Zuyderland Medical Center, The Netherlands), and Anna Moltó (Cochin Hospital, Paris, France). Ethical approval was granted by ethical committees in all countries: Argentina, Comité de Docencia e Investigaciones Hospital de Clínicas Dr Nicolas Avellaneda; Canada, Health Research Ethics Board University of Alberta and Alberta Health Services; Chile, Comite Ético-Cientifico Servicio Salud Metropolitano Sur Oriente; China, Ethics committee Third Affiliated Hospital of Sun Yat-sen University; Colombia, Comité de Ética en Investigación del Hospital Militar Central; Egypt, Research Ethics Committee Cairo University Faculty of Medicine; France, Comité de protection des personnes Ile de France III; Germany, Ethics Committee from the medical council Westphalia-Lippe and the Westphalian Wilhelms University; Hungary, Ethics Committee Semmelweis Egyetem Hospital; India, NHL Institutional Review Board (NHLIRB). SMT NHL Municipal Medical College; Italy, Comitato Etico Pavia; Japan, Ethics Committee St Luke's International University; Lebanon, Comite d'ethique Hotel-Dieu de France; Mexico, Comité de Investigación Hospital

General de Mexico Eduardo Liceaga; Morocco, Comite d'Ethique pour la Recherche Biomedicale de Rabat; The Netherlands, Commissie Medische Ethiek Leids Universitair Medisch Centrum; Portugal, Comissao de Etica para a Saude do Centro Hospitalar de Lisboa Ocidental; Romania, Comisia de Etica UMF Iuliu Hatieganu Cluj Napoca; South Korea, Ethics Committee Chonnam National University Medical School from Gwangju; Spain, Comité de Ética de la Investigación con Medicamentos, Hospital Universitario La Paz; Taiwan, Chang Gung Medical Foundation Institutional Review Board; Turkey, Marmara University School of Medicine Clinical Research Ethics Committee; US, Metrohealth Institutional Review Board. Written informed consent was obtained from all subjects.

Funding: No funding was provided for the current analysis. The ASAS-perSpA study was conducted under the umbrella of ASAS with an unrestricted grant from Abbvie, Pfizer, Lilly, Novartis, UCB, Janssen and Merck. The funders did not have any role in the design or conduct of the study; collection, management, analysis or interpretation of the data; preparation, review or approval of the manuscript, or decision to submit the manuscript for publication.

Disclosure statement: The authors have declared no conflicts of interest.

Data availability statement

Data from the ASAS-perSpA study are available to investigators on reasonable request. For information on how to access data, contact the Assessment of SpondyloArthritis international Society (www.asas-group.org).

Supplementary data

Supplementary data are available at *Rheumatology* online.

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