

 Open access • Journal Article • DOI:10.1136/ANNRHEUMDIS-2017-212457

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Published on: 01 Mar 2018 - [Annals of the Rheumatic Diseases](#) (BMJ Publishing Group)

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**INEQUITY IN BIOLOGIC DMARD PRESCRIPTION FOR SPONDYLOARTHRITIS ACROSS THE GLOBE:
RESULTS FROM THE ASAS COMOSPA STUDY**

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WORD COUNT: ~~2610~~2755

KEYWORDS: Spondyloarthritis; biologics; disease-modifying anti-rheumatic drugs; socio-economic factors; comorbidities.

Abstract

Objectives: The value of biologic DMARDs (bDMARDs) in SpA is well recognized but global access to these treatments can be limited due to high costs and other factors. This study explores country-variation in the use of bDMARDs in SpA in relation to country-level socio-economic factors.

Methods: Patients fulfilling the ASAS SpA criteria in the multi-national, cross-sectional ASAS COMOSPA study were studied. Current use of bDMARDs or conventional synthetic DMARDs (csDMARDs) was investigated, in separate models, with multilevel logistic regression analysis, taking the country level into account. Contribution of socio-economic factors including country health expenditures, gross domestic product (GDP) and human development index (HDI) as independent country-level factors, was explored individually, in models adjusted for socio-demographic as well as clinical variables.

Results: In total, 3370 patients from 22 countries were included (mean[SD] age 43[14] years; 66% male; 88% axial disease). Across countries, 1275 (38%) were bDMARD users. Crude mean bDMARD-use varied between 5% (China) to 74% (Belgium). After adjustment for relevant socio-demographic and clinical variables, important variation in bDMARD-use across countries remained ($p < 0.001$). Country-level socio-economic factors, specifically higher health expenditures were related to higher bDMARD uptake, though not meeting statistical significance (OR 1.96;95%CI 0.94,4.10). csDMARD uptake was significantly lower in countries with higher health expenditures (OR 0.32;95%CI 0.15,0.65). Similar trends were seen with the other socio-economic variables.

Conclusions: There remains important residual variation across countries in bDMARD uptake of patients with SpA followed in specialized SpA centers. This is independent of well-known factors for bDMARD use such as clinical and country-level socio-economic factors.

1 **INTRODUCTION**

2 The role of biological disease-modifying anti-rheumatic drugs (bDMARDs) in Spondyloarthritis
3 (SpA) has been extensively studied and robust scientific evidence supports their efficacy in
4 reducing disease activity and improving functional ability, spinal mobility and quality of life.[1]
5 bDMARDs are therefore recommended for use in the presence of active disease and following
6 failure of two non-steroidal anti-inflammatory drugs (NSAIDs).[2] However, an important barrier
7 to their use is their high cost which also influences the development of national guidelines and
8 prescribing patterns.

9

10 On the other hand, the use of conventional synthetic DMARDs (csDMARDs) in SpA, unlike
11 rheumatoid arthritis (RA) and other inflammatory arthritides with peripheral joint involvement is
12 less-well established. Currently there is a general lack of evidence on their role in axSpA,[3] and
13 the existing evidence consistently shows no efficacy[4–6] making their role debatable[7] and
14 resulting in the Assessment in SpondyloArthritis international Society (ASAS) and the European
15 League Against Rheumatism (EULAR) not supporting their use in patients with only axial
16 disease.[2]

17

18 Existing literature supports inequity in bDMARD prescription in RA, both at an individual and
19 country level,[8–13] but the evidence for this is lacking in SpA. Increasing insight into patterns of
20 treatment use across countries and potential differential access to biologic drugs can help
21 highlight potential sources of inequity and drive change through informing service delivery,
22 refining drug reimbursement criteria and access to these treatments nationally, in line with
23 international recommendations. This is particularly important, since access and use of healthcare
24 services that prevent and treat disease is one of the key determinants of health.[14]

25 This study aimed to explore individual and country-level variation in the uptake of DMARDs in
26 patients with SpA and unravel gaps in literature regarding how they are used and possible factors
27 that could influence this. The ASAS COMOrbidities in SPondyloArthritis (COMOSPA) study, an
28 international study including patients from 22 countries and initially designed to estimate the
29 prevalence of comorbidities in SpA,[15] provided an ideal setting to answer these questions.

