DOI:
10.1093/rheumatology/keab638

Document Version
Peer reviewed version

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

Dafne Capelusnik[1], Sizheng Steven Zhao[2], Annelies Boonen[3,4], Nelly Ziade[5,6], Clementina López Medina[7,8], Maxime Dougados[7,9], Elena Nikiphorou[10,11], Sofia Ramiro[12,13]

1 Department of Rheumatology, Instituto de Rehabilitación Psicofísica, CABA, Argentina
2 Musculoskeletal biology, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK
3 Department of Rheumatology, Maastricht University medical center, Maastricht, the Netherlands
4 Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, the Netherlands
5 Department of Rheumatology, Saint Joseph University, Beirut, Lebanon
6 Department of Rheumatology, Hotel-Dieu De France, Beirut, Lebanon
7 Université de Paris. Department of Rheumatology, Hôpital Cochin, Assistance Publique, Hôpitaux de Paris, Paris, France
8 Department of Rheumatology, Reina Sofia Hospital, IMIBIC, University of Cordoba, Cordoba, Spain
9 INSERM (U1153): Clinical epidemiology and biostatistics, PRES Sorbonne Paris-Cité. Paris, France
10 Centre for Rheumatic Diseases, King's College London, London, UK
11 Department of Rheumatology, King's College Hospital, London, UK
12 Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
13 Department of Rheumatology, Zuyderland Medical Center, Heerlen, the Netherlands

Correspondence to:
Sofia Ramiro
Department of Rheumatology, Leiden University Medical Center
Albinusdreef 2, 2333 GA Leiden, the Netherlands, P.O. Box 9600, 2300RC Leiden, the Netherlands.
E-mail: sofiaramiro@gmail.com

ABSTRACT:

Objectives: To investigate the association between individual and country-level socioeconomic (SE) factors and health outcomes across spondyloarthritis (SpA) phenotypes.

Methods: Patients with axial SpA, peripheral SpA or psoriatic arthritis (PsA) from the ASAS-perSpA study (23 countries) were included. The effect of individual (age, gender, education and marital status) and country-level (e.g Gross Domestic Product [GDP]) SE factors on health outcomes (ASDAS≥2.1, ASDAS, BASFI, fatigue and 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 b/tsDMARD 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 (0.35 (0.25-0.45)) and single marital status (0.09 (0.01-0.17)) were associated with higher ASDAS. Living in lower GDP countries was also associated with higher ASDAS (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 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, -0.46 (-0.89 to -0.04)). No differences across disease phenotype were found.

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

Keywords: spondylarthritis, psoriatic arthritis, peripheral arthritis, disease outcomes, socioeconomic factors.

Key points:

- Individual socioeconomic factors (female gender, low educational level and living alone -single status or divorced or widowed-) are independently associated with poorer outcomes in SpA.
- Living in a low GDP country is independently associated with higher disease activity, but paradoxically with lower fatigue levels.
- There are no differences in the effects of socioeconomic factors across different SpA phenotypes.
- The use of b/tsDMARDS only marginally explain the relationship between living in a low GDP country and higher disease activity.

Introduction

Social determinants of health encompass social and economic conditions that influence the health of individuals and communities.(1) These conditions are shaped by individual's socioeconomic (SE) background (e.g. gender, educational level, occupation or income) as well as by country-level socioeconomic factors (including government health spending and access to 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 rheumatoid arthritis (RA).(7, 8) More recently, multi-national studies clarified the independent impact of individual 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, multi-national ASAS-COMOSPA (COMOrbidities in spa) study largely reported similar findings in axial spodyloarthritis (axSpA), although a) effects were smaller and b) the lack of fatigue data prevented its analysis.(11) Interestingly, although in a different proportion, studies in both RA and SpA, confirmed that lower access to costly biological disease modifying antirheumatic drugs (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 is different 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), including non-radiographic axial spondyloarthritis (nr-axSpA) and radiographic axSpA (r-axSpA), and peripheral spondyloarthritis (pSpA) which includes psoriatic arthritis (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, as backpain, peripheral arthritis or skin disease, might have differential impact on patients depending in SE context, and thus it would be reasonable to explore the role of SE background between the various phenotypes. It is imperative therefore, to understand whether the effect of individual and country-level 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, among which disease activity (reflecting inflammation), physical functioning, fatigue, and overall functioning and health. A higher disease activity is known to lead to a worse physical functioning(16); however, it is not known whether this relationship varies across countries and particularly across SES status of different countries. The multinational ASAS-peripheral involvement in SpondyloArthritis (ASAS-perSpA) study provides an ideal setting to investigate the above-mentioned unaddressed questions.

