Research output on systemic sclerosis and socio-economic factors: An analysis of country-level panel data

Wei Guo
Peking University Third Hospital Department of Rheumatology and Immunology
Zeyu Zhou
Peking University School of Economics
Yinhe Liang
Central University of Finance and Economics School of Economics
Chuanhui Xu
Tan Tock Seng Hospital Department of Rheumatology, Allergy and Immunology
Lin Zeng
Peking University Third Hospital Research Center of Clinical Epidemiology
Zhiyong Dong
Peking University School of Economics
Rong Mu (murongster@gmail.com)
Peking University Third Hospital https://orcid.org/0000-0001-7332-4135

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Abstract

Background Systemic sclerosis (SSc) is a rare detrimental disease warranting mobilization of global research efforts. We aimed to evaluate impacts of country factors on research output over SSc to identify solutions promoting research. Methods Publication production on SSc during 1969–2018 and data for structural and policy factors were collected from public sources. Effects of country-level factors were investigated through panel regression in WHO member countries. Difference-in-differences analysis assessed the impacts of rare disease legislation. Effect heterogeneity across income levels was evaluated using group regression. Results SSc publications showed increasing annual growth rate (−0.3% during 1969–1983 vs. 6.9% during 2000–2018). Totally, ten countries published 12 261 (77.5%) SSc publications but another 87 countries produced none. High-income countries with higher GDP, larger population, and higher health expenditure tended to publish more ($p<0.001$). Whereas in middle-income countries (MICs) SSc scientific output was significantly associated with expenditure on research and development($p <0.001$). Rare disease legislation increased annual publication production by 62.8% (95% CI 0.390–0.867; $p <0.001$) averagely. Notably, the effect of legislation was swift and lasting in MICs during the first five years. No significant impact was found with GDP per capita, female percentage, and political indicators. Conclusions SSc research output increased over time with substantial country disparities. Effective health policies facilitating research should be expanded especially among MICs to accelerate global advancement.

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by vasculopathy and fibrosis.[1] Being unpredictable, unpreventable, and incurable, SSc has multiple devastating complications and the highest mortality among rheumatic diseases,[1] imposing substantial disease and cost burden on patients and society.[2] With SSc patients distributed in all races,[3] it is important to urge worldwide research forces for further progress. Exploration of factors affecting research output might help to identify measures promoting SSc research.

Previous studies reported several country-level factors to be associated with research output on other diseases.[4, 5] Another possible solution improving the insufficiency of research over rare diseases like SSc is rare disease legislation. Though how legislation affects SSc research has not been examined, evidence showed increased approval of orphan drugs in the United States, Japan, and European Union ever since the hallmarking 1983 Orphan Drug Act. [6] However, whether the progress originated from rare disease legislation or was simply a reflection of general scientific development remains unknown. Also, the effects need to be assessed in middle-income countries (MICs) to consider the variance caused by economic disparities.[7]

Using recent data for research, legislative, and socio-economic indicators available from public data sources, we aimed to quantitatively describe the global SSc academic output and evaluate the impact of

country-specific factors to explore solutions supporting research conduction on SSc in countries of different economic levels.

Methods

Data collection

Scopus was searched on October 15, 2019 to retrieve SSc journal publications for its wide indexing of journals.[8] Publications with “systemic sclerosis” or “scleroderma” but not “localised/localized scleroderma” in titles or keywords were identified as SSc publications. The search was limited to the period from January 1, 1969 to December 31, 2018 to avoid data bias caused by database updating. Retracted publications, letters, editorials, and erratum were excluded. No language restriction was set.

Data on country level structural and policy factors were collected from different sources as listed in Supplemental Table S1 (including definitions and data coverage) [see Additional file 1]. Country intrinsic structural indicators were composed of gross domestic product (GDP),[9] population,[9] GDP per capita calculated as GDP/population, female population percentage,[10] and government political measures including voice and accountability, government effectiveness, and political stability, and absence of violence/terrorism.[11] Country stratification according to income level was retrieved and used as country grouping criteria but not included as a variable in the regression analysis.[10] Country-level policy factors examined in the present study included investment into related areas, research and development (R&D) and health,[10, 12] presented as percentage of GDP as well as the status of rare disease legislation in 2017 and year of commencement from the recently published policy review by Chan et al.,[7] which was revalidated through Internet and PubMed search. During 2000–2017, all indicators were with available data.

