



Disparities in the organisation of national healthcare systems for treatment of patients with psoriatic arthritis and axial spondyloarthritis across Europe

Brigitte Michelsen^{a,b,c,*}, Mikkel Østergaard^{a,d}, Michael John Nissen^e, Adrian Ciurea^f, Burkhard Möller^g, Lykke Midtbøll Ørnbjerg^a, Pavel Horák^{h,i}, Bente Glintborg^{d,j}, Alan MacDonald^k, Karin Laas^l, Tuulikki Sokka-Isler^m, Bjorn Gudbjornsson^{n,o}, Florenzo Iannone^p, Pasoon Hellamand^{q,r}, Tore Kristian Kvien^c, Ana Maria Rodrigues^{s,t,u}, Catalin Codreanu^v, Ziga Rotar^{w,x}, Isabel Castrejón^{y,z}, Johan Karlsson Wallman^{aa}, Karel Pavelka^{ab,ac}, Anne Gitte Loft^{ad,ae}, Maureen Heddle^{af}, Sigrid Vorobjov^{ag}, Heikki Relas^{ah,ai}, Gerdur Gröndalⁿ, Elisa Gremese^{aj}, Irene van der Horst-Bruinsma^{ak}, Eirik Klami Kristianslund^c, Maria José Santos^{al,am}, Corina Mogosan^v, Matija Tomsic^{w,x}, Federico Diaz-Gonzalez^{an,ao}, Daniela Di Giuseppe^{ap}, Stig Winther Nielsen^{aq}, Merete Lund Hetland^{a,d}

^a Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre for Head and Orthopaedics, Rigshospitalet, Glostrup, Denmark

^b Research Unit, Sørlandet Hospital, Kristiansand, Norway

^c Center for Treatment of Rheumatic and Musculoskeletal Diseases (REMEDI), Diakonhjemmet Hospital, Oslo, Norway

^d Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

^e Department of Rheumatology, Geneva University Hospital, Geneva, Switzerland

^f Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

^g Department of Rheumatology and Immunology, Inselspital - University Hospital Bern, Switzerland

^h Third Department of Internal Medicine- Nephrology, Rheumatology and Endocrinology, Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic

ⁱ Olomouc University Hospital, Olomouc, Czech Republic

^j DANBIO and Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre for Head and Orthopaedics, Rigshospitalet, Glostrup, Denmark

^k NHS Grampian, Scotland, UK

^l Department of Rheumatology, East-Tallinn Central Hospital, Tallinn, Estonia

^m University of Eastern Finland, Faculty of Health Sciences and Rheumatology, Jyväskylä Central Hospital, Jyväskylä, Finland

ⁿ Centre for Rheumatology Research, Landspítali University Hospital, Reykjavík, Iceland

^o Faculty of Medicine, University of Iceland, Reykjavík, Iceland

^p Rheumatology Unit, DiMePre-J, University of Bari, Italy

^q Department of Rheumatology and Clinical Immunology, Amsterdam University Medical Centers, Amsterdam, Netherlands

^r Amsterdam Rheumatology Immunology Center (ARC), Reade and Amsterdam UMC, Amsterdam, Netherlands

^s Reuma.pt, Sociedade Portuguesa de Reumatologia, Lisbon, Portugal

^t EpiDoC unit, CHRC, Nova Medical School, Lisbon, Portugal

^u Rheumatology Unit, Hospital dos Lusíadas, Lisbon, Portugal

^v Center for Rheumatic Diseases, University of Medicine and Pharmacy, Bucharest, Romania

^w Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia

^x Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

^y Department of Rheumatology, Hospital General, Universitario Gregorio Marañón, Madrid, Spain

^z Faculty of Medicine, Complutense University of Madrid, Spain

^{aa} Department of Clinical Sciences Lund, Rheumatology, Skåne University Hospital, Lund University, Lund, Sweden

^{ab} Institute of Rheumatology, Prague, Czech Republic

^{ac} Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic

^{ad} Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark

* Corresponding author at: Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre for Head and Orthopaedics, Rigshospitalet University Hospital - Glostrup, Valdemar Hansens Vej 17, 2600 Glostrup, Denmark.

E-mail address: brigitte.michelsen@regionh.dk (B. Michelsen).

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^{ae} Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

^{af} Aberdeen Centre for Arthritis and Musculoskeletal Health (Epidemiology Group), University of Aberdeen, UK

^{ag} National Institute for Health Development, Tallinn, Estonia

^{ah} Rheumatology, Inflammation Center, Helsinki University Hospital, Helsinki, Finland

^{ai} University of Helsinki, Helsinki, Finland

^{aj} Clinical Immunology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy

^{ak} Radboud University Medical Centre, Nijmegen, the Netherlands

^{al} Department of Rheumatology, Hospital Garcia de Orta, Almada, Portugal

^{am} Instituto Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Portugal

^{an} Department of Rheumatology, Hospital Universitario de Canarias, Universidad de La Laguna, Spain

^{ao} Department of Internal Medicine, Dermatology and Psychiatry, Universidad de La Laguna, Spain

^{ap} Clinical Epidemiology Division, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

^{aq} Patient research partner, Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Centre for Head and Orthopaedics, Rigshospitalet, Glostrup, Denmark

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ABSTRACT

Background: Studies on national policies for biologics are warranted.

Objectives: To map and compare national healthcare set-ups for prescription, start, switch, tapering, and discontinuation of biologic/targeted synthetic disease-modifying antirheumatic drugs (DMARDs) in patients with psoriatic arthritis and axial spondyloarthritis across Europe, and assess the healthcare set-ups in relation to countries' socio-economic status.

Methods: An electronic survey was developed to collect and compare information on national healthcare systems. The relationship between the cumulative score of biologic/targeted synthetic DMARD regulations, socioeconomic indices, and biologic originator costs were assessed by linear regression.

Results: National healthcare set-ups differed considerably across the 15 countries, with significantly fewer regulations with increasing socioeconomic status measured by GDP/current health expenditure/human development index, and with increasing biologic originator costs. In most countries, the biologic/targeted synthetic DMARD prescribing doctor was required to adhere to country and/or hospital recommendations, and about a third of countries had a national/regional tender process. Prescription regulations for biologic/targeted synthetic DMARDs, including pre-treatment and disease activity requirements, varied substantially. Approximately a third of countries had criteria for discontinuation and tapering, whereas only few had for switching. Notably, two countries disallowed biologic/targeted synthetic DMARD retrials, and one imposed limit on the maximum number of biologic/targeted synthetic DMARDs permitted.

Conclusion: The findings highlight substantial variability in healthcare set-ups for biologic/targeted synthetic DMARD use in psoriatic arthritis and axial spondyloarthritis across Europe and their association with socioeconomic status and drug costs. These insights provide a basis for rheumatology societies, policymakers, and stakeholders to evaluate and potentially optimize healthcare policies.

Research in context

What is already known about the topic?

Patient populations with spondyloarthritis who receive treatment with biologics or targeted synthetic DMARDs are heterogeneous, but the underlying reasons behind this heterogeneity remain poorly explored. Spondyloarthritis patients in less socio-economically advanced countries have been reported to have higher disease activity than patients in more socio-economically advanced countries. In rheumatoid arthritis, stricter eligibility criteria for initiation of biologics are found in countries with lower socioeconomic welfare.

What does this study add to the literature?

This is the first comparison of national healthcare set-ups for prescription, start, switch, tapering, and discontinuation of biologic/targeted synthetic DMARDs in patients with psoriatic arthritis and axial spondyloarthritis across Europe, and their relation to socioeconomic measures and bio-originator costs. Our findings highlight substantial variability in healthcare set-ups for biologic/targeted synthetic DMARD use, and their association with socioeconomic status and bio-originator costs.

What are the policy implications?

Rheumatology societies, policymakers, and stakeholders should evaluate national healthcare policies for management of psoriatic arthritis and axial spondyloarthritis with biologic/targeted synthetic DMARDs in relation to those in other countries, to seek potential for optimisation of own policies. Furthermore, focus

should be put on cost spendings of biologic/targeted synthetic DMARDs across Europe.

1. Background

Spondyloarthritis is a group of common chronic rheumatic inflammatory joint diseases, including sub-types such as axial spondyloarthritis (predominantly affecting the spine and sacroiliac joints) and psoriatic arthritis (which is related to the skin psoriasis and commonly affects both small and large joints) [1,2]. Both axial spondyloarthritis and psoriatic arthritis may also cause inflammation of tendons (tendinitis or tenosynovitis) or at the tendon insertions which are known as the entheses (enthesitis), and may lead to joint destruction, disability and impaired quality of life [1,2]. Over the past decades, the introduction of new treatment options, namely the biologic disease-modifying antirheumatic drugs (bDMARDs, also termed biologics), and targeted synthetic DMARDs, as well as the treat-to-target strategy (i.e. active treatment until achievement of an agreed-upon target, most commonly remission) has improved patient outcomes and long-term prognosis [1–3].

However, heterogeneity across countries in patient populations with spondyloarthritis who receive treatment with biologics or targeted synthetic DMARDs may be challenging for international studies [4]. The disparities encompass various factors such as disease activity levels, proportions of patients using concomitant conventional synthetic DMARDs and proportions of smokers. However, the underlying reasons behind this heterogeneity remain poorly explored [5,6].

Patients with spondyloarthritis in less socio-economically advanced countries have been reported to have higher disease activity than patients in more socio-economically advanced countries [4,7]. This has also been found in rheumatoid arthritis, where stricter regulations for prescription and reimbursement of biologics in some countries impact the proportion of patients treated with biologics [8]. However, in spondyloarthritis, the use of biologics was not a mediator in explaining the relationship between less socioeconomically advanced countries and worse health outcomes in one study [4], but accounted for seven percent of the observed association in another study [9], underscoring the complex relationship between socioeconomic factors and disease outcomes. An important aspect to take into consideration is the various healthcare set-ups in different countries, which may impact patients' access to diagnosis, thereby influencing diagnostic delay, treatment initiation and follow-up. Few and mostly older studies have addressed this topic in spondyloarthritis [10–12]. In two reports from 2011 [10] and 2014 [11] some comparisons of treatment regulations for tumour necrosis factor inhibitors in ankylosing spondylitis and psoriatic arthritis were done, and in a recent paper similarities and differences between the European Alliance of Associations for Rheumatology/Assessment of SpondyloArthritis international Society recommendations and national treatment recommendations across Europe were addressed [12].

However, there is no study comparing the various national healthcare set-ups for biologic/targeted synthetic DMARD treatment (i.e. including newer options like targeted synthetic DMARDs) in psoriatic arthritis and axial spondyloarthritis across Europe, nor their relation to socioeconomic measures.

Given the unmet need for extended and updated information on this topic, information should be collected and analysed in order to gain deeper insight into the influence of diverse national healthcare systems on the management of spondyloarthritis patients [10]. This is in particular of relevance for high-cost treatments like biologic/targeted synthetic DMARDs.

Hence, the aim of this study was to map and compare national healthcare set-ups for prescription, start, switch, tapering, and discontinuation of biologic and targeted synthetic DMARDs in patients with psoriatic arthritis and axial spondyloarthritis across Europe. A secondary aim was to assess the healthcare set-ups in relation to the countries' socio-economic status, using gross domestic product (GDP) per capita, the current health expenditure per capita, and the human development index as surrogate markers.

