Country-level socioeconomic status relates geographical latitude to the onset of RA: a worldwide cross-sectional analysis in the METEOR registry

Bergstra, S.A.; Sepriano, A.; Chopra, A.; Winchow, L.L.; Vega-Morales, D.; Salomon-Escoto, K.; ... ; Landewe, R.B.

EPIDEMIOLOGICAL SCIENCE

Country-level socioeconomic status relates geographical latitude to the onset of RA: a worldwide cross-sectional analysis in the METEOR registry

Sytske Anne Bergstra ,[1] Alexandre Sepriano ,[1,2] Arvind Chopra,[3] Lai-Ling Winchow,[4] David Vega-Morales ,[5] Karen Salomon-Escoto,[6] Xanthe M E Matthijssen,[1] Robert BM Landewé [7,8]

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For numbered affiliations see end of article.

Correspondence to
Sytske Anne Bergstra, Department of Rheumatology, Leiden University Medical Center, Leiden, 2333, The Netherlands;
s.a.bergstra@lumc.nl

ABSTRACT

Objective Age at rheumatoid arthritis (RA) onset varies by geographical latitude. We have investigated to what extent differences in patient-specific factors and country-level socioeconomic indicators explain this variability.

Methods Patients with RA from the worldwide METEOR registry were included. Bayesian multilevel structural equation models were used to study the relationship between the absolute value of (hospital) geographical latitude and age at diagnosis (as a proxy for age at RA onset). We examined to what extent this effect is mediated by individual patient characteristics and by country-specific socioeconomic indicators and disentangled whether the observed effects occurred at the patient, hospital, or country levels.

Results We included 37 981 patients from 93 hospitals in 17 geographically widespread countries. Mean age at diagnosis per country ranged from 39 (Iran) to 55 (Netherlands) years. Per degree increase in country latitude (between 9.9° and 55.8°), mean age at diagnosis increased by 0.23 years (95% credibility interval: 0.095 to 0.38) (reflecting >10 years difference in age at RA onset). For hospitals within a country, this latitude effect was negligible. Inclusion of patient-specific factors (eg, gender, anticitrullinated protein antibodies status) in the model augmented the main effect from 0.23 to 0.36 years. Inclusion of country-level socioeconomic indicators (eg, gross domestic product per capita) in the model almost effaced the main effect (from 0.23 to 0.051 (−0.37 to 0.38)).

Conclusions Patients living closer to the equator get RA at a younger age. This latitude gradient was not explained by individual patient characteristics, but rather by countries' socioeconomic status, providing a direct link between countries' level of welfare and the clinical onset of RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies with populations of different ethnicities report differences in the age at onset of rheumatoid arthritis (RA). An international survey that evaluated the age at onset of RA in consecutive patients in 77 cities worldwide reported that the age at RA onset increased with the geographical latitude of the city. This younger age of RA onset at lower geographical latitudes has been suggested to be a proxy for differences in genetic (nature) as well as environmental (nurture) risk factors. Several studies have identified isolated patient-specific factors, which have been suggested to be related to the onset of RA. Nevertheless, the jury is still out about which factor(s) or compilations thereof dominate the onset of RA.

WHAT THIS STUDY ADDS

⇒ We performed an analysis in a large worldwide prevalence cohort of 37 981 patients from 17 countries with large geographical spread. By building a sophisticated structural equation model, we were able to distinguish ('deconflate') patient-specific characteristics from hospital-specific and country-specific characteristics and showed that the latitude gradient in age at onset of RA could not be explained by differences in patients (eg, genes), but almost fully by socioeconomic factors (ie, environment) of the countries people were living in.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ RA starts at a younger age in people living at lower latitudes (ie, closer to the equator). We showed that this can be explained by a direct link between countries' level of socioeconomic welfare and the time of onset of RA. This contributes to mutually reinforcing factors working towards inequity: people in low-income countries will not only get RA at a younger age, with an inherently longer disease course and a worse prognosis, but they also face poorer healthcare conditions and social support, which will further deteriorate their prognosis.