The aims of this study were 1) to investigate the association between individual 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 biological or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) therapy; (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, multi-center 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 centers 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 (C-Reactive Protein [CRP] or Erythrocyte Sedimentation Rate) as a measure of inflammation. ASDAS was calculated with CRP and explored both as a continuous as well as 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 Bath Ankylosing Spondylitis Functional Index (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 Bath Ankylosing Spondylitis Disease Activity Index (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 and country-level socioeconomic factors

Individual socioeconomic 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 status, single and divorced or widowed).

Country-level socioeconomic 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 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 from 2012 to 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 reference, except for the Gini Index, where higher values (corresponding to higher inequities) were chosen as 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), body mass index (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 inflammatory bowel disease and the presence of concomitant fibromyalgia diagnosed by the rheumatologist (yes/no). Lastly, non-steroidal anti-inflammatory drugs (NSAIDs) use during last month, history of conventional synthetic disease-modifying antirheumatic drug (csDMARD) and b/tsDMARD therapy since diagnosis and current steroids intake were also recorded. Finally, disease activity assessed by ASDAS and functional ability by BASFI were included in some models, as appropriate.

Statistical analysis

The association between individual socioeconomic factors and each health outcome was analyzed 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 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 being 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 entered each separately to 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 statically ($p<0.10$) 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 varies 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 socioeconomic factor on disease activity into natural direct (NDE; e.g. the effect of GDP on disease activity) and indirect effects (NIE; 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 (PM) was computed as: $PM=NIE/(NIE+NDE)$. 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. Confidence intervals 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 (SD 14) and 2562 (61%) were male. Only 17% of the patients did not achieve an educational degree beyond primary school, while 43% and 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.

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 (SD) 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. (Supplementary Figure S1). b/tsDMARDS were used by 46% of the patients across countries, with a marked variance of frequency, from 14% in India to 77% in Italy or 92% in Canada.

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 to 1.54), educational level (primary vs university OR=1.76; 95%CI 1.40 to 2.20) and being divorced or widowed (OR=1.68; 95%CI 1.25 to 2.28) (Figure 1).

Female gender was likewise associated with worse PROs: 0.12 points higher BASFI (95%CI 0.01 to 0.24), 0.88 points higher ASAS-HI (95%CI 0.68 to 1.09), and 0.62 points higher fatigue (95%CI 0.48 to 0.75). Lower 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 (around 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. No significant differences were found across disease phenotype (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 β=0.39; 95%CI 0.16 to 0.63), and higher odds of active disease (OR=1.74; 95%CI 1.22 to 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 (β=-0.46; 95%CI -0.89 to -0.04). Comparable patterns were seen for fatigue for the remaining of the country-level socioeconomic factors. Physical function and ASAS-HI were not associated with country-level SE factors. These results were not modified by disease phenotype

Individual 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 and country-level SE factors were not statistically significant nor clinically relevant. With other words, the effect of the individual SE factors on the different outcomes was not different according to 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, interaction terms between disease activity and country-level socioeconomic factors were not statistically significant (data not shown).

Mediation analysis

Use of b/tsDMARDs had a small but statistically significant mediation effect in 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 to 0.41) higher ASDAS units, and 0.02 (95%CI 0.01 to 0.03) of those units (7%; 95%CI 0 to 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 to 16.8) for HCE and 14.3% (95%CI6.4 to 22.2) for HDI mediated effect through b/tsDMARDs).

DISCUSSION

This worldwide study of patients across the SpA spectrum demonstrates associations between individual and country-level socioeconomic factors and various health outcomes. Female gender, lower educational level and single marital status were related 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 also with more fatigue. Interestingly, living in wealthier countries was related to lower disease activity but with higher reports of fatigue.

To the best of our knowledge, this is the first study 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 to patients the most, namely fatigue and overall functioning and health status, in SpA patients; and additionally, the relationship between individual and country-level socioeconomic factors and across different disease phenotypes.

Our findings are in line with the recent ASAS-COMOSPA study, where female gender and lower educational level were associated with higher disease activity, functional disability and higher odds of ASDAS score ≥2.1.(11) The present study includes 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 of variable across disease phenotype.