2. Methods

A Research Electronic Data Capture (REDCap) survey was developed to collect information on national healthcare set-ups for prescription, start, switch, tapering, and discontinuation of biologic/targeted synthetic DMARDs from 15 European countries between October 11, 2021 and April 7, 2022 [13,14]. The survey was conducted within the European Spondyloarthritis Research Collaboration Network (EuroSpA RCN) including the following registries (countries): ATTRA (Czech Republic), DANBIO (Denmark), ESRBTR (Estonia), ROB-FIN (Finland), ICEBIO (Iceland), GISEA (Italy), ARC (Netherlands), NOR-DMARD (Norway), Reuma.pt (Portugal), RRBR (Romania), biorx.si (Slovenia), BIOBADASER (Spain), SRQ (Sweden), SCQM (Switzerland), and BSRBR-AS (United Kingdom (UK) [12]. The survey results were checked for accuracy by co-authors and the respondents to the survey, who were leading experts and researchers in the field of rheumatology, and any ambiguities were resolved through queries by email or by video correspondence [12]. For the UK, the study focused on the treatment recommendations in England and Wales. Information on countries' GDP per capita and current health expenditure per capita (expressed in current international dollars converted by the purchasing power parity conversion factor (PPP) to ensure comparability among countries) was collected from the World Bank, and information on the human development index from the United Nations Development Program, using the most recent years

available (i.e. 2021, 2020, and 2021, respectively) [15,16]. An overview of commonly used abbreviations is given in Supplementary Table 1. We calculated scores for biologic/targeted synthetic DMARD regulations as defined in Supplementary Table 2, and cumulative scores of biologic/targeted synthetic DMARD regulations for each of the countries as shown in Supplementary Table 3. To assess the relationship between the cumulative score of biologic/targeted synthetic DMARD regulations and GDP per capita, current health expenditure per capita, and human development index, linear regression and Spearman correlations were performed. Estimated costs paid in 2021 by the public health insurance/tax-paid system for healthcare costs for three biologic originators (i.e. Humira (adalimumab originator, 20 × 40 mg syringe), Enbrel (etanercept originator, 4 × 50 mg syringe/pen), and Cimzia (certolizumab pegol, 2 × 200 mg syringe/pen)) were obtained from the registries, and their relationship with GDP per capita and with the cumulative score of biologic/targeted synthetic DMARD regulations were assessed by linear regression. P-values <0.05 were considered statistically significant. SPSS statistics version 29.0.0 was utilized.

3. Results

3.1. Regulation of biologic/targeted synthetic DMARD prescription

3.1.1. Authority to prescribe biologic/targeted synthetic DMARDs

Generally, rheumatologists, dermatologists, and gastroenterologists in all countries were authorized to prescribe biologic/targeted synthetic DMARDs for certain diseases, with additional specialists in some countries (Table 1). For patients with psoriatic arthritis and axial spondyloarthritis, only rheumatologists were authorized to prescribe biologic/targeted synthetic DMARDs in the Czech Republic, Estonia, Finland, Iceland, Slovenia, and Spain (Table 1). For psoriatic arthritis patients, dermatologists could additionally prescribe biologic/targeted synthetic DMARDs in Denmark, Italy, Netherlands, and Slovenia (only if required for psoriasis), Norway, Portugal, Sweden, Switzerland, and the UK. Gastroenterologists could prescribe biologic/targeted synthetic DMARDs for psoriatic arthritis and axial spondyloarthritis patients in Denmark, Netherlands, and Slovenia (only if active inflammatory bowel disease), Norway, Portugal, and Sweden. In some countries also other specialists could prescribe biologic/targeted synthetic DMARDs, although this was typically done by the specialities responsible for the care of the relevant disease (e.g. uveitis, juvenile arthritis). In Switzerland, the authorization to prescribe biologic/targeted synthetic DMARDs depended on the indications in the national medication compendium [17]. In Portugal, only doctors in certified centres recognized by the national health directorate had the authority to prescribe biologic/targeted synthetic DMARDs. In Denmark, biologic/targeted synthetic DMARDs could only be prescribed by doctors in public hospitals.

3.1.2. Prescription by a specialist in a university-teaching hospital

None of the countries required biologic/targeted synthetic DMARD prescription to be performed by a specialist in a university-teaching hospital.

3.1.3. Adherence to recommendations and regulations

In most countries, the biologic/targeted synthetic DMARD prescribing doctor was *required* to adhere to national and/or hospital recommendations (Table 1), but exceptions could be made on a case-by-case basis in several countries. In Finland, the Netherlands and Sweden, country and/or hospital recommendations should preferably be followed, but the decision was up to the treating rheumatologist. In the Czech Republic, the main reimbursement regulation was given by The State Institute for Drug Control and in Estonia by the national insurance company. In Portugal, in both public and private hospitals, the prescribing doctor of biologic/targeted synthetic DMARDs was required to obtain approval from a public hospital internal committee and adhere to the public hospital's prescription rules/guidance, mainly driven by

Table 1

National healthcare set-ups for prescription and initiation of biologic/targeted synthetic DMARDs in patients with psoriatic arthritis and axial spondyloarthritis, seen in relation to countries' gross domestic product per capita.

Countries ordered by increasing GDP per capita in 10 000 international dollars (2021)														
3.54	3.59	4.08	4.22	4.36	4.43	4.59	4.97	5.50	5.76	5.93	6.38	6.47	7.73	7.92
Romania	Portugal	Spain	Estonia*	Slovenia*	Czech Republic	Italy	UK	Finland*	Iceland	Sweden	Netherlands*	Denmark	Switzerland*	Norway
Regulations of biologic/targeted synthetic DMARD prescription														
→ Who has the authority to prescribe biologic/targeted synthetic DMARDs in your country in general?														
R,D,G,I	R,D,G,O,I	R,D,G,O	R,D,G	R,D,G,O	R,D,G	R,D,G	R,D,G,O	R,D,G,O	R,D,G	R,D,G,O,I,GP	R,D,G	R,D,G,O	R,D,G,O,I,GP	R,D,G
→ Who has the authority to prescribe biologic/targeted synthetic DMARDs in your country for patients with psoriatic arthritis and axial spondyloarthritis?														
R, I	R, O, I	R	R	R	R	R, D	R, D	R	R	R,D,G,O,I,GP	R, D, G	R, D, G, O	R,D,O,I,GP	R, D, G
→ In your country, does the initial biologic/targeted synthetic DMARD prescription have to be performed by a specialist in a university-teaching hospital?														
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
→ Is the prescribing doctor <i>required</i> to adhere to country and/or hospital recommendations in order to prescribe a biologic/targeted synthetic DMARD?														
+	+/-	-	+	+	+	+	+	-	+	-	-	+	-	-
→ When were your latest national treatment recommendations for patients with <i>psoriatic arthritis</i> made available? (Question posed October 2021)														
2021	2015	2018	NA	NA	2016	2017	2012	2021	2019	2021	NA	2018	NA	2019
→ When were your latest national treatment recommendations for patients with <i>axial spondyloarthritis</i> made available? (Question posed October 2021)														
2021	2017	2018	NA	NA	2021	2021	2012	NA	2017	2021	2014	2021	NA	2021
→ Does your country have an annual sequence of biologic/targeted synthetic DMARDs to follow (tender)?														
-	-	+	+	-	-	-	-	-	+	+	-	+	-	+
→ Is the prescribing doctor required to obtain approval from the patients' insurance company or a centralized committee in order to prescribe a biologic/targeted synthetic DMARD?														
-	-	-	-	-	-	-	-	+	+	-	-	-	+	-
→ Is it mandatory in your country that at least two rheumatologists approve the start of a biologic/targeted synthetic DMARD?														
+	-	-	+	-	-	-	-	-	-	-	-	+	-	-
→ In your country, is inclusion in your registry a prerequisite for reimbursement of biologic/targeted synthetic DMARDs?														
+	-	-	-	+	+	-	-	-	+	-	-	-	-	-
→ Does the prescribing doctor have any financial benefit for including patients treated with biologic/targeted synthetic DMARDs in your registry?														
-	-	-	-	-	+	-	-	-	-	-	-	-	-	-
Initiation of biologic/targeted synthetic DMARDs														
→ Start of biologic/targeted synthetic DMARDs are mostly led by: National treatment recommendations* (NTR), local recommendations (LR) or a combination of these:														
NTR	NTR + LR	NTR + LR	NTR	NTR	NTR	NTR + LR	NTR	NTR + LR	NTR	NTR + LR	NTR	NTR	NTR	NTR + LR
→ Is an inadequate response to conventional synthetic DMARDs before biologic/targeted synthetic DMARD initiation <i>required</i> in psoriatic arthritis according to national treatment recommendations* in your country?														
+	+	-	+	+	+	+	+	+	+	+	+	+	+	-
→ Failure to how many csDMARDs?														
2	1	NA	2	1	NS	2	2	1	1	1	1	1	1	NA
→ Is an inadequate response to non-steroidal anti-inflammatory drugs before biologic/targeted synthetic DMARD initiation <i>required</i> in axial spondyloarthritis according to national treatment recommendations* in your country?														
+	+	-	+	+	+	+	+	+	+	+	+	+	+	-
→ Failure to how many non-steroidal anti-inflammatory drugs and total length of non-steroidal anti-inflammatory drug treatment? Please specify the answer in numbers and months (n/m)														
2/3m	2/1m	NA	2/3m	2/1m	NS	2/2m	2/0.5- 2m	2, and 1 csDMARD	NS	2/3m	2/1m	2/1m	NS	NA
→ Do your most recent national recommendations* for starting a biologic/targeted synthetic DMARD currently recommend co-medication with a conventional synthetic DMARD in <i>psoriatic arthritis</i> ?														
-	-	-	-	-	-	-	-	+	+	-	+	+	+	+
→ Do your most recent national recommendations* for starting a biologic/targeted synthetic DMARD currently recommend co-medication with a conventional synthetic DMARD in <i>axial spondyloarthritis</i> ?														
-	-	-	-	-	-	-	-	+	-	-	-	-	-	-
→ Are there any requirements for a minimum <i>disease activity</i> before start of a biologic/targeted synthetic DMARD in <i>psoriatic arthritis</i> according to national treatment recommendations* in your country?														
+	+	-	+	+	-	-	+	-	+	+	-	-	-	-
→ Are there any requirements for a minimum <i>disease activity</i> before start of a biologic/targeted synthetic DMARD in <i>axial spondyloarthritis</i> according to national treatment recommendations* in your country?														
+	+	-	+	+	+	-	+	+	+	+	-	+	-	-
→ Is there any requirement for a minimum <i>disease duration</i> before start of a biologic/targeted synthetic DMARD in psoriatic arthritis according to national treatment recommendations* in your country?														
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
→ Is there any requirement for a minimum <i>disease duration</i> before start of a biologic/targeted synthetic DMARD in axial spondyloarthritis according to national treatment recommendations* in your country?														
-	-	-	-	-	-	-	-	+	-	-	-	-	-	-
→ Do your most recent national treatment recommendations* have different treatment recommendations for psoriatic arthritis patients with <i>extra-musculoskeletal</i> manifestations?														
-	-	-	+	-	-	+	-	-	-	+	-	+	-	-
→ Do your most recent national treatment recommendations* have different treatment recommendations for axial spondyloarthritis patients with <i>extra-musculoskeletal</i> manifestations?														
-	-	+	+	-	+	+	-	-	-	+	+	+	-	+
→ In your country, is smoking cessation <i>required</i> in order to initiate a biologic/targeted synthetic DMARD or get a biologic/targeted synthetic DMARD reimbursed?														
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

+, yes; -, no; +/-, please see text. R, rheumatologists; D, dermatologists; G, gastroenterologists; I, internal medicine doctors; O, other specialists; GDP, gross domestic product; GP, general practitioners; NA, not applicable; NS, not specified. *Other national regulations, please see text for details. The table shows the situation in October 2021-April 2022, when the survey was conducted. GDP per capita is expressed in current international dollars converted by the purchasing power parity conversion factor. Additional information on the regulations is presented in the main text.

current pricing.