30

31 **METHODS**

32 **Study design and patient recruitment**

33 ASAS-COMOSPA is a multi-centre cross-sectional observational study with 22 participating
34 countries across four continents (Africa, America, Asia and Europe).[15] Consecutive patients (age
35 18 years or over) with a clinical diagnosis of SpA according to the treating rheumatologist, either
36 axial or peripheral, were included in ASAS-COMOSPA, provided they were able to understand and
37 complete the questionnaires. For the present study, analyses were restricted to patients fulfilling
38 the ASAS criteria for SpA, either axial or peripheral.[16] The study was conducted according to
39 guidelines for good clinical practice in all countries with all local ethics committees approving the
40 ASAS-COMOSPA study protocol. Written informed consent was obtained from all subjects before
41 enrolment.

42

43 **Data collection**

44 Data collection in the ASAS-COMOSPA ranged from patient demographic variables to disease-
45 related variables and treatment data, including: treatment with non-steroidal anti-inflammatory
46 drugs (NSAIDs) with computation of the ASAS NSAID score (0-400)[17] reflecting NSAID-use over
47 the past 3 months; current and past use of csDMARDs and bDMARDs (see below).

48

49

50 **Outcome measures**

51 The main outcome of interest was current bDMARD uptake, studied as a binary variable to
52 indicate current bDMARD use versus all other (including csDMARD use and/or NSAIDs). In
53 addition, current csDMARD uptake as a binary variable to indicate current csDMARD use versus
54 all other (including bDMARD use with or without csDMARDs and/or NSAID use) was also examined
55 in separate models as another outcome measure.

56

57 **Individual-level variables**

58 Variables of interest potentially influencing the uptake of DMARDs, aside from age and gender,
59 included socio-demographic factors such as educational status (secondary and university
60 education vs primary education); HLA B27 status (positive vs negative); measures of disease
61 activity such as the Ankylosing Spondylitis Disease Activity Score calculated with CRP (ASDAS);
62 measures of functional ability (Bath Ankylosing Spondylitis Functional Index [BASFI], range 0-10);
63 presence of axial vs peripheral disease (yes for axial disease); radiographic sacroiliitis (yes vs no);
64 presence of peripheral enthesitis, dactylitis or extra-articular manifestations (uveitis, psoriasis or

65 inflammatory bowel disease), (yes vs no) and comorbidity burden using the Rheumatic Disease
66 Comorbidity Index (RDCI, range 0-9).[18]

67

68 **Country-level variables**

69 Country socio-economic variables were studied as the main independent variables of interest and
70 included: country health expenditures per capita[19] (adjusted for purchasing power parity [PPP],
71 measured in international dollars); gross domestic product (GDP)[20] (adjusted for PPP, measured
72 in international dollars); Gini index[21,22], as a measure of income inequality across a country
73 (range 0 [absolute equality]-100 [absolute inequality]); human development index (HDI)[23], a
74 composite measure of average achievement in key dimensions of human development used to
75 rank countries based on their performance in these. These variables were split into tertiles with
76 the top two compared to the bottom tertile in regression analyses: for country health
77 expenditures, GDP and Gini, high/medium versus low. For HDI, an external classification system
78 was used[23] as opposed to creating a new dichotomization, with categories compared being
79 high/very high versus medium. All country-level socioeconomic variables are presented in ~~the~~
80 supplementary table 1. The country health expenditures variable was *a priori* chosen as the main
81 independent variable of interest, as the outcome refers to uptake of a drug, falling into health
82 expenditures. Therefore, we hypothesized that country health expenditures would be the most
83 relevant socio-economic variable in the context of health spending and a good reflection of
84 country wealth.