As for the country level socioeconomic 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 socioeconomic and clinical variables. As 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 socioeconomic factors can be explained by inequities in the 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, differences in knowledge and medical decision making, medical and patient beliefs, preferences and cultural background.(28) Our study indicates the effect of gender on disease activity (although with differences in magnitude) was not different among countries but seems 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 fibromyalgia diagnosis, that female gender is consistently and independently associated to higher reports fatigue. Aside from variations in fatigue levels across countries, our study demonstrates significant associations with country-level socioeconomic factors: patients living in higher GDP countries, were more likely to have higher levels of fatigue vs those living in lower GDP countries; the same results were found with HCE and HDI, and also with Gini index, where 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 to 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 socioeconomic 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 also has 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 health system, insurance schemes, accessibility of rheumatology services and cost of health and social service, which may represent a more reliable national determinants of health outcomes.(27) A clear example is the United States (US): In spite of being the highest income country, (although among within the ones with higher GINI index) it consistently remains among the

countries with poorer outcomes. A second limitation is that macroeconomic indicators do not tell the whole story about access, as level of co-payment, type of services reimbursed or number of rheumatologists would play a major role in further explaining country-level SE variation in disease activity. Furthermore, we appreciate that the country-level factors herein do not capture all aspects of socioeconomics, for example language, however previous research already showed that country influence over health outcomes is mainly determined by SE factors, like GDP and HDI, whereas other characteristic like climate or language are not associated(9). We neither included some well-known determinants of fatigue like comorbidities (anemia, hypothyroidism, etc.) and sleep disturbance, as they were not collected.(36)

Another limitation is the fact that the participating centers of each country were specialized tertiary institutions, with ASAS members, may have contributed to some selection bias; not to mention that the number of patients included by each country varied considerably. 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, and not directly in PsA or pSpA. However, since there is a known overlap between the diseases(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 socioeconomic 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 socioeconomic 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 facts that pose a great challenge not only to public health policies about the necessity of improvement in educational and social strategies and policies, but also for the daily life medical attention, where physicians should be more perceptive and look for patients needs in a more overall approach 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), Mª 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).

Steering committee: Joaquim Sieper (Charité University, Berlin, Germany), Desirée van der Heijde (Leiden University Medical Center, The Netherlands), Robert Landewé ((Zuyderland Medical Center, The Netherlands), Anna Moltó (Cochin Hospital, Paris, France).

Contribution: SR, EN and AB designed the study. DC analysed the data and all authors were involved in the interpretation and discussion of the results. DC wrote the manuscript, with significant input from all co-authors.

Funding: None for the current analysis. The ASAS-perSpA study was conducted under the umbrella of ASAS with unrestricted grant of Abbvie, Pfizer, Lilly, Novartis, UCB, Janssen and Merck. The funders did not have any role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript and decision to submit the manuscript for publication.

Disclosures: The authors declare no conflicts of interest.

Data availability: 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).

REFERENCE

1. Sheiham A. Closing the gap in a generation: health equity through action on the social determinants of health. A report of the WHO Commission on Social Determinants of Health (CSDH) 2008. Community Dent Health. 2009;26(1):2-3.
2. Marmot M, Friel S, Bell R, Houweling TA, Taylor S. Closing the gap in a generation: health equity through action on the social determinants of health. Lancet. 2008;372(9650):1661-9.
3. Marmot M, Allen J, Bell R, Bloomer E, Goldblatt P. WHO European review of social determinants of health and the health divide. Lancet. 2012;380(9846):1011-29.
4. Houlihan J, Leffler S. Assessing and Addressing Social Determinants of Health: A Key Competency for Succeeding in Value-Based Care. Prim Care. 2019;46(4):561-74.
5. Hood CM, Gennuso KP, Swain GR, Catlin BB. County Health Rankings: Relationships Between Determinant Factors and Health Outcomes. Am J Prev Med. 2016;50(2):129-35.
6. World Health Organization. The world health report 2000 - Health systems: improving performance 2000 [Available from: https://www.who.int/whr/2000/en/.
7. Massardo L, Pons-Estel BA, Wojdyla D, Cardiel MH, Galarza-Maldonado CM, Sacnun MP, et al. Early rheumatoid arthritis in Latin America: low socioeconomic status related to high disease activity at baseline. Arthritis Care Res (Hoboken). 2012;64(8):1135-43.
8. Callahan LF, Pincus T. Formal education level as a significant marker of clinical status in rheumatoid arthritis. Arthritis Rheum. 1988;31(11):1346-57.
9. Putrik P, Ramiro S, Hifinger M, Keszei AP, Hmamouchi I, Dougados M, et al. In wealthier countries, patients perceive worse impact of the disease although they have lower objectively assessed disease activity: results from the cross-sectional COMORA study. Ann Rheum Dis. 2016;75(4):715-20.
10. Putrik P, Ramiro S, Keszei AP, Hmamouchi I, Dougados M, Uhlig T, et al. Lower education and living in countries with lower wealth are associated with higher disease activity in rheumatoid arthritis: results from the multinational COMORA study. Ann Rheum Dis. 2016;75(3):540-6.
11. Putrik P, Ramiro S, Moltó A, Keszei AP, Norton S, Dougados M, et al. Individual-level and country-level socioeconomic determinants of disease outcomes in SpA: multinational, cross-sectional study (ASAS-COMOSPA). Ann Rheum Dis. 2019;78(4):486-93.