3.1.4. National treatment recommendations

As recently reported, ten of the fifteen countries had national treatment recommendations for psoriatic arthritis and axial spondyloarthritis, and two countries for one of the diagnoses, with last updates between 2012 and 2021 (at the time of the survey; Table 1) [12]. Regarding the countries without national treatment recommendations for psoriatic arthritis and/or axial spondyloarthritis, Finland had expert recommendations adapted from the Assessment of SpondyloArthritis international Society/European Alliance of Associations for Rheumatology recommendations for spondyloarthritis patients, the Netherlands followed European Alliance of Associations for Rheumatology and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis recommendations for psoriatic arthritis, Slovenia had unpublished national treatment recommendations for psoriatic arthritis and axial spondyloarthritis, Estonia followed the European Alliance of Associations for Rheumatology and Assessment of SpondyloArthritis international Society/European Alliance of Associations for Rheumatology recommendations together with regulations from the Estonian Health Insurance Fund, and Switzerland followed drug-class specific recommendations from the Clinical Affairs Committee of the Swiss Society of Rheumatology [12].

3.1.5. National/regional tender systems

In a third of the countries, the recommended sequence of prescription of biologic/targeted synthetic DMARDs from the national/regional price based tender system should preferably be followed, but exceptions based on clinical judgement could be made (Table 1).

3.1.6. Approval from a patient's insurance company or a centralized committee

In Finland, Iceland, and Switzerland, the prescribing doctor was required to obtain approval from the patient's insurance company or a centralized committee to prescribe biologic/targeted synthetic DMARDs. In Finland, reimbursement authorities approved the medication upon application on a case-by-case basis. In Spain, only for patients with private insurance, authorization from the insurance company was required prior to biologic/targeted synthetic DMARD prescription. In the Czech Republic, although the main reimbursement regulation was given by the by the State Institute for Drug Control, some insurance companies could have slightly different policies.

3.1.7. Required agreement between rheumatologists to prescribe a biologic/targeted synthetic DMARD

In Romania and Denmark, the prescription of a biologic/targeted synthetic DMARD required agreement between at least two rheumatologists (and sometimes three, based on department level instructions in Denmark), and in Estonia, between at least three rheumatologists. In Norway, agreement between at least two rheumatologists for prescription of biologic/targeted synthetic DMARDs was no longer mandatory, but still common practice.

3.1.8. Inclusion in the registry as a prerequisite for reimbursement of a biologic/targeted synthetic DMARD

In the Czech Republic, Iceland (with a few private practice exceptions), Romania, and Slovenia (not strictly enforced), inclusion in the respective registry (ATTRA/ICEBIO/RRBR/biorx.si) was required for biologic/targeted synthetic DMARD reimbursement.

3.1.9. Benefits of inclusion of patients in the registry

Only in the Czech Republic did the prescribing doctor have a financial benefit from including patients treated with biologic/targeted synthetic DMARDs in the registry, as there was a minor compensation for each visit. In Denmark, Finland, Portugal, Sweden, and Switzerland, the doctor could use the respective registry (DANBIO/ROB-FIN/Reuma-

pt/SRQ/SCQM) for clinical/quality management (i.e. visualization of a patient's disease score and treatment over time). In Switzerland, the number of registered patients in the national registry for an individual prescriber could offset costs above the average and prevent claims of healthcare providers following cost-effectiveness performance audits.

3.2. Initiation of biologic/targeted synthetic DMARDs

3.2.1. Basis for initiation of biologic/targeted synthetic DMARDs

The initiation of biologic/targeted synthetic DMARDs was mostly guided by national treatment recommendations and regulations in all countries, and additionally by local recommendations in Finland, Italy, Norway, Portugal, Spain, and Sweden. All countries also used international recommendations to varying extent as guidance for biologic/targeted synthetic DMARD initiation.

3.2.2. Inadequate response to conventional synthetic DMARDs before biologic/targeted synthetic DMARD initiation in psoriatic arthritis

Inadequate response to conventional synthetic DMARD(s) was required to start a biologic/targeted synthetic DMARD in all countries, except Norway and Spain, although inadequate response to at least one conventional synthetic DMARD was recommended (but not required) in these countries over 3–6 months in Norway and 4–6 weeks in Spain (Table 1). In some countries, the requirement could be overridden in individual cases at the specialist's discretion. In the Czech Republic, the number of conventional synthetic DMARDs was not specified, but inadequate response to conventional synthetic DMARDs in general was required. In Denmark, Sweden, Portugal, the Netherlands, Slovenia, and Switzerland, inadequate response to at least one conventional synthetic DMARD was required for 3–6 months in Denmark, three months in Sweden, Portugal, the Netherlands, and Slovenia, and of unspecified treatment duration in Switzerland. In Sweden, for patients with very high disease activity, initiation of a tumor necrosis factor inhibitor could be considered without any prior use of a conventional synthetic DMARD. In Estonia, Romania, and Italy, inadequate response to at least two conventional synthetic DMARDs was required over at least three months in Estonia and Romania and of unspecified treatment duration in Italy. In Finland, methotrexate should have been tried for at least 3–6 months, and in Iceland 15–25 mg methotrexate/week for at least three months.

3.2.3. Inadequate response to non-steroidal anti-inflammatory drugs before biologic/targeted synthetic DMARD initiation in axial spondyloarthritis

Inadequate response to non-steroidal anti-inflammatory drugs before biologic/targeted synthetic DMARD initiation was required in all countries except Norway and Spain, where inadequate response to at least two non-steroidal anti-inflammatory drugs during at least one month in total was recommended but not required. In all other countries, failure of at least two non-steroidal anti-inflammatory drugs was required, except for Iceland and Switzerland, where the number of non-steroidal anti-inflammatory drugs was unspecified and up to clinical judgment. The minimum required total length of non-steroidal anti-inflammatory drug treatment before biologic/targeted synthetic DMARD initiation varied from one month in Denmark, Portugal, Netherlands, and Slovenia, to three months in Estonia and Romania. Moreover, in Finland, inadequate response to a conventional synthetic DMARD (e.g. sulfasalazine or methotrexate) was additionally required before initiation of a biologic/targeted synthetic DMARD in axial spondyloarthritis.

3.2.4. Co-medication with conventional synthetic DMARDs in psoriatic arthritis

In Denmark, Finland, Iceland, The Netherlands, Norway, and Switzerland (only for infliximab), co-medication with a conventional synthetic DMARD together with a biologic/targeted synthetic DMARD was recommended in psoriatic arthritis (Table 1).

3.2.5. Co-medication with conventional synthetic DMARDs in axial spondyloarthritis

In Finland, a conventional synthetic DMARD was recommended before the start of a biologic/targeted synthetic DMARD in patients with axial spondyloarthritis (usually sulfasalazine, but could be any conventional synthetic DMARD), and preferably also as co-medication with a biologic/targeted synthetic DMARD. In several countries, only in the case of spondylitis accompanied by arthritis in peripheral joints, co-medication with a conventional synthetic DMARD was recommended. (Table 1).

3.2.6. Minimum disease activity requirement for biologic/targeted synthetic DMARD initiation in psoriatic arthritis

Seven countries had defined requirements for a minimum disease activity before initiation of a biologic/targeted synthetic DMARD in psoriatic arthritis (Table 1). In Estonia, at least three swollen and tender joints and/or four painful entheses and/or axial disease were required. In Iceland, the requirements were 28-joint disease activity score >3.2 or Bath Ankylosing Spondylitis Disease Activity Index >4. However, if signs of aggressive disease, (e.g. radiographic changes, or limited working capacity due to dactylitis/enthesitis) and inadequate response to methotrexate, a biologic/targeted synthetic DMARD could be initiated irrespective of the level of 28-joint disease activity score and Bath Ankylosing Spondylitis Disease Activity Index. In Portugal, biologic/targeted synthetic DMARD treatment was considered for patients with ≥5 swollen joints (of 66) on two separate occasions, at least one month apart. In patients with mono or oligoarthritis, the decision to treat patients with biologic/targeted synthetic DMARDs was made on a case-by-case basis, according to the rheumatologist's opinion, taking disease severity and the presence of poor prognostic factors into account. Patients with psoriatic arthritis and active axial disease were eligible for biologic/targeted synthetic DMARDs if they had Bath Ankylosing Spondylitis Disease Activity Index ≥4 or Ankylosing Spondylitis Disease Activity Score ≥2.1 on two separate occasions with at least a one-month interval. In Romania, disease activity index for psoriatic arthritis >28 was required to start a biologic/targeted synthetic DMARD, as well as both 68 tender and 66 swollen joint counts ≥5, or C-reactive protein three times the upper reference value. In Slovenia, 28-joint disease activity score >3.2 and 28 + 26 swollen joint counts (28 joint count + acromioclavicular joints, sternoclavicular joints, distal interphalangeal joints, ankles, metatarsophalangeal joints) >3 were required. In Sweden, patients with at least moderate disease activity and insufficient response to at least three months of conventional synthetic DMARDs qualified for biologic/targeted synthetic DMARD treatment, as well as DMARD naïve patients with very high disease activity. In the UK, at least three swollen joints and three tender joints were required.