85

86 **Data analysis**

87 Multilevel modeling analyses were conducted in order to account for patients being recruited
88 from different countries. Multilevel models take into account the dependency of the
89 observations, in this instance by accounting for the two-level structure in the data, namely
90 patients at the 'lower' level are nested within countries at the 'higher' level.[24] Multi-level mixed
91 effects logistic regression models with random intercept for country were constructed with
92 current use of bDMARDs and current use of csDMARDs as the dependent variables, in separate
93 models. Odds ratios (ORs) and 95% Confidence Intervals (CI) were estimated. Variations in impact
94 of patient-level socio-demographic variables (age, gender and educational status) on DMARD use
95 across countries were first tested by incorporating random slopes for the variable, which is
96 comparable to testing for interactions in a simple regression model. The effect of level of

97 education was found to vary significantly ($p < 0.001$) across countries in relation to bDMARD
98 uptake; therefore, education was included with a random slope in multivariable models where
99 bDMARD was the outcome to control for potential confounding at the country as well as
100 individual level. Potential confounders were entered in the models in a manual forward procedure
101 (cut-off $p < 0.05$) provided they were meaningful in the univariable analyses (defined as $p < 0.10$) or
102 if considered clinically relevant. In a final step, the contribution of country health expenditures,
103 GDP, Gini and HDI as independent country level factors, was individually explored in models
104 adjusted for socio-demographic (age, gender, education level) as well as clinical variables
105 (presence of axial vs peripheral disease, disease activity, sacroiliitis on X-ray, history of extra-
106 articular manifestations, total NSAID score, past cs/bDMARD use) known to determine bDMARD-
107 use (or csDMARD use, respectively) in SpA. All analyses were conducted with the statistical
108 software Stata v13.

109

110 **RESULTS**

111 **Patient, disease characteristics and treatment**

112 From a total of 3984 patients included in ASAS-COMOSPA across 22 countries, 3370 (85%) fulfilled
113 the ASAS SpA criteria for axial or peripheral disease and were included in this study. The majority
114 of patients were male (66%); mean age was 43 years (SD 14), mean disease duration 8.4 years (SD
115 9.5) and 88% had axial disease. Table 1 summarizes the patient demographics, clinical
116 characteristics and type of treatment used. [Results by individual country are shown in](#)
117 [supplementary table 2](#). Across countries, 1275 (38%) patients were bDMARD users, 1168 (35%)
118 csDMARD users (25% without bDMARDs). Crude mean bDMARD and csDMARD uptake varied
119 considerably across countries (see figure 1).

120

121 ***bDMARD uptake***

122 Table 2 shows the model with bDMARD uptake as the outcome. Higher country health
123 expenditure was associated with higher bDMARD uptake (OR 1.96; 95%CI 0.94,4.10), though
124 without reaching statistical significance. In the same models, past b/csDMARD use was associated
125 with almost double odds of using bDMARDs. Similarly, male gender, presence of axial (vs
126 peripheral) disease, sacroiliitis on X-ray and presence of extra-articular manifestations were all
127 significantly associated with higher bDMARD use. The results also suggest an association between
128 lower disease activity with lower bDMARD use, likely to be a reflection of the cross-sectional

129 nature of the study (i.e. simply an observation of less disease activity in those already on
130 bDMARDs). Figure 1 shows the crude and adjusted percentage of bDMARD uptake by country.
131 The model demonstrated significant variation in bDMARD use by country ($p < 0.001$) despite full
132 adjustment.