Research output determination

Global annual production and a list of contributing countries of SSc publications were exported using the analyze function provided by the Scopus website. Annual numbers of publications in the area of health and life sciences were exported similarly. Bibliometric information of SSc publications including publication years, affiliations, and correspondence addresses was extracted and processed using Excel to generate SSc publication production of given countries in the given time. The attribution of publications to countries was based on affiliations and correspondence addresses, with one authorship to each contributing country. Publications without country information were dropped in country-level analysis.

Outcome and explanatory variables

SSc scientific output was measured by the number of SSc publications. Studied country-level factors included economic, demographic, political, and policy factors as stated above. Depending on models

fitted, two different variables were used to represent rare disease legislation. The first is a time-invariant categorical variable for which one indicating with rare disease legislation and zero indicating otherwise in 2017. The second is a time-variant variable to indicate the status of rare disease legislation in a given country and given year, with value one assigned to countries after one year from rare disease legislation commencement, and zero to other conditions. Other explanatory variables were all time-variant and continual. To reduce skewness and stabilize the variance, SSc publications, GDP, GDP per capita, and population were transformed to ln (SSc publications + 1), ln GDP, ln GDP per capita, and ln population in regression analysis; one was added to SSc publications before the logarithmic transformation to avoid zero values. Coefficients derived from regression assessing ln of SSc publications represented the increased percentage of SSc publications with one-unit change of the explanatory variable given *ceteris paribus*.

Sample characteristics

WHO member countries found with available data were included in corresponding analysis. Totally, 1442 observations from 132 countries were analyzed by panel regression for association analysis with all country factors on the period 2000–2017 and 7649 observations from 167 countries were included in the DID analysis assessing legislation effect on 1969–2018 (Table 1). Countries were stratified as high, middle, and low-income countries (LICs) using gross national income (GNI) per capita for 2018 according to the World Bank. Half of the countries were MICs (68 [51.5%] in the 2000–2017 dataset; 89 [53.3%] in the 1969–2018 dataset). Most high-income countries (HICs) with rare disease legislation commenced the implementation before 2007, while most MICs adopted their rare disease legislation after that. None of the LICs were with rare disease legislation.

Statistical analysis

A multivariate linear regression model was used to evaluate associations between SSc scientific output and all country-level indicators with data on the period 2000–2017 considering data availability mentioned beforehand. Impacts of GDP per capita, population, female population percentage, voice and accountability, government effectiveness, political stability and absence of violence/terrorism, R&D expenditure, health expenditure, and rare disease legislation with the time-invariant , were assessed over countries with available data. GDP per capita, population, and GDP cannot be present in the same model due to collinearity. In an additional model, we replaced GDP per capita and population with GDP to evaluate the effect of total economy size. We included year fixed effects affecting countries equally and changing over time but not country fixed effects controlling for country inherent factors to avoid omission of coefficient due to data collinearity. Observations with missing data were dropped in both models. We used standard errors clustered to countries in all regression analyses.

Difference-in-differences (DID) models (M1–M3) were used to assess the effects of rare disease legislation on SSc scientific output more accurately using the DID variable with panel data spanning

1969–2018. Coefficients of represented the average effect of rare disease legislation on country SSc scientific output. GDP per capita, population, and female population, of which data were accessible over the studied period, were controlled in all three models. Country and year fixed effects were added sequentially in M2 and M3. Observations with other data missing were excluded from the DID analysis. Standard errors clustered to countries were used. Sensitivity analysis was done using imputed 2018 data on population and GDP per capita with data on 2017 when available.

Inference of causal effect using DID analysis is based on the assumption that without rare disease legislation, all countries included in DID analysis would have the same trends with the outcome measure. [13] This parallel trend assumption was tested by including leading dummies of the legislation variable in a supplementary model. Coefficients of the leads should not be statistically different from zero when the parallel trend assumption is satisfied. Moreover, we included lags to assess the effect of rare disease legislation over time. Leads up to five years before legislation and lags up to ten years after legislation were included in the supplementary regression to testify parallel trend assumption and assess the effect dynamics of legislation.

Two-sided significance tests were used and significance was set at *p* less than 0.05. Statistical analysis was conducted using Stata 16 (Stata-Corp LP, College Station, TX).