3.2.7. Minimum disease activity requirement for biologic/targeted synthetic DMARD initiation in axial spondyloarthritis

Ten countries had minimum disease activity requirements before the start of a biologic/targeted synthetic DMARD in axial spondyloarthritis (Table 1). In the Czech Republic, Bath Ankylosing Spondylitis Disease Activity Index >4 and elevated C-reactive protein/erythrocyte sedimentation rate were required, in Finland, Ankylosing Spondylitis Disease Activity Score ≥2.1 or Bath Ankylosing Spondylitis Disease Activity Index >4, in Estonia, Iceland, and Slovenia Bath Ankylosing Spondylitis Disease Activity Index >4, and in UK Bath Ankylosing Spondylitis Disease Activity Index and spinal pain visual analogue scale >4. In Portugal and Denmark, Ankylosing Spondylitis Disease Activity Score ≥2.1 or Bath Ankylosing Spondylitis Disease Activity Index ≥4, on two separate occasions with at least a one-month interval was required (with emphasis on Bath Ankylosing Spondylitis Disease Activity Index question 5 and 6 in Denmark), and in Romania, Bath Ankylosing Spondylitis Disease Activity Index >6 at two successive evaluations at least four weeks apart, as well as Ankylosing Spondylitis Disease Activity Score ≥2.5. Sweden required high disease activity to start a biologic/

targeted synthetic DMARD, and recommended use of validated measures of axial disease activity (e.g. Ankylosing Spondylitis Disease Activity Score ≥2.1 or Bath Ankylosing Spondylitis Disease Activity Index ≥4). For non-radiographic axial spondyloarthritis, biologics were only formally approved for patients with objective signs of inflammation (elevated C-reactive protein and/or inflammation on MRI). Italy, The Netherlands, Norway, Spain, and Switzerland had no requirement for a minimum disease activity, although Bath Ankylosing Spondylitis Disease Activity Index ≥4 or Ankylosing Spondylitis Disease Activity Score ≥2.1 was recommended (but not required) in Norway and The Netherlands, and in the case of non-radiographic axial spondyloarthritis, also elevated C-reactive protein and/or active sacroiliitis on MRI.

3.2.8. Requirements for a minimum disease duration in psoriatic arthritis

None of the countries had requirements for a minimum disease duration before initiation of a biologic/targeted synthetic DMARD in psoriatic arthritis.

3.2.9. Requirements for a minimum disease duration in axial spondyloarthritis

Finland had requirements for a minimum disease duration of at least 3 months before initiation of a biologic/targeted synthetic DMARD in axial spondyloarthritis (Table 1).

3.2.10. Extra-musculoskeletal manifestations in psoriatic arthritis

Estonia had different treatment recommendations for patients with concomitant uveitis, and Denmark, Italy, and Sweden for patients with concomitant uveitis, inflammatory bowel disease, and according to the severity of psoriasis (Table 1).

3.2.11. Extra-musculoskeletal manifestations in axial spondyloarthritis

The Czech Republic, Italy, Denmark, Norway, and Spain had specific treatment recommendations for patients with concomitant inflammatory bowel disease or uveitis, The Netherlands and Sweden for patients with concomitant inflammatory bowel disease, uveitis or psoriasis, and Estonia for patients with concomitant uveitis.

3.2.12. Smoking cessation

No country required smoking cessation to initiate or to obtain reimbursement for a biologic/targeted synthetic DMARD.

3.3. Change and discontinuation of biologic/targeted synthetic DMARDs

3.3.1. Insufficient response

None of the countries had national recommendations to alter the frequency and/or dose of biologic/targeted synthetic DMARDs if there was an insufficient response, neither in psoriatic arthritis nor in axial spondyloarthritis (Table 2).

3.3.2. Criteria for biologic/targeted synthetic DMARD switching in psoriatic arthritis

In Romania, switching a biologic/targeted synthetic DMARD was required if disease activity index for psoriatic arthritis was >14 and if a 50 % improvement in disease activity index for psoriatic arthritis was not achieved after 24 weeks (Table 2). However, in all countries, switch of biologic/targeted synthetic DMARDs was generally recommended if insufficient response.

3.3.3. Criteria for biologic/targeted synthetic DMARD switching in axial spondyloarthritis

In the Czech Republic, at least a 50 % reduction in Bath Ankylosing Spondylitis Disease Activity Index or an absolute change of 2 (0–10 scale) at week 12 was required, following which an expert opinion on the appropriateness of continuing treatment was obtained. If there was no response, the treatment should be modified. In Romania, improvement of <50 % in Bath Ankylosing Spondylitis Disease Activity Index

Table 2
Regulations for switch, tapering, and discontinuation of biologic/targeted synthetic DMARDs in patients with psoriatic arthritis and axial spondyloarthritis, seen in relation to countries' gross domestic product per capita.

Countries ordered after increasing GDP per capita in 10 000 international dollars (2021)															
3.54 Romania	3.59 Portugal	4.08 Spain	4.22 Estonia*	4.36 Slovenia*	4.43 Czech Republic	4.59 Italy	4.97 UK	5.50 Finland*	5.76 Iceland	5.93 Sweden	6.38 Netherlands*	6.47 Denmark	7.73 Switzerland*	7.92 Norway	
→ Are there national requirements to alter frequency and/or dose of biologic/targeted synthetic DMARDs if <i>insufficient response</i> in <i>psoriatic arthritis</i> patients?															
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
→ Are there national requirements to alter frequency and/or dose of biologic/targeted synthetic DMARDs if <i>insufficient response</i> in <i>axial spondyloarthritis</i> patients?															
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
→ Are there national treatment recommendations* (criteria) for <i>switching</i> of a biologic/targeted synthetic DMARD in <i>psoriatic arthritis</i> (e.g. after 6 months) in your country?															
+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
→ Are there national treatment recommendations* (criteria) for <i>switching</i> of a biologic/targeted synthetic DMARD in <i>axial spondyloarthritis</i> (e.g. after 6 months) in your country?															
+	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-
→ Does your country have <i>insurance company rules</i> for <i>switching</i> of a biologic/targeted synthetic DMARD in <i>psoriatic arthritis</i> ?															
-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
→ Does your country have <i>insurance company rules</i> for <i>switching</i> of a biologic/targeted synthetic DMARD in <i>axial spondyloarthritis</i> ?															
-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
→ Does your country have criteria for response/disease activity level for <i>discontinuation</i> of a biologic/targeted synthetic DMARD in <i>psoriatic arthritis</i> patients?															
+	+	-	-	+	-	-	+	-	-	-	-	-	-	-	-
→ Does your country have criteria for response/disease activity level for <i>discontinuation</i> of a biologic/targeted synthetic DMARD in <i>axial spondyloarthritis</i> patients?															
+	+	-	-	+	-	-	+	-	-	-	+	-	-	-	+
→ Discontinuations of biologic/targeted synthetic DMARDs are mainly led by: National treatment recommendations (issued by the national society for rheumatology or health authority [NTR]), local recommendations (LR) and/or clinical situation (CS)															
NTR, CS	CS	CS	CS	NTR	CS	CS	NTR, CS	CS	CS	CS	CS	CS	CS	CS	LR, CS
→ Does your country have <i>insurance company rules</i> for <i>discontinuation</i> of a biologic/targeted synthetic DMARD in <i>psoriatic arthritis</i> ?															
-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
→ Does your country have <i>insurance company rules</i> for <i>discontinuation</i> of a biologic/targeted synthetic DMARD in <i>axial spondyloarthritis</i> ?															
-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
→ Does your country have national treatment recommendations* (criteria) for <i>tapering</i> of biologic/targeted synthetic DMARDs in <i>psoriatic arthritis</i> patients in remission?															
+	+	-	-	-	-	-	-	-	-	+	+	-	-	-	-
→ Does your country have national treatment recommendations* (criteria) for <i>tapering</i> of biologic/targeted synthetic DMARDs in <i>axial spondyloarthritis</i> patients in remission?															
+	+	-	-	-	-	-	-	-	-	+	-	-	-	-	+
→ Can patients who have previously failed a biologic/targeted synthetic DMARD try the same biologic/targeted synthetic DMARD again in your country?															
-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
→ Does your country have restrictions of a maximum duration of treatment with biologic/targeted synthetic DMARDs allowed in <i>psoriatic arthritis</i> patients?															
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
→ Does your country have restrictions of a maximum duration of treatment with biologic/targeted synthetic DMARDs allowed in <i>axial spondyloarthritis</i> patients?															
-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
→ Does your country have restriction of a maximum number of biologic/targeted synthetic DMARDs allowed in <i>psoriatic arthritis</i> patients?															
-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-
→ Does your country have restriction of a maximum number of biologic/targeted synthetic DMARDs allowed in <i>axial spondyloarthritis</i> patients?															
-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-

+, yes; -, no; *Other national regulations, please see text for details. The table shows the situation in October 2021-April 2022, when the survey was conducted. GDP per capita is expressed in current international dollars converted by the purchasing power parity conversion factor. Additional information on the regulations is presented in the main text.

required a switch of biologic/targeted synthetic DMARD. However, in all countries a switch of biologics was generally recommended if the response was insufficient.

3.3.4. Insurance company rules for switch of a biologic/targeted synthetic DMARD in psoriatic arthritis and axial spondyloarthritis

Estonia had insurance company rules for switching of a biologic/targeted synthetic DMARD in psoriatic arthritis and axial spondyloarthritis, according to which the two first biologics had to be tumor necrosis factor inhibitors.

3.3.5. Criteria for response/disease activity level for discontinuation of biologic/targeted synthetic DMARDs in psoriatic arthritis

Portugal, Romania, Slovenia, and the UK had criteria for response/disease activity level for discontinuation of biologic/targeted synthetic DMARDs in psoriatic arthritis (Table 2). In Portugal, for peripheral arthritis, response should be defined by Psoriatic Arthritis Response Criteria/American College of Rheumatology criteria at three and six months after starting a biologic, together with the rheumatologist's opinion and other clinical, laboratory, and/or radiological parameters. For axial disease, response should be assessed after at least three months of continuous treatment with a biologic. Response criteria were: 1) a decrease in Bath Ankylosing Spondylitis Disease Activity Index $\geq 50\%$ or ≥ 2 units (0–10 scale) or 2) a decrease in Ankylosing Spondylitis Disease Activity Score ≥ 1.1 . In Romania, a biologic/targeted synthetic DMARD had to be withdrawn if the disease activity index for psoriatic arthritis > 14 at 24 weeks' treatment. In Slovenia, there was a general agreement to discontinue a biologic/targeted synthetic DMARD if the predetermined conditions were not met, e.g., 28-joint disease activity score < 3.2 , or change in 28-joint disease activity score < 1.2 on two consecutive visits. This, however, could be overridden by the attending rheumatologist. In the UK, adequate response according to the Psoriatic Arthritis Response Criteria (i.e. improvement in at least two of the four Psoriatic Arthritis Response Criteria items with no worsening in any item), after 16 weeks was required to continue a biologic/targeted synthetic DMARD. Finally, in the case of an inadequate response, discontinuation of a biologic/targeted synthetic DMARD was recommended also in other countries, but without specifically defined response criteria/disease activity levels for discontinuation.