133

134 ***csDMARD uptake***

135 Table 3 shows the model with csDMARD uptake as the outcome. Higher country health
136 expenditure was associated with lower csDMARD uptake (OR 0.32; 95%CI 0.15,0.65). The results
137 of the csDMARD model are complimentary to those of the bDMARD model, with the same
138 variables demonstrating an association with csDMARD uptake in the opposite direction to those
139 of bDMARD uptake. In other words, male gender, axial disease and sacroiliitis on X-ray and past
140 csDMARD use were all significantly associated with lower csDMARD use. Higher disease activity
141 was associated with higher csDMARD use, again likely to be a reflection of the cross-sectional
142 nature of the study (i.e. higher disease activity in those using csDMARDs). Figure 2 shows the
143 crude and adjusted percentage of csDMARD uptake by country. A significant variation across
144 countries was also seen in relation to csDMARD uptake ($p < 0.001$) and also independent of
145 adjustment for socio-demographic, clinical and socio-economic relevant variables.

146 ***Other country-level socio-economic variables***

147 Across other socio-economic variables studied, the only significant association in univariable
148 analyses was between HDI and csDMARD uptake. Replacing country health expenditures in the
149 final adjusted models with other country-level socio-economic variables revealed higher use of
150 bDMARDs and lower use of csDMARDs with higher GDP and HDI, although significance was only
151 reached for GDP and csDMARD use (OR 0.44; 95%CI 0.21,0.91) (Table 4). Higher country-income
152 inequality as measured by Gini was associated with lower bDMARD than csDMARD uptake,
153 although no statistical significance was reached (Table 4).

154

155 **DISCUSSION**

156 The ASAS-COMOSPA study enabled the systematic study of b- and cs-DMARD uptake across 22
157 countries. It demonstrates important residual variation, which is not explained by socio-
158 demographic and clinical characteristics. The study suggests that country-level socio-economic
159 indicators may in part, but not entirely, explain some of the differences. The csDMARD findings
160 are supportive of the bDMARD results, highlighting that higher country welfare seems to be

161 associated not only with higher bDMARD use (although not reaching statistical significance),
162 independent of all other characteristics including country of residence, but also with lower
163 csDMARD use. Given the lack of evidence for efficacy of csDMARDs in axSpA[3] and the available
164 evidence consistently showing no efficacy,[2,4–7] this reflects an unjust selection of treatment
165 for patients in countries of lower socio-economic welfare, based on decisions other than clinical
166 indication.

167

168 bDMARD use was almost double in countries with higher compared to lower country health
169 expenditures. Although not reaching statistical significance, the effect is of interest, since power
170 to detect country level predictors is driven largely by the number of countries. The number of
171 countries included in ASAS-COMOSPA, though impressive for a multinational study with the
172 logistic challenges it represents, is relatively small in statistical terms and a limiting factor when
173 analyzing country-level variables. This, in turn, is reflected in a lack of power to identify potentially
174 significant relationships.

175

176 To date, only few studies have systematically studied access to biologics across countries and
177 these have been mainly in RA.[8–13] Our study observations find support in the existing literature
178 of bDMARD use in RA which suggests country-level socioeconomic factors to play a
179 role.[11,13,25,26] In particular, existing evidence shows that patients living in countries with a
180 higher welfare have lower disease activity states, likely to be at least in part mediated by a higher
181 likelihood of receiving bDMARDs.[13] The high costs of these drugs have undoubtedly influenced
182 reimbursement but also national recommendations and guidelines across countries, in order to
183 regulate access to these treatments while keeping a balance between clinical and economic
184 demands.[27,28] Indeed, costs of bDMARDs vary widely by country, driven by socio-economic
185 welfare among other factors [10] with countries of lower socio-economic welfare ~~have been~~
186 ~~shown to have~~ demonstrating stricter eligibility criteria for bDMARDs ~~in RA~~. [12]

187

188 The existence of international recommendations in SpA[29] encourage comparable management
189 in these patients. In fact, evidence suggests that most national recommendations follow the
190 international ASAS recommendations and despite some countries requiring, for example,
191 additional objective signs of inflammation and/or more pre-treatment, limiting access, general
192 consensus exists about the use of, for example, TNF-inhibitor therapies.[30] Still, there could be