Results

SSc publications production increased rapidly in the new century

The literature search through Scopus retrieved 18 175 publications in the area of SSc published from January 1, 1969 to December 31, 2018. Figure 1 showed the time trend of SSc publication growth with comparison to that of total publications in the area of health and life medicines. Annual SSc publication production fluctuated under 200 (135–186, average annual growth rate [AAGR]: −0.3% with SSc *vs.* 3.4% with whole health and life sciences) before 1983, then increased in parallel with health and life sciences, reaching an annual production of 300 (AAGR: 3.2% with SSc *vs.* 3.1% with whole health and life sciences) until around the year of 2000. An accelerated publication of SSc literature was shown from 2000. Two-thirds of SSc publications (66.0%, 11 987/18 175) were published from 2000–2018. Annual production increased 3.3 folds–1004 in 2018 compared to two folds in the whole health and life sciences area (AAGR: 6.9% with SSc *vs.* 4.0% with whole health and life sciences).

SSc scientific output varied significantly among countries

After 2354 publications without country information excluded, the remaining 15 821 journal articles on SSc were attributed to 107 (55.2%) of the 194 WHO member countries (Figure 2). SSc academic output varied remarkably among different countries and regions. Four (2.1%) countries were found to over 1500

SSc publications, while 55(28.3%) countries produced fewer than 15 and 87 (44.8%) WHO member countries, mostly located in Africa, had no SSc publications identified. Countries with more than 150 (1% of global publications) SSc publications were mainly developed countries and emerging economies, such as the United States, Japan, United Kingdom, China, India, and Brazil. The top ten countries produced 77.5% of the global SSc publications and were all from North America, Europe, and Asia. Specifically, nearly one fourth (24.8%, 3920/15 821) SSc publications were contributed by the United States. The full list of country production can be found in the online supplemental table S2 [see Additional file 2].

SSc publication production was associated with country-level factors

Regression analysis on 2000–2017, when the data of all country-level factors were available, was performed to explore the association between these factors and the number of SSc journal publications. R&D expenditure showed the strongest association with SSc research output especially in MICs (p<0.001; Table 2). Countries with rare disease legislation tended to have more SSc publications (p=0.010), but the effect appeared insignificant in group analysis for countries of high or middle levels. Health expenditure was also positively associated with SSc research output (p=0.005) and an even higher association was detected in HICs but not in low to middle-income countries. Population (p<0.001) and GDP (p<0.001) were two structural factors associated with SSc research output [see Additional file 3]. However, the effects differed with income groups. The positive association was higher in HICs while a minor negative association without statistical significance was shown in LICs. No association was detected between SSc scientific production and GDP per capita, sex percentage, or governance indicators.

Rare disease legislation increased SSc scientific productivity

We performed DID analysis over a longer time period of 1969–2018, focusing on the coefficients of the legislation variable , to assess the impact of orphan drug legislation more accurately. Regression on all 167 countries with available data showed that rare disease legislation increased SSc publication production by 93.7% (95% CI 0.707–1.168; p<0.001; Table 2). The effects remained significant with control for country fixed effects (0.933; 95% CI 0.701–1.165; p<0.001) and year fixed effects (0.628; 95% CI 0.390–0.867; p<0.001). The effect can be observed in both HIC (0.443; 95% CI 0.076–0.811; p=0.019) and MIC (0.447; 95% CI 0.051–0.842; p=0.027) groups. Full results with coefficients of covariates (LICs included) were shown in online supplemental table S4 [see Additional file 4]. Sensitivity analysis in which missing 2018 data were imputed using 2017 data when available showed similar results (see Supplemental Table S5) [see Additional file 5].

The leads-falsification test confirmed the parallel trend in all included countries as well as in both HIC and MIC groups that countries with or without rare disease legislation shared similar trends of SSc

publication output. The effect was shown to be significant and long-lasting with regression on all 167 countries of three income groups, but intriguing differences were shown in the group regression of HICs and MICs (Figure 3). There was a swift increase of SSc publications the year after implementation of rare disease legislation in MICs, which lasted for at least five years but dropped gradually after that. However, no significant effect was observed except on year ten in the HIC group. The full results of the lags and leads analysis are available in the supplementary materials (Supplemental Table S6) [see Additional file 6].