3.3.6. Criteria for response/disease activity level for discontinuation of biologic/targeted synthetic DMARDs in axial spondyloarthritis

The Netherlands, Norway, Portugal, Romania, Slovenia, and the UK had criteria for response/disease activity level for discontinuation of biologic/targeted synthetic DMARDs in axial spondyloarthritis (Table 2). Additionally, in several countries in case of an inadequate response, discontinuation of a biologic/targeted synthetic DMARD was recommended, but without specifically defined response criteria/disease activity levels for discontinuation. In The Netherlands, discontinuation was recommended if, after 3–6 months, the patient did not achieve 50 % improvement in Bath Ankylosing Spondylitis Disease Activity Index, ≥ 2 units Bath Ankylosing Spondylitis Disease Activity Index decrease (0–10 scale), Ankylosing Spondylitis Disease Activity Score < 1.3 , or > 1.1 improvement in Ankylosing Spondylitis Disease Activity Score, provided it was also supported by the rheumatologist. In Norway, improvement in Ankylosing Spondylitis Disease Activity Score ≥ 1.1 or Bath Ankylosing Spondylitis Disease Activity Index ≥ 2.0 after 3–4 months was recommended to continue a biologic. In Portugal, switching biologic/targeted synthetic DMARDs was recommended after 3–6 months in non-responders. Response criteria were decrease in Ankylosing Spondylitis Disease Activity Score ≥ 1.1 or decrease in Bath Ankylosing Spondylitis Disease Activity Index $\geq 50\%$ or ≥ 2 units (0–10 scale). In Romania, discontinuation of biologic/targeted synthetic DMARDs was recommended if Ankylosing Spondylitis Disease Activity Score > 2.1 . In Slovenia, there was a general agreement to discontinue a biologic/targeted synthetic DMARD if the predetermined conditions

were not met, e.g., 50 % improvement in Bath Ankylosing Spondylitis Disease Activity Index or change in Bath Ankylosing Spondylitis Disease Activity Index < -2.0 on two consecutive visits. This, however, could be overridden by the attending rheumatologist. In the UK, after 12 weeks' treatment (16 weeks for secukinumab), a reduction in Bath Ankylosing Spondylitis Disease Activity Index by 50 % or ≥ 2 units (0–10 scale), and a reduction in spinal pain Visual Analogue Scale by ≥ 2 cm was required to continue a biologic/targeted synthetic DMARD.

3.3.7. Factors influencing biologic/targeted synthetic DMARD discontinuation decisions in psoriatic arthritis and axial spondyloarthritis

Discontinuation of biologic/targeted synthetic DMARDs was mainly led by national treatment recommendations in Slovenia, local recommendations and the clinical situation in Norway, national treatment recommendations and the clinical situation in Romania, and by the clinical situation in the remaining countries. Estonia additionally had health authority rules for when to discontinue biologic/targeted synthetic DMARDs.

3.3.8. Insurance company rules for biologic/targeted synthetic DMARD discontinuation in psoriatic arthritis and axial spondyloarthritis

Estonia had insurance company rules for discontinuation of biologic/targeted synthetic DMARDs, according to which a biologic/targeted synthetic DMARD had to be discontinued if it was not effective after three months' treatment. For patients with peripheral arthritis, insufficient response was defined as $< 30\%$ decrease in at least two of the items of Psoriatic Arthritis Response Criteria (one should be either tender or swollen joints), for patients with enthesitis by $< 50\%$ reduction in the number of painful entheses, and for patients with spondylitis by $< 50\%$ improvement in Bath Ankylosing Spondylitis Disease Activity Index after three months' treatment. In Switzerland, although no specific insurance company rules exist, some insurance companies could request confirmation of a "significant" improvement (definition up to the treating rheumatologist) after 3–6 months' therapy to justify ongoing reimbursement.

3.3.9. Tapering of biologic/targeted synthetic DMARDs in psoriatic arthritis and axial spondyloarthritis

The Netherlands, Norway, Portugal, Romania, and Sweden had recommendations for tapering of biologic/targeted synthetic DMARDs in psoriatic arthritis and/or axial spondyloarthritis. The Netherlands followed European Alliance of Associations for Rheumatology recommendations for tapering of biologic/targeted synthetic DMARDs in psoriatic arthritis. In Norway, for axial spondyloarthritis patients, tapering of biologic/targeted synthetic DMARDs could be attempted for patients in sustained remission (> 6 –12 months), by gradually increasing the dosing interval. In Portugal, for psoriatic arthritis, tapering of biologic/targeted synthetic DMARDs by expanding the dosing interval or reducing the dose, could be considered in individual cases (e.g. if remission ≥ 12 months in the absence of steroid or non-steroidal anti-inflammatory drug treatment), according to the rheumatologist's opinion (potentially supported by imaging methods), and especially if the treatment was being combined with a conventional synthetic DMARD. In Portugal, axial spondyloarthritis patients with sustained inactive disease (Ankylosing Spondylitis Disease Activity Score < 1.3) for > 12 months, could undergo biologics optimization by gradually increasing the dosing interval or decreasing each dose, on an individual basis. In Romania, tapering of biologic/targeted synthetic DMARDs could be considered for patients in remission ≥ 12 months. In Sweden, dose reduction of a biologic was recommended for patients with long-standing low disease activity (duration not further specified).

3.3.10. Retry of a biologic/targeted synthetic DMARD in psoriatic arthritis and axial spondyloarthritis

Patients who had previously failed a biologic/targeted synthetic DMARD could try the same biologic/targeted synthetic DMARD again in

all countries, except for Estonia and Romania.

3.3.11. Maximum duration and maximum number of biologic/targeted synthetic DMARDs in psoriatic arthritis and axial spondyloarthritis

None of the countries had restrictions on the maximum duration of treatment with biologic/targeted synthetic DMARDs allowed. Only Estonia had restrictions on the maximum number of biologic/targeted synthetic DMARDs, allowing a maximum of four biologic/targeted synthetic DMARDs per patient.

3.3.12. Cumulative scores of biologic/targeted synthetic DMARD regulations

In Supplementary Table 2, definitions of scores regarding regulations for prescription, start, switch, tapering, and discontinuation of biologic/targeted synthetic DMARDs across the countries are listed. Lower scores indicate fewer regulations. Cumulative scores of the regulations (according to the definitions in Supplementary Table 2) are shown in Supplementary Table 3 and visualized in Fig. 1. The cumulative score of

biologic/targeted synthetic DMARD regulations reflects the physician-facing regulations and not the overall regulatory complexity of each country's system.

3.3.13. National socioeconomic indicators versus the cumulative score of biologic/targeted synthetic DMARD regulations

In Fig. 2, the cumulative score of regulations for biologic/targeted synthetic DMARD prescription, start, switch, tapering, and discontinuation are shown in relation to countries' a) GDP per capita in 10 000 current international dollars converted by the PPP, b) current health expenditure in 1000 current international dollars converted by the PPP, and c) human development index. The regression lines in the figures show a negative association between the cumulative score of biologic/targeted synthetic DMARD regulations and a) GDP per capita, $R^2 = 0.42$, $B = -2.11$, 95 %CI $(-3.60, -0.63)$, $p = 0.009$, b) current health expenditure per capita, $R^2 = 0.56$, $B = -1.92$, 95 %CI $(-2.94, -0.90)$, $p = 0.001$, and c) human development index, $R^2 = 0.48$, $B = -77.3$, 95 %CI $(-125.9, -28.7)$, $p = 0.004$. The Spearman correlations between the

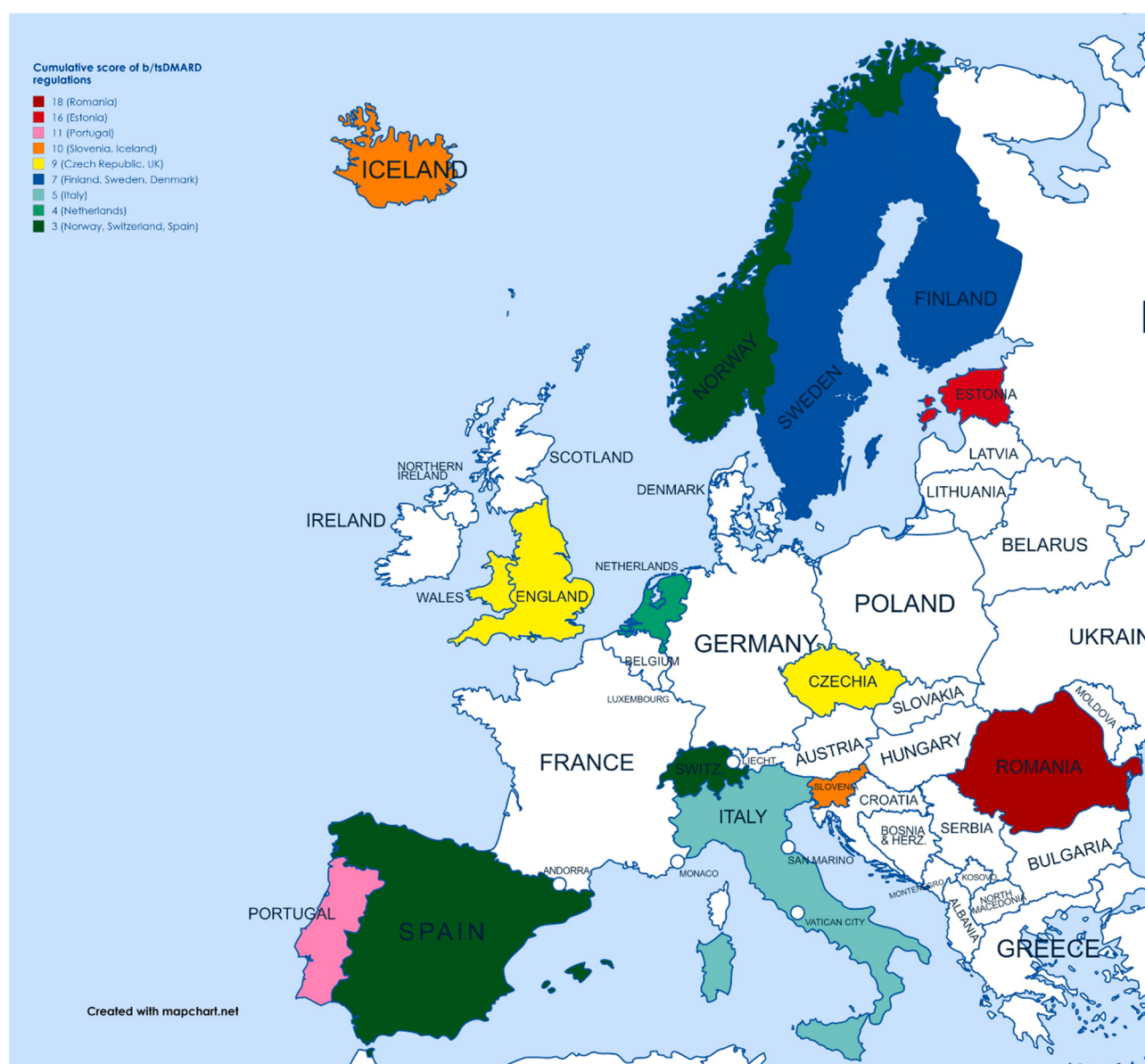


Fig. 1. Cumulative scores of regulations for biologic/targeted synthetic DMARD prescription, start, switch, tapering and discontinuation in patients with spondyloarthritis, including psoriatic arthritis and axial spondyloarthritis (higher scores indicate more regulations). Map lines delineate study areas and do not necessarily depict accepted national boundaries.