12. Putrik P, Ramiro S, Kvien TK, Sokka T, Pavlova M, Uhlig T, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis. 2014;73(1):198-206.
13. Nikiphorou E, van der Heijde D, Norton S, Landewé RB, Molto A, Dougados M, et al. Inequity in biological DMARD prescription for spondyloarthritis across the globe: results from the ASAS-COMOSPA study. Ann Rheum Dis. 2018;77(3):405-11.
14. Dougados M, Baeten D. Spondyloarthritis. Lancet. 2011;377(9783):2127-37.
15. Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70(1):25-31.
16. Landewé R, Dougados M, Mielants H, van der Tempel H, van der Heijde D. Physical function in ankylosing spondylitis is independently determined by both disease activity and radiographic damage of the spine. Ann Rheum Dis. 2009;68(6):863-7.
17. López-Medina C, Molto A, Sieper J, Duruöz T, Kiltz U, Elzorkany B, et al. Prevalence and distribution of peripheral musculoskeletal manifestations in spondyloarthritis including psoriatic arthritis: results of the worldwide, cross-sectional ASAS-PerSpA study. RMD Open. 2021;7(1).
18. van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68(12):1811-8.
19. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis. 2011;70(1):47-53.
20. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, 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(12):2281-5.
21. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21(12):2286-91.
22. Kiltz U, van der Heijde D, Boonen A, Cieza A, Stucki G, Khan MA, et al. Development of a health index in patients with ankylosing spondylitis (ASAS HI): final result of a global initiative based on the ICF guided by ASAS. Ann Rheum Dis. 2015;74(5):830-5.
23. The World Bank. World Bank Open Data 2020 [cited 2020. Available from: https://data.worldbank.org.
24. United Nations Development Programme. Beyond income, beyond averages, beyond today: Inequalities in human development in the 21st century 2019 [Available from: http://hdr.undp.org/sites/default/files/hdr2019.pdf.
25. Twisk J. Applied Mixed Model Analysis: A practical Guide (2nd ed., Practical Guides to Biostatistics and Epidemiology): Cambridge: Cambridge University Press; 2019.
26. Emsley R LH. PARAMED: Stata module to perform causal mediation analysis using parametric regression models 2013 [Available from: https://econpapers.repec.org/software/bocbocode/s457581.htm.
27. Carlson MD, Roy B, Groenewoud AS. Assessing Quantitative Comparisons of Health and Social Care Between Countries. Jama. 2020;324(5):449-50.
28. Mortada M, Abdul-Sattar A, Gossec L. Fatigue in Egyptian patients with rheumatic diseases: a qualitative study. Health Qual Life Outcomes. 2015;13:134.
29. López-Medina C, Schiotis RE, Font-Ugalde P, Castro-Villegas MC, Calvo-Gutiérrez J, Ortega-Castro R, et al. Assessment of Fatigue in Spondyloarthritis and Its Association with Disease Activity. J Rheumatol. 2016;43(4):751-7.