Discussion

This is the first study quantitatively describing the global SSc academic publications and explore the effect of multiple country-level factors. Our study showed that SSc publications increased rapidly last two decades but with substantial geo-economic inequalities. Rare disease legislation increased SSc publications significantly and continually, especially in MICs. Expenditure on R&D and health was also positively correlated with SSc research output. No positive effects with statistical significance were found with GDP per capita.

SSc publications identified in our study (18 175 during 1969–2018) were substantially fewer than publications identified in studies over diseases with higher prevalence (obesity:[14] 117 340 publications, 1993–2012; Hepatitis B:[15] 49 166 publications, 1971–2011; lung cancer:[16] 32 161 publications, 2004–2013). The low profile of SSc research can be accounted for by the disease rarity but also implied underlying research inefficiency, which was supported by the lagging of increase in comparison to general health and life sciences. Encouragingly, the rate of SSc publication increase in the recent two decades exceeded that in general health and life sciences, indicating the state of under-research for SSc is being improved.

On country levels, our results showed SSc publications were mainly from North America, Europe, and Asia, which is consistent with a previous study analyzing the interventional trials on SSc.[17] In contrast, most African countries had no SSc publications. The disadvantageous situation of Africa's research was also reported on other rare diseases.[18, 19] These results collectively indicated noteworthy between-country inequalities over SSc to be addressed in the future.

The global inequalities might be originated from socio-economic variance. Though we found economically developed countries played a leading role in SSc research, the overall economic development level proxied by GDP per capita had no significant association with SSc scientific research output. Our results are consistent with most bibliometric studies.[5, 20]These results indicated substantial variance among economically developed countries, implying other factors affecting country scientific output. In our study, GDP and population were identified as the two structural factors significantly correlated with country academic output, which is consistent with the high production of SSc publications of emerging economies, such as China and Brazil. GDP was also positively related to country total scientific productivity or on other specific topics,[5, 20, 21] supporting the logic that larger

economies are at a research advantage with more allocable resources. The positive association between population and scientific output is in congruence with the speculation that research studies on a rare disease like SSc are challenged with insufficient funding as well as a limited number of patients and researchers.[22] Populous countries have more patients, research practitioners, and usually more material resources. These results also indicated that patients from countries with lower GDP or a smaller population are at higher risk of being scientifically under-researched. More interestingly, the associations were detected to be higher and more significant in HICs than the other two groups, implying that HICs might have more optimal conditions to translate population and economic advantage to research output, which might help to explain the leading role of HICs in SSc research and indicate potential directions for developing countries.

Policy stimulators should be considered as solutions addressing research inefficiency in scientifically disadvantageous countries. We confirmed the significant and long-lasting positive effect of rare disease legislation on SSc publication. The positive effect of rare disease legislation might be attributed to regulatory and economic incentives provided to researchers and pharmaceutical companies.[23] According to our results, rare disease legislation should be adopted by more countries, especially MICs to promote SSc research. The decreasing of the legislation effect might be associated with the fact that most MICs adopted rare disease legislation only in recent years. Future studies assessing the long-term impact of legislation in MICs may provide additional information.

Expenditure on R&D and health may affect research studies on all biomedical topics through increased investment into science and health. Our regression analysis revealed that expenditure on R&D and health is also associated with increased SSc publications, consistent with studies over other areas.[24, 25] Furthermore, we noticed the association between expenditure and output varied with income groups. MICs might benefit more from R&D expenditure increase rather than health expenditure. More efforts are required to analyze the economic and clinical value of investment into related areas and rare diseases.

In our study, Africa was identified as a key under-researched region. Most African countries were populous but economically disadvantaged LICs, among which we found no significant correlation between country-level factors and SSc research output. Still, our results cannot preclude the potential impact of rare disease legislation, which none LICs have adopted. Technical support and coordinated global efforts are needed to address the research inadequacy of SSc and other rare diseases in Africa, which is also called for by the 17th International Conference on Rare Diseases and Orphan Drugs.[26]