193 'hidden' barriers across individual countries limiting access to these drugs, ranging from
194 differences in the funding of health-care provision, to local/regional variation in budget
195 availability and feasibility of access to these more expensive, albeit more effective treatments,
196 through to differences in guideline interpretation and personal approach as well as preference by
197 the treating rheumatologist. It may be, for example, that knowledge about the potential side
198 effects of bDMARDs poses resistance to their use by some individuals, who may in turn seek out
199 to alternative treatments. This may explain the differences observed even between countries
200 with comparable health expenditures. We can only speculate on the reasons for the residual
201 degree of variation in bDMARD uptake in our study, despite adjustment for patient, disease and
202 country-level characteristics. It is also possible that patient selection at inclusion into the study
203 may have played a role in these observations. For example, preferential review of patients on
204 bDMARDs by some centers would not provide an accurate reflection of the wider practice at a
205 specific clinical setting and less so across the entire country. Furthermore, it is possible that not
206 always consecutive patients may have been selected for inclusion into the study. The fundamental
207 issue though remains that, assuming the patient needs for bDMARD use are similar across
208 countries, differential access to these treatments raises concerns regarding the risk of inequity.

209

210 Male patients, presence of axial disease, sacroiliitis on X-ray and presence of extra-articular
211 disease were all associated with higher bDMARD use. In the csDMARD model, these associations
212 were reversed and therefore supportive of the bDMARD findings. These observations are
213 reassuring, since all these factors are indicators of worse disease or better response and justify
214 higher bDMARD use.[31–33]

215

216 The study has some important limitations. Firstly, selection bias cannot be excluded and the
217 uptake of bDMARDs in the group of patients included per country may not be fully representative
218 of the general bDMARD uptake across all SpA patients. More specifically, the study has been
219 conducted in centers that are associated with ASAS and this may be a bias towards higher
220 bDMARD prescription, independent of the country and related socio-economic factors. Better
221 selection of patients for bDMARD use is possible in ASAS centers. This reflects potential sources
222 of bias to the findings of the study. However, consecutive patients were included in the study and
223 the disease characteristics of the population studied is reflective of a typical SpA population.
224 Secondly, it was not possible to explore all possible reasons for barriers to access of bDMARDs

225 and as mentioned above, explanations for the residual variation seen in bDMARD use after
226 adjusting for socio-economic, socio-demographic and clinical variables remain speculative. The
227 aim, however, was to investigate whether differential access could be a problem and potentially
228 leading to inequities. Further research should unveil possible other explanations for treatment
229 choices. Furthermore, the cross-sectional nature of ASAS-COMOSPA precludes the study of causal
230 links; instead, it only allows for associations to be seen. Finally, the cross-sectional nature of the
231 analysis prevents the adjustment of disease activity before the start of bDMARDs, another
232 important limitation.

233

234 Important strengths of the study include the large patient numbers and the uniqueness of ASAS-
235 COMOSPA as one of the largest multi-national SpA datasets to date, which includes a wealth of
236 information ranging from socio-demographic, to disease-related clinical and radiographic
237 measures of disease as well as country-level macro-economic data. The study population is typical
238 and representative for SpA, characterized by predominantly male patients with an average age in
239 the early 40s. The occurrence of disease at the peak of the productive lifespan of young
240 individuals[34,35] with the known considerable impact on work ability[36] makes it imperative
241 that access to treatments that are known to be effective in suppressing inflammation is feasible
242 and unrestricted. This, alone, makes our study particularly relevant.

243

244 In conclusion, this study provides insights into complex contributions between patient and
245 disease-related factors and country-level socio-economic factors, raising concerns regarding
246 equity in access to effective (biologic) treatments in SpA. The findings suggest unequal and unjust
247 selection of treatment for SpA independent of clinical indication, an observation that necessitates
248 urgent attention on the health equality and public health agenda.