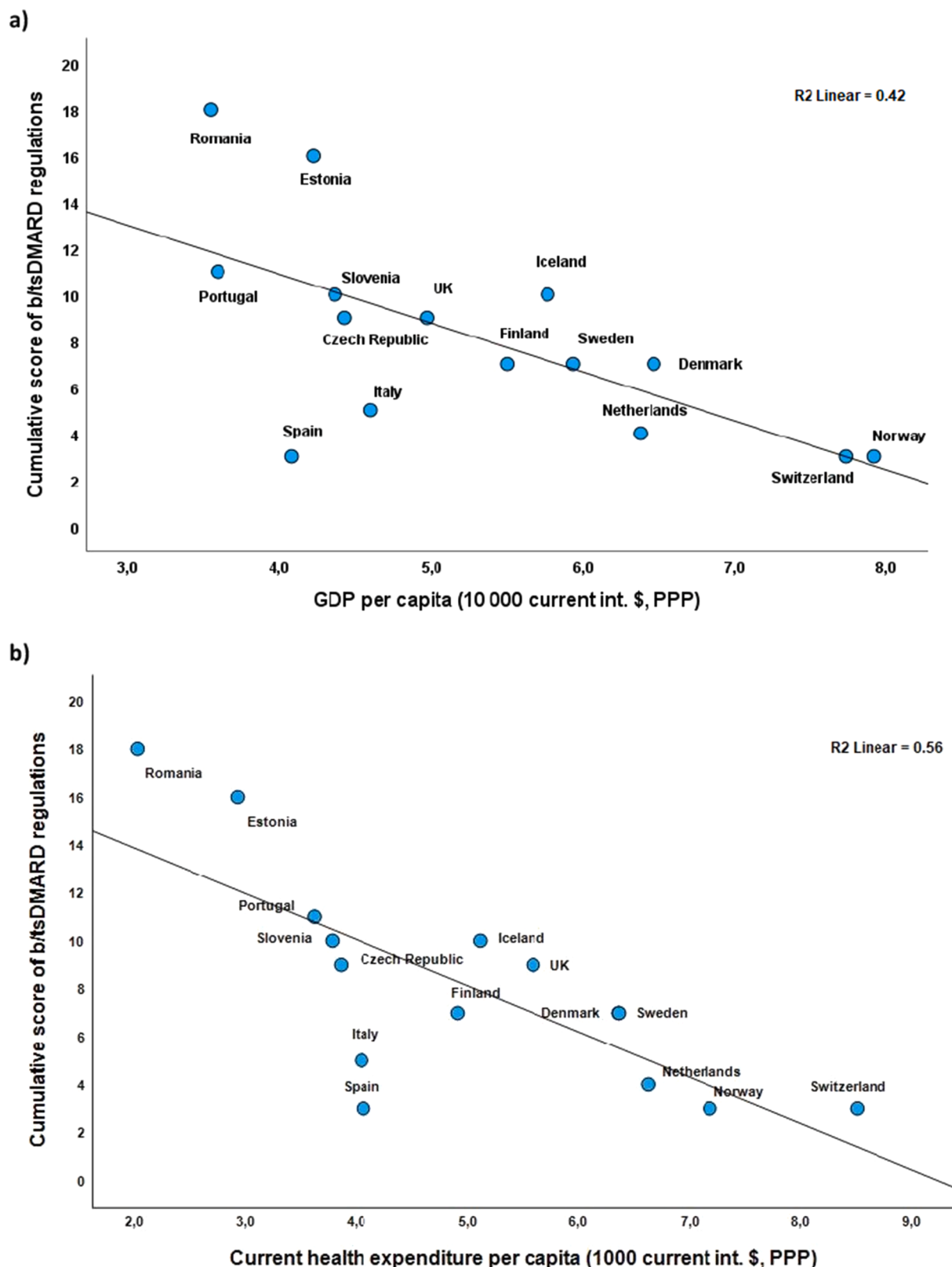


Fig. 2. Scatterplot of the cumulative score of biologic/targeted synthetic DMARD regulations and a) gross domestic product (GDP) per capita (expressed in 10 000 current international dollars converted by the purchasing power parity conversion factor (PPP)), b) current health expenditure per capita (expressed in 1000 current international dollars converted by the PPP), and c) human development index. Higher cumulative scores indicate more regulations. The cumulative score of biologic/targeted synthetic DMARD regulations reflects the physician-facing regulations and not the overall regulatory complexity of each country's system. An interactive version of figure 2 can be assessed in the attached html files.

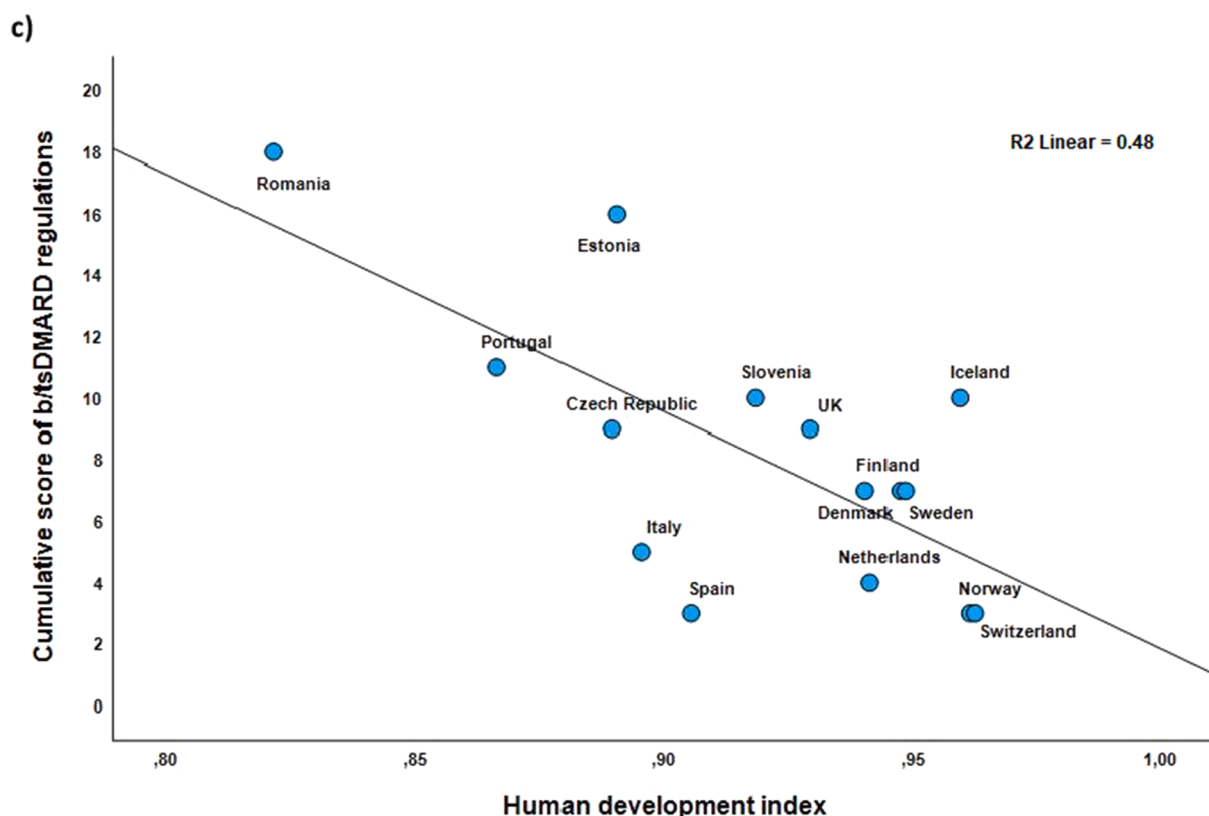


Fig. 2. (continued).

cumulative score of regulations and a) GDP per capita is $\rho = -0.65$, $p = 0.009$, b) current health expenditure per capita $\rho = -0.78$, $p < 0.001$, and c) human development index, $\rho = -0.61$, $p = 0.016$.

3.3.14. Estimated costs of biologic originators versus GDP and versus biologic/targeted synthetic DMARD regulations

In Fig. 3, estimated costs of biologic originators paid by the public health insurance/tax paid system for healthcare costs in 2021 are shown in relation to GDP per capita in 10 000 current international dollars converted by the PPP. In Fig. 4, the estimated costs are shown in relation to the cumulative score of biologic/targeted synthetic DMARD regulations. The regression lines in the figures show a positive association between biologic originator costs and GDP per capita, and a negative association between biologic originator costs and the cumulative score of biologic/targeted synthetic DMARD regulations.

4. Discussion

This is the first comparison of national healthcare set-ups for prescription, start, switch, tapering, and discontinuation of biologic/targeted synthetic DMARDs in patients with psoriatic arthritis and axial spondyloarthritis across Europe, also seen in relation to the countries' socioeconomic status. The national healthcare set-ups varied considerably across the 15 countries. Furthermore, there were significantly fewer biologic/targeted synthetic DMARD regulations with countries' increasing socioeconomic status, measured by GDP per capita, current healthcare expenditure per capita and human development index. Estimated costs of biologic originators were higher with increasing GDP per capita, and lower with increasing biologic/targeted synthetic DMARD regulations.

In most countries, the biologic/targeted synthetic DMARD prescribing doctor was required to adhere to country and/or hospital recommendations, and about a third of the countries had a national/

regional tender process with instructions on the yearly sequence of biologic/targeted synthetic DMARDs to follow. Most countries required an inadequate response to conventional synthetic DMARDs before biologic/targeted synthetic DMARD initiation in psoriatic arthritis, and an inadequate response to non-steroidal anti-inflammatory drugs before biologic/targeted synthetic DMARD initiation in axial spondyloarthritis, and one country also required an inadequate response to a conventional synthetic DMARD in axial spondyloarthritis.

Requirements for a minimum disease activity for initiation of biologic/targeted synthetic DMARDs varied considerably from no requirement to a requirement of high disease activity, whereas only one country had requirement for a minimum disease duration. Regarding patients with extra-musculoskeletal manifestations, more countries had specific treatment recommendations for axial spondyloarthritis than psoriatic arthritis. None of the countries required smoking cessation for initiation of biologic/targeted synthetic DMARDs, although smoking is known to reduce tumour necrosis factor inhibitor treatment adherence and response [18]. About one-third of the countries had criteria for discontinuation of biologic/targeted synthetic DMARDs, few had criteria for switching, whereas about one-third had recommendations for tapering. Notably, retrying a biologic/targeted synthetic DMARD was not allowed in two countries, and one country imposed restrictions on the maximum number of biologic/targeted synthetic DMARDs allowed.