There are several limitations in our study warranting notice. Firstly, because our study was carried out on SSc publications in countries with available data, these results may not apply to other rare diseases and countries. However, considering the factors we studied were not specially targeted on SSc research and that at least 2/3 of WHO member countries were included, our results can still provide decision-makers with an important message of how country factors affected research output. Secondly, missing data for country-level factors might impair the validity of our results. For example, though revealed to be related to SSc research output, R&D expenditure and health expenditure weren’t included in the DID regression

analysis because of imbalanced data missing. Thirdly, there are other factors possibly confounding the results not included due to substantial data gaps, including disease prevalence as well as the proportion of researchers, technicians, doctors, and other relevant practitioners in the population. More stringent studies could be carried out when relevant data become available. Still, the construction of a data panel spanning 50 years using the most recent and reliable data, the inclusion of fixed effects in regression analysis, supplementary tests for parallel trends and sensitivity analysis with imputed data ensured the reliability of the association revealed between country-level factors and SSc research output, especially the causal effect of rare disease legislation.

Overall, our study revealed the increasing pace of SSc publication accumulation in the recent 20 years and points to the substantial imbalance of SSc research distribution among countries. Findings from our study suggested substantial insufficiency but also opportunities for research on SSc and other rare rheumatic diseases in regions like Africa, and provided evidence for decision-makers to facilitate domestic research and eliminate research inequality.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The original list of publications retrieved from Scopus and annual production of publication are available from the corresponding author on reasonable request. Data for country-level factors are available from public sources as cited. Other data are available in the article or supplementary materials.

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

WG, ZZ, YL, ZD, and RM were involved in the study concept and design. WG and ZZ compiled the data, did the empirical analysis, and wrote the first draft of the manuscript. YL, CX, and ZL facilitated the analysis and interpretation of the data. YL, CX, RM, and ZD revised versions of the manuscript. All authors have seen and approved the final version of the manuscript.

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Not applicable.

Abbreviations

AAGR: Average annual growth rate

GDP: Gross domestic product

GNI: Gross national income

HIC: High-income country

LIC: Low-income country

MIC: Middle-income country

R&D: Research and development

SSc: Systemic sclerosis

WHO: World Health Organization

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Tables

Table 1. Characteristics of regression samples

	2000–2017 dataset	1969–2018 dataset
Annual SSc publications	6.22 (18.24)	2.33 (8.06)
Number of countries (HICs/MICs/LICs)	132 (49/68/15)	167 (52/89/26)
Number of observations (HICs/MICs/LICs)	1442 (694/659/89)	7649 (2451/4026/4115)
Rare disease legislation	45 (34.1%)	45 (26.9%)
Legislation before 1998, n (HICs/MICs/LICs)	2 (2/0/0)	2 (2/0/0)
Legislation during 1998–2007, n (HICs/MICs/LICs)	32 (28/4/0)	32 (28/4/0)
Legislation during 2008–2017, n (HICs/MICs/LICs)	11 (1/10/0)	11 (1/10/0)
GDP per capita, 2011US$	18766.83 (19368.52)	12176.86 (15163.10)
Population, million	48.13 (158.54)	32.72 (118.49)
GDP, million 2011US$	627.72 (1814.24)	314.69 (1032.69)
Female percentage, % of population	49.96 (3.71)	50.14 (2.58)
Voice and accountability	0.02 (0.97)	NA
Government effectiveness	0.16 (0.94)	NA
Political stability and absence of violence/terrorism	−0.06 (0.90)	NA
R&D expenditure, % of total GDP	0.75 (0.87)	NA
Health expenditure, % of total GDP	6.29 (2.28)	NA

Results were presented in n (%) or mean (SD) unless specified. Continual statistics were summarized by average values during the same period of regression analysis. Number of countries adopting rare disease legislations in given period were presented as in total and income groups. Data for world governance indicators, R&D expenditure, and health expenditure were only available over 2000–2017 and were therefore not included in the 1969–2018 regression or summarized here.

GDP, gross domestic product; HICs, high-income countries; LICs, low-income countries; MICs, middle-income countries; NA, not applicable; R&D, research and development.