249

250

251 **COMPETING INTERESTS:**

252 The authors declare they have no conflicts of interest relating to this study.

253

254 **CONTRIBUTORSHIP:**

255 The authors take responsibility for the integrity of the work , from inception to published article
256 and they should indicate that they had full access to all the data in the study and take
257 responsibility for the integrity of the data and the accuracy of the data analysis.

258

259 **ACKNOWLEDGEMENTS:**

260 The COMOSPA study was conducted under the umbrella of the International Society for
261 Spondyloarthritis Assessment (ASAS).

262

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265 Alejandro Alvarellos MD, Argentina; Maria Aparicio Espinar MD, SPAIN; Pamir Atagunduz MD, TURKEY; Pauline Bakker
266 MD, NETHERLANDS; Juan C. Barreira MD. Argentina; Leila Benbrahim MD, MOROCCO; Bahia Benchekroun MD,
267 MOROCCO; Alberto Berman MD, ARGENTINA; Juergen Braun MD, GERMANY; Alain Cantagrel MD PhD, FRANCE;
268 Roberto Caporali MD, ITALY; Pedro Carvalho MD, PORTUGAL; Gustavo Casado MD, ARGENTINA; James Cheng-Chung
269 Wei MD, PhD, TAWIAN; Francisco Colombres MD, ARGENTINA; Eugenio del Miguel Mendieta MD PhD, SPAIN; Juan D.
270 Diaz-Garcia MD, MEXICO; Michel De Bandt MD PhD, FRANCE; Vanesa Duarte MD, ARGENTINA; Cristina Fernandez
271 Carballido MD, SPAIN; Mari Cruz Fernandez Espartero MD, SPAIN; Manuel Fernandez-Prada MD, SPAIN; Rene-Marc
272 Flipo MD PhD, FRANCE; Pilar Font Ugalde MD. PhD, SPAIN; Philippe Gaudin MD PhD, FRANCE; Philippe Goupille MD,
273 FRANCE; Dolores Grados Cánovas MD, SPAIN; Jordi Gratacós Masmitjà MD PhD, SPAIN; Vittorio Grosso MD, ITALY;
274 Naomi Ichikawa, MDJAPAN; Hisashi Inoue MD, JAPAN; Yuko Kaneko MD PhD, JAPAN; Taku Kawasaki MD PhD, JAPAN;
275 Shigeto Kobayashi MD, JAPAN; Manjari Lahiri MD, SINGAPORE; Hernán Maldonado-Ficco MD, ARGENTINA; Marhadour
276 MD, FRANCE; Alejandro Martínez MD, ARGENTINA; Kazuo Matsui MD, JAPAN; Ramón Mazzuchelli Esteban MD, SPAIN;
277 Corinne Micelli MD PhD, FRANCE; Chisun Min MD, JAPAN; Mitsuhiro Morita MD PhD, JAPAN; Juan Mulero Mendoza
278 MD PhD, SPAIN; Jose Raul Noguera Pons MD, SPAIN; Masato Okada MD, JAPAN; Alberto Ortiz MD, ARGENTINA; Jon
279 Packham DM FRCP, UNITED KINGDOM; Gisela Pendón MD, ARGENTINA; Dora Pereira MD, ARGENTINA; José A Pereira
280 da Silva MD, PORTUGAL; Fernando Pimentel-Santos MD, PORTUGAL; Hanan Rkain, MD MOROCCO; Oscar Rillo MD,
281 ARGENTINA; Carlos Rodriguez Lozano MD, SPAIN; Adeline Ruysen-Witrand MD PhD, FRANCE; Adrián Salas MD,
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283 Sengupta FRCP PGCM, UNITED KINGDOM; Stefan Siebert PhD, UNITED KINGDOM; Martin Soubrier MD PhD CHU,
284 FRANCE; Caroline Spiegel, GERMANY; Carmen Stolwijk MD, NETHERLANDS; Kurisu Tada MD, JAPAN; Naoho Takizawa
285 MD, JAPAN; Yoshinori Taniguchi MD PhD, JAPAN; Atsuo Taniguchi MD PhD, JAPAN; Chung Tei Chou MD, TAIWAN; Lay-
286 Keng Teoh SINGAPORE; Tetsuya Tomita MD PhD, JAPAN; Wen-Chan Tsai MD, PhD, TAIWAN; Shigeyoshi Tsuji MD PhD,
287 JAPAN; Olga Tsyplenkova, GERMANY; Astrid van Tubergen MD PhD, NETHERLANDS; Kiana Vakil-Gilani BS, MPH, USA;
288 Rafael Valle-Oñate MD, COLOMBIA; Gaele Varkas MD, BELGIUM; Virginia Villaverde MD, SPAIN; Ai Yap SINGAPORE;
289 Pedro Zarco Montejo MD PhD, SPAIN.