A particularly negative impact for patients may be expected when high thresholds for disease activity or strict pre-treatment requirements are mandated before initiating biologic/targeted synthetic DMARDs, as delays in treatment may render it more difficult to achieve remission (i. e., the absence of active disease) and increase the risk of joint damage and long-term disability. Furthermore, restrictions on the maximum number of biologic/targeted synthetic DMARDs a patient can access, as well as prohibitions on re-trials of these therapies, may particularly affect patients for whom remission is especially challenging to achieve. Therefore, from the patient's perspective, healthcare systems without

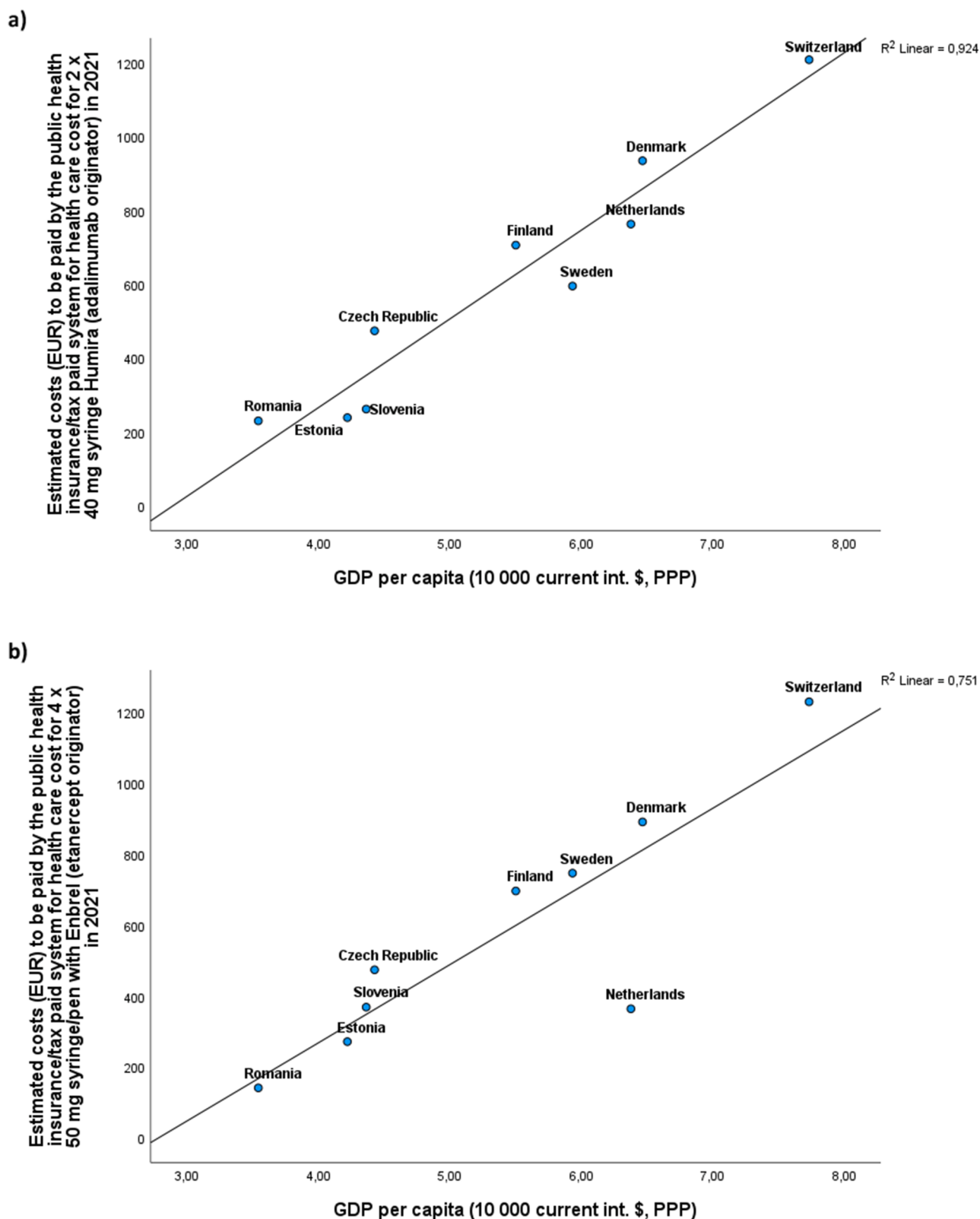


Fig. 3. Scatterplot of estimated costs paid by the public health insurance/tax paid system for healthcare costs in 2021 for biologic originators, and GDP per capita in 10 000 current international dollars converted by the PPP (2021); a) Humira (adalimumab originator), $R^2 = 0.92$, $B = 240.1$, 95 %CI (178.8, 301.4), $p < 0.001$; b) Enbrel (etanercept originator), $R^2 = 0.75$, $B = 220.4$, 95 %CI (107.0, 333.9), $p = 0.003$; c) Cimzia (certolizumab pegol), $R^2 = 0.92$, $B = 197.0$, 95 %CI (139.2, 254.7), $p < 0.001$. Only countries with available costs are shown in the figure.

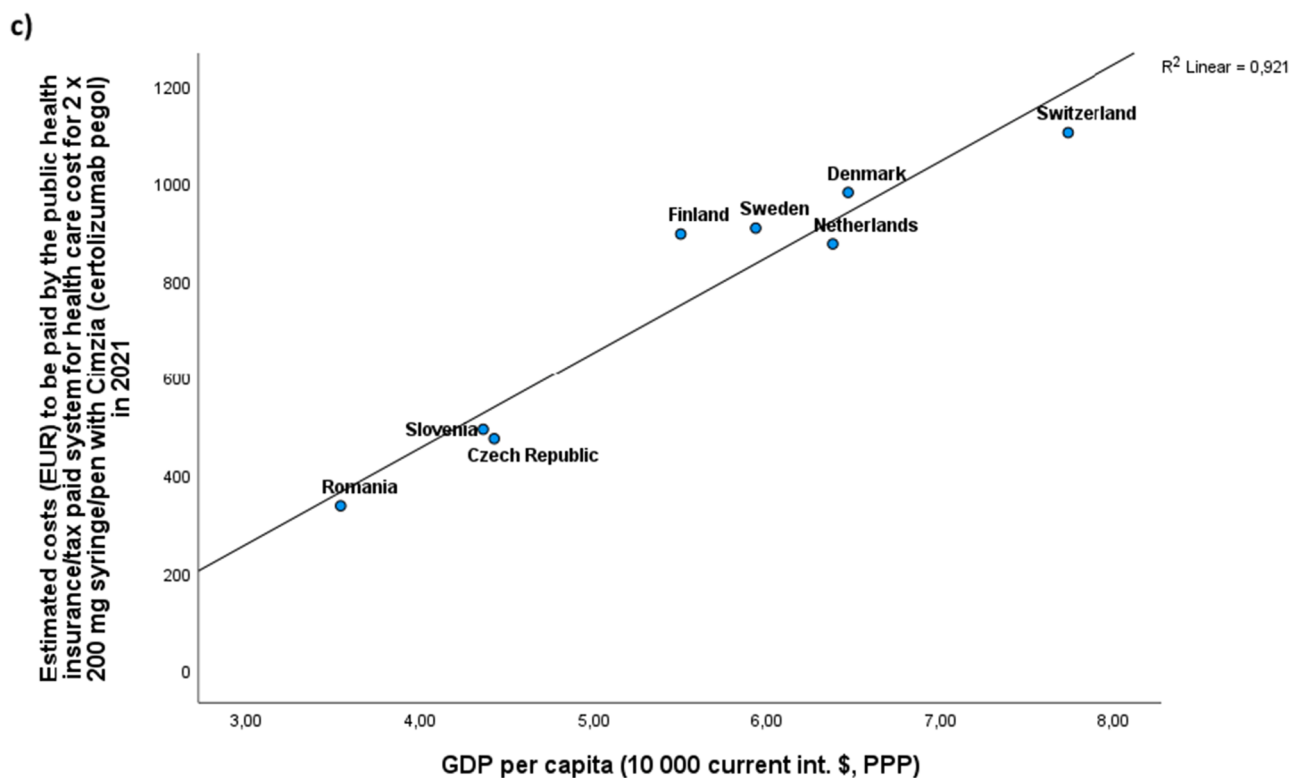


Fig. 3. (continued).

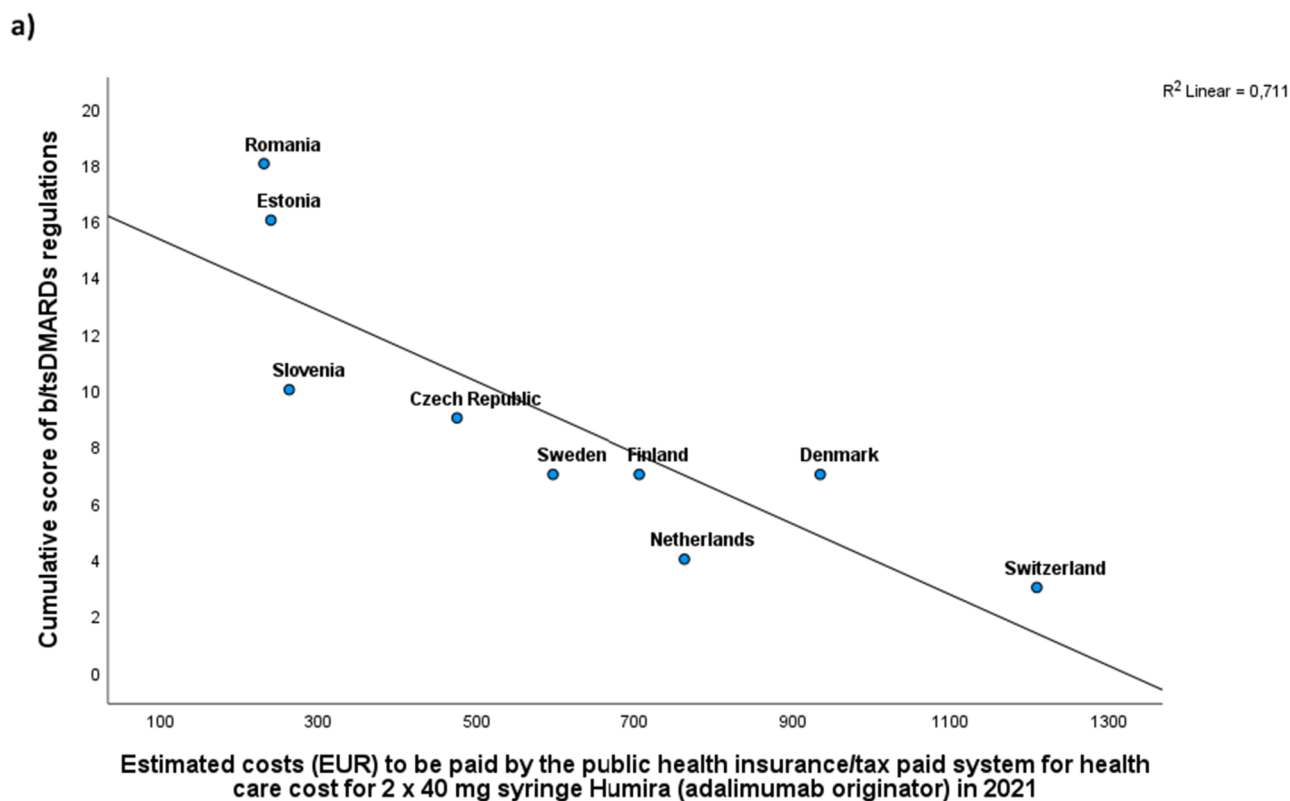


Fig. 4. Scatterplot of the cumulative score of biologic/targeted synthetic DMARD regulations and costs paid by the public health insurance/tax paid system for healthcare costs in 2021 for biologic originators; a) Humira (adalimumab originator), $R^2 = 0.71$, $B = -56.5$, 95 %CI $(-88.7, -24.3)$, $p = 0.004$; b) Enbrel (etanercept originator), $R^2 = 0.55$, $B = -50.6$, 95 %CI $(-91.6, -9.7)$, $p = 0.02$; c) Cimzia (certolizumab pegol), $R^2 = 0.73$, $B = -52.0$, 95 %CI $(-83.8, -20.2)$, $p = 0.007$. Only countries with available costs are shown in the figure.