INTRODUCTION

Rheumatoid arthritis (RA) is a heterogeneous autoimmune disease, thought to be initiated both by genetic (eg, HLA (human leukocyte antigen) class 2) and environmental factors (eg, smoking).[1] While the contribution of each risk factor to the precise onset and clinical presentation of RA is unknown, it is well documented that these risk factors differ across the world. This variability may explain the heterogeneous disease presentation of RA across

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the world.[2–4] One of those characteristics of RA that varies worldwide is the age at clinical disease onset.

Most studies in RA have been performed in developed countries, in which the average age at onset of RA is over 50 years.[5 6] Studies with populations of different ethnicities report differences in the age at onset of RA.[4 7 8] An international survey evaluated the age at onset of RA in 77 cities worldwide (20 consecutive patients per city) and reported that the age at disease onset increased with the geographical latitude of the city.[8] Patients with a young age at RA onset (<36 years) were more frequent at lower latitudes (closer to the equator) compared with higher latitudes (closer to the poles).

Younger age at RA onset implies a longer disease course and a higher personal, societal and economic burden, because of worse disease outcomes (prognosis).[9 10] Age at onset can therefore be considered as a proxy for burden of disease that varies across countries. Several patient-specific factors have been suggested to determine the age at RA onset; male gender, obesity and a higher fish intake were associated with a higher age at RA onset; a lower socioeconomic status, smoking, the presence of rheumatoid factor (RF), anticitrullinated protein antibodies (ACPA) and the presence of a 'shared epitope'—a variation in HLA class 2 molecules associated with an increased susceptibility of RA—were associated with a lower age at RA onset.[9 11–16] Educational level appeared an ambiguous factor.[12 17] Younger age of RA onset at lower geographical latitudes has been suggested to be a proxy for differences in genetic (nature) as well as environmental (nurture) risk factors, and the jury is still out about which factor(s) or compilations thereof dominate the onset of RA.[8 18] Here, we studied in a worldwide cohort of patients with RA whether geographical latitude was associated with the age at RA onset and to what extent patient-specific characteristics and country socioeconomic factors contribute.

METHODS

Patients and study design

Patients from the METEOR (Measurement of Efficacy of Treatment in the "Era of Outcome" in Rheumatology) registry with a clinical diagnosis of RA were studied. The METEOR registry is an international, observational registry capturing data from patients with a physician-reported clinical diagnosis of RA worldwide. Countries with different socioeconomic status, from Europe, Asia, Africa, North America and South America, are represented. METEOR collects data on patient and disease characteristics, disease activity, physical functioning and medication of patients at any disease stage in a non-protocolised and fully anonymised manner. Additional information about the METEOR registry has been previously published.[19] For the current study, data from the first visit in the database from patients with available data on age at diagnosis, from countries with at least 60 available patients, were included. Since METEOR only includes patients with a clinical diagnosis of RA, the first visit in the database cannot occur before disease onset.

Outcomes and latitude

The main outcome was the age at RA onset, measured as the age at diagnosis of RA. Age at symptom onset was used as a secondary outcome. Both variables measure the construct of age of clinical disease onset, but the latter is more susceptible to recall bias. Both age at diagnosis and age at symptom onset were collected by the treating rheumatologists at local hospitals. Geographical latitude of the hospital in which the patient was treated was expressed in degrees in relation to the equator. Values for the Northern Hemisphere are positive and values for the Southern Hemisphere are negative (range: −90° to +90°).

Patient-level and country-level characteristics

The following binomial patient characteristics were collected: gender (male/female), RF presence (negative/positive), ACPA presence (negative/positive) and smoking status (ever/never). RF and ACPA were determined locally, and positivity was defined according to local standards. Symptom duration (in months), year of the first visit and body mass index (BMI; kg/m^2) were evaluated as continuous variables. Symptom duration was operationalised as the difference between date of symptom onset and date of diagnosis.