30. Chauffier K, Paternotte S, Burki V, Durnez A, Elhaï M, Koumakis E, et al. Fatigue in spondyloarthritis: a marker of disease activity. A cross-sectional study of 266 patients. Clin Exp Rheumatol. 2013;31(6):864-70.
31. Gossec L, Dougados M, D'Agostino MA, Fautrel B. Fatigue in early axial spondyloarthritis. Results from the French DESIR cohort. Joint Bone Spine. 2016;83(4):427-31.
32. van Steenbergen HW, Tsonaka R, Huizinga TW, Boonen A, van der Helm-van Mil AH. Fatigue in rheumatoid arthritis; a persistent problem: a large longitudinal study. RMD Open. 2015;1(1):e000041.
33. Bedaiwi M, Sari I, Thavaneswaran A, Ayearst R, Haroon N, Inman RD. Fatigue in Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis: Analysis from a Longitudinal Observation Cohort. J Rheumatol. 2015;42(12):2354-60.
34. Chen HH, Chen YM, Lai KL, Hsieh TY, Hung WT, Lin CT, et al. Gender difference in ASAS HI among patients with ankylosing spondylitis. PLoS One. 2020;15(7):e0235678.
35. Min HK, Lee J, Ju JH, Park SH, Kwok SK. Predictors of Assessment of Spondyloarthritis International Society (ASAS) Health Index in Axial Spondyloarthritis and Comparison of ASAS Health Index between Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis: Data from the Catholic Axial Spondyloarthritis COhort (CASCO). J Clin Med. 2019;8(4).
36. Kroenke K, Wood DR, Mangelsdorff AD, Meier NJ, Powell JB. Chronic fatigue in primary care. Prevalence, patient characteristics, and outcome. Jama. 1988;260(7):929-34.
37. Feld J, Chandran V, Haroon N, Inman R, Gladman D. Axial disease in psoriatic arthritis and ankylosing spondylitis: a critical comparison. Nat Rev Rheumatol. 2018;14(6):363-71.

Table 1. Patient characteristics according to spondyloarthritis 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				
University	1178 (43)	320 (31)	197 (46)	<0.001
Secondary School	1140 (42)	472 (46)	180 (42)	
Primary School	399 (15)	239 (23)	56 (13)	
Current marital status				
Married or living together	1735 (64)	748 (73)	267 (62)	<0.001
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				
Never smoker	1532 (56)	538 (52)	304 (70)	<0.001
Current or past smoker	1185 (44)	494 (48)	128 (30)	
HLA-B27 positive	1709 (63)	86 (8)	197 (46)	<0.001
Axial involvement†	2651 (98)	367 (36)	238 (55)	<0.001
Peripheral arthritis†	978 (36)	938 (91)	410 (95)	<0.001
Dactylitis†	164 (6)	382 (37)	100 (23)	<0.000
Enthesitis†	1113 (41)	473 (46)	248 (57)	<0.001
Uveitis†	588 (22)	27 (3)	75 (10)	<0.001
IBD†	132 (5)	6 (1)	25 (6)	<0.001
Psoriasis†	187 (7)	946 (92)	64 (15)	<0.001
Fibromyalgia	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‡	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

Results reflect mean (SD) or n (%).

Disease phenotype and fibromyalgia 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), fibromyalgia (n=2).

†Manifestation ever present.

‡During last month.

axSpA, axila spondyloarthritis; PsA, psoriatic arthritis; pSpA, peripheral spondyloarthritis, IBD, inflammatory bowel disease; CRP, C-Reactive Protein; ASDAS, AS Disease Activity Score; BASFI, Bath AS Functional Index; ASAS-HI, ASAS Health Index; EQ-5D, Euro Quality of life 5 Dimensions; NSAIDs, Non-steroidal Anti-Inflammatory Drugs; cs/b/tsDMARDs, conventional synthetic/biological/targeted synthetic Disease Modifying Antirheumatic Drugs.