Table 2. Associations between country-level factors and SSc scientific output

	All countries	HICs	MICs	LICs
Ln of GDP per capita	0.163 (−0.012, 0.337)	−0.028 (−0.508, 0.451)	0.081 (−0.104, 0.266)	−0.043 (−0.122, 0.035)
Ln of population	0.292*** (0.198, 0.385)	0.534*** (0.379, 0.689)	0.119* (0.016, 0.222)	−0.017 (−0.047, 0.013)
Female population percentage	0.004 (−0.029, 0.037)	0.019 (−0.041, 0.079)	0.019 (−0.107, 0.145)	−0.020 (−0.057, 0.018)
Voice and accountability	0.152 (−0.029, 0.334)	−0.022 (−0.484, 0.441)	0.179 (−0.011, 0.370)	0.027 (−0.026, 0.080)
Government effectiveness	−0.125 (−0.346, 0.095)	−0.329 (−0.727, 0.068)	0.018 (−0.234, 0.271)	0.060 (−0.055, 0.175)
Political stability and absence of violence/terrorism	0.006 (−0.109, 0.121)	0.125 (−0.091, 0.342)	−0.100 (−0.233, 0.033)	−0.025 (−0.075, 0.024)
R&D expenditure (% of total GDP)	0.526*** (0.292, 0.760)	0.269* (0.046, 0.492)	1.315*** (0.743, 1.887)	−0.006 (−0.123, 0.110)
Health expenditure (% of total GDP)	0.073** (0.019, 0.127)	0.142*** (0.059, 0.224)	0.000 (−0.062, 0.062)	−0.004 (−0.014, 0.005)
Rare disease legislation	0.395* (0.094, 0.695)	0.306 (−0.184, 0.797)	0.061 (−0.250, 0.373)	NA
Number of countries	132	49	68	15
Number of observations	1442	694	659	89

Panel regression analysis during 2000–2017 assessed association between country level indicators and SSc scientific output measured on all countries with available data and within different income groups. The entries are regression coefficients (95% CI). With the

legislation variable, value one was assigned to all countries with rare disease legislation and zero to others. The coefficient of legislation for LICs was omitted for none of the 14 countries had rare disease legislation. Year fixed effects were controlled in all regression analysis.

GDP, gross domestic product; HICs, high-income countries; LICs, low-income countries; MICs, middle-income countries; R&D, research and development; SSc, systemic sclerosis.

*** p<0.001, ** p<0.01, * p<0.05

Table 3. Estimated effect of rare disease legislation on SSc scientific output

	M1	M2	M3
All countries	0·937***	0·933***	0·628***
(167 countries, 7649 observations)	(0·707 to 1·168)	(0·701 to 1·165)	(0·390 to 0·867)
HICs	0·807***	0·813***	0·443*
(52 countries, 2451 observations)	(0·552 to 1·062)	(0·553 to 1·073)	(0·076 to 0·811)
MICs	0·652***	0·640**	0·447*
(89 countries, 4026 observations)	(0·277 to 1·026)	(0·264 to 1·017)	(0·051 to 0·842)
Country fixed effects	Uncontrolled	Controlled	Controlled
Year fixed effects	Uncontrolled	Uncontrolled	Controlled

Panel regression assessed effects of rare disease legislation on SSc scientific output measured by ln of SSc publications. With the legislation dummy variable, value one was assigned to countries from the year after rare disease legislation adoption, and zero to other conditions. Effect heterogeneity among countries of different income levels was evaluated using group analysis. Coefficients of legislation in LICs were not reported, for none of the 26 countries had rare disease legislation. Country covariates available were controlled in all three models (M1–M3). Country fixed effects and year fixed effects were included sequentially in M2 and M3.

HICs, high-income countries; MICs, middle-income countries; SSc, systemic sclerosis.

*** p<0.001, ** p<0.01, * p<0.05

Figures

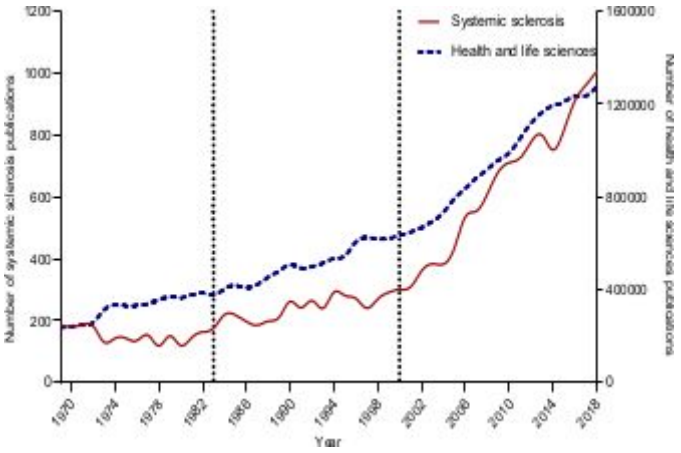

Figure 1

Time distribution of SSc publications Numbers of SSc (red solid line) and health and life sciences (blue dashed line) publications are shown by year during 1969–2018, which was divided into three stages according to the speed of publication accumulation.