At the country-level, we collected data about the health expenditure per capita in international dollars (reported per 10.000 IntI$), life expectancy at birth (years), gross domestic product (GDP) per capita (reported per 10.000 IntI$), country income categories according to the World Bank definition (lower income, lower middle, upper middle, high income), gross enrolment ratio at secondary school (%) and physician density (number of physicians per 1000 inhabitants). These variables were derived from web-based sources.[20–22]

Statistical analyses

Patient-level and country-level characteristics were described per country. We visualised the relationship between hospital latitude and age at diagnosis and age at symptom onset using scatter plots. The number of hospitals with a negative latitude was limited (n=8). Since there was no statistical interaction between latitude and hemisphere (p=0.564 for the interaction term, tested in a mixed effects model with age at diagnosis as outcome), negative latitudes were all converted into positive latitudes.

It was hypothesised that geographical latitude serves as a proxy for unknown and unmeasured factors that mediate the relationship between latitude and age at disease onset. Since traditional regression models handle multiple mediators inappropriately, we constructed structural equation models (SEMs).[23] SEM accommodates complex relationships among variables and allows to quantify effects at different measurement levels. Here, we proposed three levels: a higher level with country statistics only; an intermediate level with geographical latitude of each hospital; and a lower level with individual patient characteristics. Subsequently, we disentangled at which level the main effects took place (deconflation).[24] As an example, a patient-level variable can vary at the patient level, hospital level and country level, whereas a hospital-level variable can vary at the hospital level and the country level. This allowed us to differentiate between hospital latitude or country latitude as determinant of age at onset of diagnosis. If country-level latitude affects age at diagnosis more than hospital-level latitude, this implies that not latitude in the strict sense, but rather factors associated with the whole country explain age at diagnosis.

A Bayesian estimator was used to improve model performance. In SEM, Bayesian analysis gives asymptotically the same results as maximum likelihood estimation, which is unbiased under the missingness at random assumption.[25]

First, we examined the total effect of geographical latitude (measured at the hospital level) on age at diagnosis (measured at the patient level) and disentangled this into hospital-level and country-level effects (main model). Second, we examined the amount of the total effect that is mediated by patient-specific factors and disentangled this in

patient and hospital-level effects of the patient-level variables (model A, online supplemental figure 1). In this model, dichotomous variables were treated as continuous variables, to facilitate model fit.[26] In the patient-level variables, some of the data were missing. These data were considered to be missing at random. Third, we examined to what extent the total effect was mediated by country-specific factors (model B, online supplemental figure 2). All models were prespecified, and included variables that were selected based on the literature, on clinical reasoning and on availability. To facilitate the comparison across variables measured in different units, we report standardised coefficients (standardised coefficient=unstandardised coefficient×SD (independent variable)×SD (dependent variable).

Sensitivity analyses

All analyses were repeated with age at symptom onset as outcome, to verify whether the results could be explained by differences in the delay between symptom onset and diagnosis.

Some of the hospitals included a limited number of patients, which may limit the representability of the sample. Therefore, we repeated the analyses, including only hospitals with >20 patients. Analyses were also repeated excluding India, the country which contributed the largest number of patients. SEM were performed using MPlus V.7. Other analyses were performed using Stata SE V.16 (StataCorp LP). No patient representatives were included in the current project.

RESULTS

Of 44 623 patients with RA in METEOR, we could include 37 981 patients with data on age at diagnosis. These 37 981 patients are nested in 93 hospitals, which are nested in 17 countries. Four countries (7 hospitals, 14 570 patients) had lower-middle-income economies, three countries (10 hospitals, 2830 patients) had upper-middle-income economies and 10 countries (76 hospitals, 20 581 patients) had high-income economies.[22] Excluded patients had lower disease activity and shorter symptom duration at diagnosis, but were otherwise similar to included patients (online supplemental table 1). Age at symptom onset was available for 29 642 patients.

The number of patients per country ranged from 78 in Nigeria to 14 193 in India. Gender, symptom duration, the presence of RF and ACPA and the proportion of ever-smokers differed across countries. The average age at diagnosis per country ranged from 38.5 years (SD 11.9) in Iran to 55.2 years (SD 15.2) in the Netherlands (table 1). The study spanned a range of geographical latitudes between 9.9° and 55.8° (ie, from Nigeria to the UK). The average age at diagnosis and age at symptom onset were higher in hospitals at a higher latitude (figure 1).