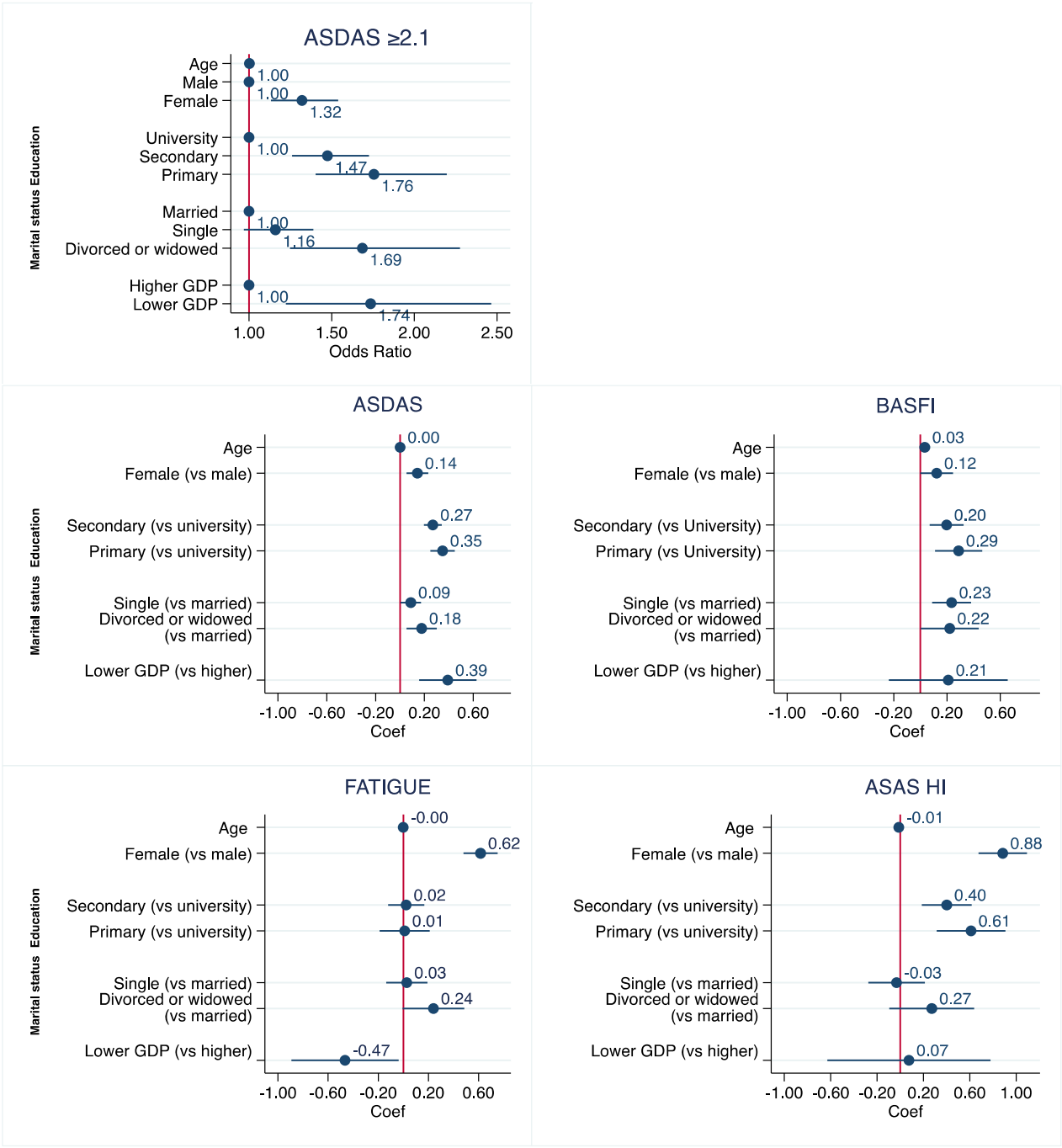

Figure 1. Effect of individual and country-level socioeconomic factors on ASDAS≥2.1, continuous ASDAS, BASFI, FATIGUE and ASAS-HI, derived from multivariable mixed-effects models adjusted by clinical confounders. (*ASDAS*≥2.1 *model:* body mass index, axial involvement, peripheral arthritis, enthesitis, fibromyalgia and Non-steroidal Anti-Inflammatory Drugs; *ASDAS model:* body mass index, smoking status, axial involvement, peripheral arthritis, enthesitis, fibromyalgia and Non-steroidal Anti-Inflammatory Drugs; *BASFI model:* body mass index, ASDAS, axial involvement, fibromyalgia and conventional disease modifying antirheumatic drugs; *fatigue model:* ASDAS, uveitis and fibromyalgia; *ASAS HI model:* smoking status, ASDAS, BASFI, peripheral arthritis and fibromyalgia) (full model coefficients in Table S3).

Table 2. Effect of country-level socioeconomic factors on disease activity (ASDAS), physical function (BASFI), fatigue and ASAS-HI.

Assessment	ASDAS ≥2.1 Odds Ratio (95% CI)	ASDAS β (95% CI)	BASFI β (95% CI)	Fatigue β (95% CI)	ASAS-HI β (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 (high vs low)	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. HCE, Gini index estimates are derived from 3 separate models (due to collinearity), by replacing GDP in the final multivariable mixed-effects models shown in Figures 2, 3 and Supplementary table S3.

*Estimates with p<0.05 are highlighted in bold.

GDP, gross domestic product; HCE, healthcare expenditure; HDI, Human Development Index. Values from 2019 (GDP), 2018 (HCE, HDI), the last available (Gini index).