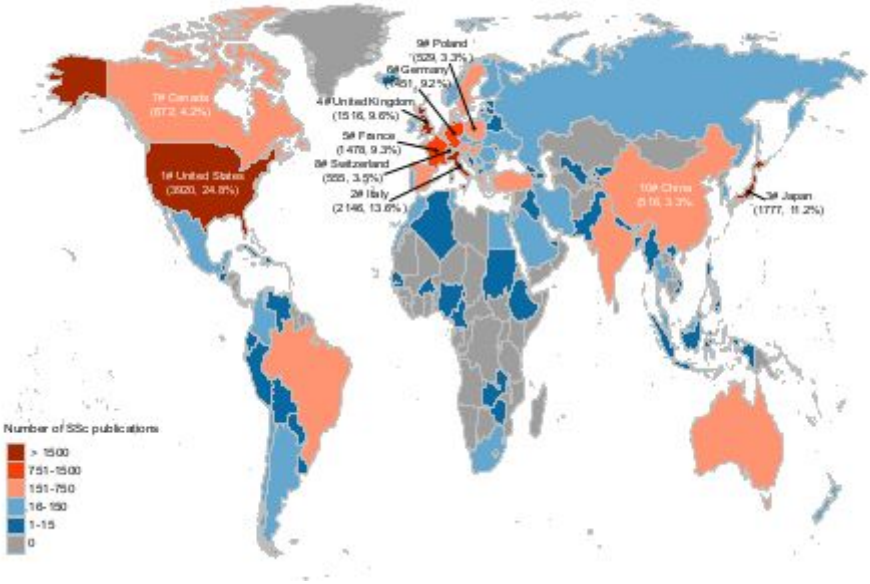

Figure 2

Landscape of SSc publications. Total SSc publication production originating from different countries during 1969–2018 is shown on the world map. Different colors were assigned to countries according to the total number of SSc publications. Warmer colors represent higher SSc publication production and cooler colors represent lower production. Countries without SSc publications were presented in the grey color. The ten countries with the most SSc publications were listed with the rank and number of SSc publications. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

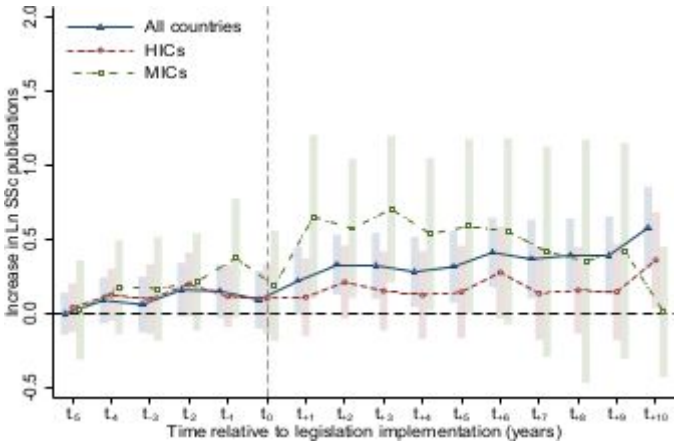

Figure 3

Estimated effects of rare disease legislation on SSc scientific output. Effects of rare disease legislation on ln of SSc publications are presented as regression coefficients (95% CI) separately for all countries (blue), HICs (red) and MICs (green). Legislation dummy variables, t−5 to t+10 are equal to one in only one year per country with rare disease legislation. t0 refers to the year after legislation implementation. Dummy variables prior t0 (t−5 to t−1) were used to test for parallel trend, and those after t0 (t+1 to t+10) showed the dynamics of legislation effect over time. Country and year fixed effects as well as country-level covariates were controlled. HICs, high-income countries; MICs, middle-income countries; SSc, systemic sclerosis.

Supplementary Files

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