290

291 **FUNDING:**

292 The COMOSPA study was conducted with the financial support of Abbvie®, Pfizer® and UCB®, who
293 provided an unrestricted grant to ASAS to fund the study. The funders did not have any role in the
294 design or conduct of the study. This ancillary study did not receive any funding and the sponsors
295 of COMOSPA did not have any interference with this current study.

296

297

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406 **Table 1.** Patient demographics, clinical characteristics and treatment in patients with SpA fulfilling
407 the ASAS classification criteria.

	Mean (SD) or n (%) N = 3370
Age, n=3334	42.9 (13.7)
Disease duration (years), n=3342	8.4 (9.5)
Male gender	2221 (66)
HLA B27 positive, n=2733	2082 (76)
Education level, n=3364	
-Primary school or less	421 (13)
-Secondary school	1497 (44)
-University	1446 (43)
BMI (kg/m ²), n=3325	26.1 (5.7)

Current or previous smoker, n=3365	1565 (46)	408
Sacroiliitis on X-ray, n=3190	2406 (75)	
Sacroiliitis on MRI, n=1782	1249 (70)	411
History of enthesitis, n=3367	1281 (38)	
History of dactylitis, n=3368	463 (14)	413
CRP (mg/L), n=3208	0.51 (11)	
Patient Global (0-10), n=3336	4.1 (2.5)	
BASDAI (0-10), n=3352	3.7 (2.4)	
BASFI (0-10), n=3349	31 (2.7)	
ASDAS (CRP), n=3155	2.0 (1.1)	
Axial involvement (+/- peripheral)	2955 (87.7)	
History of uveitis, n=3368	724 (21)	
History of psoriasis, n=3369	643 (19)	
History of IBD, n=3366	194 (6)	
Extra-articular manifestations (uveitis, IBD, psoriasis)	1369(41)	
RDCI (0-9)	0.7 (1.1)	
Treatment		
-NSAID intake, n=3363	3025(90)	
-NSAID total score (past 3 months)	37 (46)	
-current b/csDMARD	2114 (63)	
-current bDMARD	1275 (38)	
-current csDMARD	1168 (35)	
-current csDMARD only	839 (25)	

416 BMI=Body mass index; MRI=Magnetic Resonance Imaging; CRP=C-reactive protein; BASDAI=Bath Ankylosing Spondylitis
417 Disease Activity Index; BASFI= Bath Ankylosing Spondylitis Functional Index; ASDAS= Ankylosing Spondylitis Disease
418 Activity Score calculated with CRP; IBD=Inflammatory Bowel Disease; RDCI= Rheumatic Disease Comorbidity Index;
419 NSAID=Non-Steroidal Anti-inflammatory Drug; bDMARD=biologic Disease-Modifying Anti-Rheumatic Drugs; csDMARD=
420 conventional synthetic Disease-Modifying Anti-Rheumatic Drug.

421

422 **Table 2.** Uptake of bDMARDs: association with socio-demographic, clinical and treatment
423 variables as well as indicators of the country socio-economic welfare.