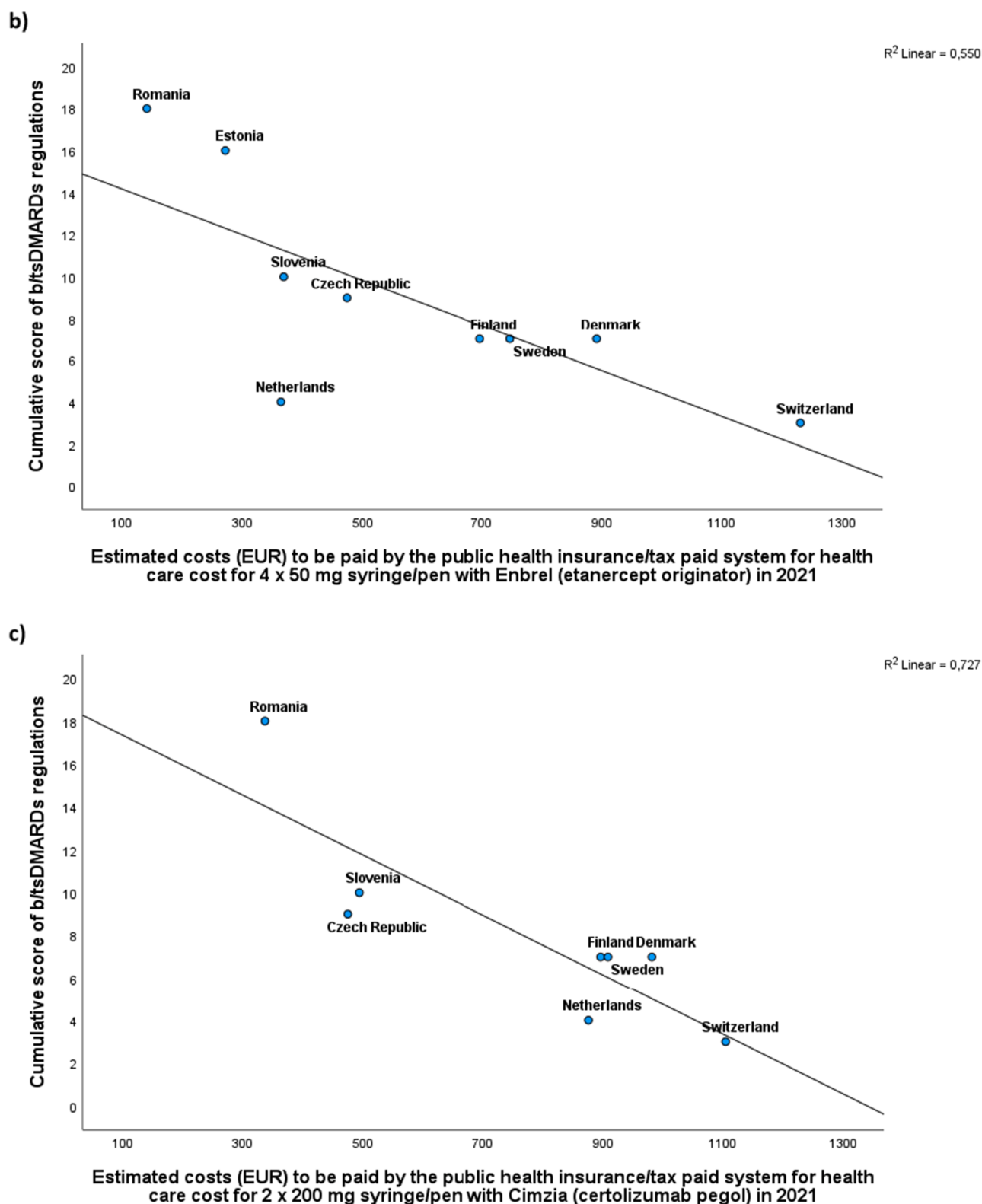


Fig. 4. (continued).

such restrictive policies may be more favorable.

In line with our report, van den Berg et al. found in 2011 that some countries had stricter requirements for disease activity and pre-treatment in order to start a tumor necrosis factor inhibitor in patients with ankylosing spondylitis [10], and Soriano et al. reported similar findings in a review in 2014, including national recommendations for

tumor necrosis factor inhibitor initiation in patients with psoriatic arthritis from four European countries [11]. In our report, we found marked differences in up-to-date recommendations not only for initiation of tumor necrosis factor inhibitors, but also for prescription, initiation, switch, tapering, and discontinuation of biologic/targeted synthetic DMARDs in general in patients with psoriatic arthritis and

axial spondyloarthritis across Europe, which may possibly explain part of the heterogeneity observed in European biologic/targeted synthetic DMARD-treated patient populations [6]. Adding to these findings, as recently reported, only a minority of the national treatment recommendations in European countries were completely in line with the European Alliance of Associations for Rheumatology and Assessment of Spondyloarthritis international Society/European Alliance of Associations for Rheumatology recommendations for psoriatic arthritis and axial spondyloarthritis, also underscoring the heterogeneity in treatment recommendations across Europe [12]. The impact of these discrepancies on the treatment outcomes of patients with psoriatic arthritis and axial spondyloarthritis should be explored in future studies.

While GDP per capita varies substantially across the world, the disparities within Europe are less pronounced than across continents [19, 20]. Nevertheless, the variations in GDP per capita within Europe seem to be of importance for treatment, as we found significantly more biologic/targeted synthetic DMARD regulations in countries with lower GDP per capita. This is not surprising, as GDP per capita is known to impact healthcare funding and accessibility [7,21]. However, as demonstrated in this report, the healthcare set-ups for biologic/targeted synthetic DMARD treatment varied substantially across Europe, but also between countries with similar GDP per capita, and may also be related to factors such as political priorities, demographics, and the prevalence of health challenges. Adding to these findings, we also found significantly more biologic/targeted synthetic DMARD regulations with countries' decreasing health expenditure per capita and decreasing human development index. In line with our findings, a study from 2014 of rheumatoid arthritis patients, also found clinical criteria regulating prescriptions of biologics to differ substantially across Europe, with stricter eligibility criteria in countries with lower socioeconomic welfare [22].

In our study, from a public health perspective, it is noteworthy that estimated costs of biologic originators increased with higher GDP per capita, as well as with decreasing biologic/targeted synthetic DMARD regulations. We were unable to find a similar study in spondyloarthritis, however, conversely, a European study on the use of biologics in rheumatoid arthritis in 2011 found a negative association between costs of biologics and GDP per capita [23]. This could indicate that health policies and industry priorities for biologics may have changed during the last decade. However, in 2021 adalimumab and etanercept biosimilars were primarily used in many countries, hence the listed adalimumab and etanercept bio-originator costs are not completely relevant for the real-world setting [24]. This limitation does not apply to certolizumab pegol, since a biosimilar is not yet available for this drug.

The main strength of this report is that it represents the first description covering national healthcare set-ups for biologic/targeted synthetic DMARDs in psoriatic arthritis and axial spondyloarthritis across Europe, also seen in relation to the countries' socioeconomic status. The main limitation is that only European countries were included. The selection of countries, however, was particularly relevant in the context of the European Spondyloarthritis Research Collaboration Network, who initiated this work, and included countries from both north, south, east, and west of Europe. In a further step, it would be valuable to include countries from other continents, beyond Europe. A second limitation is that only national healthcare set-ups were addressed, and not eventual regional differences in healthcare set-ups within the individual countries. Finally, several of the countries have confidential and/or not transparently available list prices/negotiated prices of biologic/targeted synthetic DMARDs, challenging a comparison of costs, which may also vary substantially from year to year, as well as between bio-originator and biosimilar drugs. We report the estimated costs paid by the public health insurance/tax-paid system for healthcare costs in 2021 for three bio-originators. For countries who primarily used biosimilars in 2021 (e.g. Denmark, Norway), the findings regarding costs are of less relevance [24].

5. Conclusion

In conclusion, this is the first comparison of national healthcare set-ups for prescription, start, switch, tapering, and discontinuation of biologic/targeted synthetic DMARDs in patients with psoriatic arthritis and axial spondyloarthritis across Europe. Our findings highlight substantial variability in healthcare set-ups for biologic/targeted synthetic DMARD use, and their association with socioeconomic status and bio-originator costs. These insights may provide a basis for rheumatology societies, policymakers, and stakeholders to evaluate and potentially optimize healthcare policies for management of psoriatic arthritis and axial spondyloarthritis.

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CRediT authorship contribution statement

Brigitte Michelsen: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mikkel Østergaard:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Michael John Nissen:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Adrian Ciurea:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Burkhard Möller:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Lykke Midtbøll Ørnberg:** Writing – review & editing, Validation, Methodology, Investigation, Conceptualization. **Pavel Horák:** Writing – review & editing, Validation, Investigation. **Bente Glinborg:** Writing – review & editing, Validation, Investigation. **Alan MacDonald:** Writing – review & editing, Validation, Investigation. **Karin Laas:** Writing – review & editing, Validation, Investigation. **Tuulikki Sokka-Isler:** Writing – review & editing, Validation, Investigation. **Bjorn Gudbjornsson:** Writing – review & editing, Validation, Investigation. **Florenzo Iannone:** Writing – review & editing, Validation, Investigation. **Pasoon Hellamand:** Writing – review & editing, Validation, Investigation. **Tore Kristian Kvien:** Writing – review & editing, Validation, Investigation. **Ana Maria Rodrigues:** Writing – review & editing, Validation, Investigation. **Catalin Codreanu:** Writing – review & editing, Validation, Investigation. **Ziga Rotar:** Writing – review & editing, Validation, Investigation. **Isabel Castrejón:** Writing – review & editing, Validation, Investigation. **Johan Karlsson Wallman:** Writing – review & editing, Validation, Investigation. **Karel Pavelka:** Writing – review & editing, Validation, Investigation. **Anne Gitte Loft:** Writing – review & editing, Validation, Investigation. **Maureen Heddle:** Writing – review & editing, Validation, Investigation. **Sigrid Vorobjov:** Writing – review & editing, Validation, Investigation. **Heikki Relas:** Writing – review & editing, Validation, Investigation. **Gerdur Gröndal:** Writing – review & editing, Validation, Investigation. **Elisa Gremese:** Writing – review & editing, Validation, Investigation. **Irene van der Horst-Bruinsma:** Writing – review & editing, Validation, Investigation. **Eirik Klami Kristianslund:** Writing – review & editing, Validation, Investigation. **Maria José Santos:** Writing – review & editing, Validation, Investigation. **Corina Mogosan:** Writing – review & editing, Validation, Investigation. **Matija Tomsic:** Writing – review & editing, Validation, Investigation. **Federico Diaz-Gonzalez:** Writing – review & editing, Validation, Investigation. **Daniela Di Giuseppe:** Writing – review & editing, Validation, Investigation. **Stig Winther Nielsen:** Writing – review & editing, Validation, Investigation. **Merete Lund Hetland:** Writing – review & editing, Validation,

Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

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Supplementary materials

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