Independent predictors	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI) n=2792
Country health expenditure (high/medium vs low)	1.71 (0.84,3.50)	1.96 (0.94,4.10)
Age (years)	1.01 (1.00,1.01)	1.00 (0.99,1.01)
Male gender (vs females)	1.18 (1.01,1.39)	1.26 (1.04,1.53)
Axial (vs peripheral) disease	1.48 (1.16,1.89)	1.62 (1.15,2.28)
ASDAS	0.82 (0.76,0.89)	0.80 (0.73,0.87)
Sacroiliitis on X-ray	1.75 (1.44,2.12)	1.41 (1.12,1.78)
History of extra-articular manifestations	1.46 (1.25,1.70)	1.31 (1.08,1.58)
Total NSAID score (0-400), last 3 months	0.99 (0.99,1.00)	0.99 (0.99,1.00)
Past csDMARD use	2.31 (1.96,2.73)	2.08 (1.72,2.52)
Past bDMARD use	2.64 (2.13,3.28)	2.48 (1.93,3.19)
Education (secondary/university vs primary)	0.79 (0.62,1.00)	0.76 (0.52,1.13)

424

425 **Table 3.** Uptake of csDMARDs: association with socio-demographic, clinical and treatment
426 variables as well as indicators of the country socio-economic welfare

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Independent predictors	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI) n=2792
Country health expenditure (high/medium vs low)	0.52 (0.26,1.03)	0.32 (0.15,0.65)
Age (years)	1.01 (1.00,1.02)	1.00 (1.00,1.01)
Male gender (vs females)	0.73 (0.61,0.87)	0.76 (0.62,0.94)
Axial (vs peripheral) disease	0.30 (0.24,0.39)	0.31 (0.23,0.44)
ASDAS	1.17 (1.07,1.27)	1.16 (1.06,1.28)

Sacroiliitis on X-ray	0.53 (0.43,0.65)	0.74 (0.58,0.94)
History of extra-articular manifestations	1.39 (0.00,1.16)	1.53 (1.23,1.90)
Total NSAID score (0-400) in last 3 months	1.00 (1.00,1.01)	1.00 (1.00,1.01)
Past csDMARD use	0.39 (0.32,0.48)	0.36 (0.28,0.45)
Past bDMARD use	0.55 (0.42,0.73)	0.73 (0.53,1.00)

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Table 4. Relationship between country-level socio-economic factors and bDMARD and csDMARD use, all tested individually in separate models (each cell represents a different model)

	bDMARD use		csDMARD use	
	Univariable analysis OR (95% CI)	Multivariable analysis§ OR (95% CI)	Univariable analysis OR (95% CI)	Multivariable analysis± OR (95% CI)
GDP (high/medium vs low)	1.57 (0.78,3.15)	1.93 (0.91,4.06)	0.59 (0.30,1.15)	0.44 (0.21,0.91)*
Gini (high/medium vs low)	0.84 (0.38,1.87)	0.73 (0.31,1.72)	0.76 (0.35,1.65)	0.96 (0.39,2.37)
HDI (very high/high vs medium)	2.16 (0.64, 7.27)	2.12 (0.62, 7.31)	0.32 (0.11,0.98)*	0.29 (0.08,1.07)

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* $p < 0.05$

GDP= Gross Domestic Product; Gini= measure of income inequality; HDI=Human Development Index

§ Refers to the multivariable model presented in table 2 and in which the variable health expenditures was replaced by the other country-level socio-economic factors, in separate models

442 *± Refers to the multivariable model presented in table 3 and in which the variable health expenditures was replaced by*
443 *the other country-level socio-economic factors, in separate models*

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446 **Figure 1:** bDMARD uptake (%) by country. Crude and adjusted percentage use shown along with
447 95% CI based on models with socio-economic, socio-demographic and clinical variables. Countries
448 ranked based on health expenditure: low (left) to high (right).

449

450 **Figure 2.** csDMARD uptake (%) by country. Adjusted and crude percentage use shown along with
451 95% CI based on models with socio-economic, socio-demographic and clinical variables. Countries
452 ranked based on health expenditure: low (left) to high (right).

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