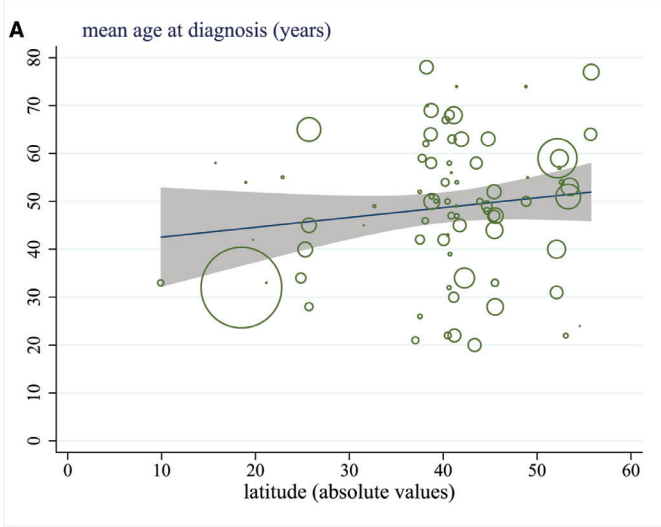
Main model: effect of latitude on age of diagnosis

In the main SEM, we confirmed an association between geographical latitude and age at diagnosis. Age at diagnosis increased by 0.19 years for every degree increase in latitude, (95% credibility interval (CrI) 0.077 to 0.29). After deconflating this effect, it

Table 1 Patient and country characteristics

	Nigeria	India	Pakistan	Qatar	Mexico	South Africa	Brazil	Iran	Japan
Included patients, n	78	14 193	217	462	1799	849	182	82	394
Included hospitals, n	1	3	2	1	3	2	5	1	2
Age at diagnosis	46.1 (12.7)	46.2 (12.2)	40.8 (11.9)	41.0 (11.3)	44.5 (12.6)	49.3 (13.2)	46.0 (13.0)	38.5 (11.9)	53.5 (15.1)
% female	79	85	86	75	91	82	85	79	81
Smoking, % ever smoking	8	2	11	11	16	29	55	8	27
RF % +	72	79	88	75	76	97	83	83	66
ACPA % +	65	80	91	81	68	95	67	69	79
Symptom duration at diagnosis (months) median (IQR)	34 (8–80)	36 (12–96)	5 (0–24)	6 (3–12)	8 (3–19)	18 (7–48)	17 (4–45)	3 (2–8)	3 (3–12)
GDP per capita Intl$	5867	5733	5249	132 938	16 490	12 393	14 533	17 046	37 872
Life expectancy (years)	53	68	66	78	77	62	75	82	84
Gross enrolment ratio secondary school (%)	56	75	46	93	97	103	100	89	102
Physician density per 1000 inhabitants	0.38	0.76	0.98	0.0008	2.23	0.82	1.85	1.14	2.37
Health expenditure per capita Intl$	215	238	134	3900	1009	1086	1392	1262	4405
	Spain	**US**	**Portugal**	**Italy**	**France**	**Netherlands**	**Ireland**	**UK**	
Included patients, n	225	1139	4544	5636	210	5094	1367	1510	
Included hospitals, n	8	3	18	26	3	8	2	5	
Age at diagnosis	49.6 (15.1)	49.7 (13.4)	48.9 (14.6)	46.6 (13.7)	44.7 (12.0)	55.2 (15.2)	44.6 (14.7)	54.3 (14.0)	
% female	83	79	81	81	76	67	65	71	
Smoking, % ever smoking	44	51	25	98	51	52	80	53	
RF % +	85	61	72	79	79	58	52	71	
ACPA % +	87	59	69	75	79	54	54	67	
Symptom duration at diagnosis median (IQR)	5 (3–12)	5 (1–14)	10 (1–24)	4 (2–12)	5 (1–12)	5 (2–20)	6 (2–12)	9 (4–24)	
GDP per capita Intl$	32 219	52 704	26 549	34 220	37 775	46 354	61 378	38 509	
Life expectancy	83	79	82	83	83	82	82	82	
Gross enrolment ratio secondary school	128	97	118	103	111	132	126	125	
Physician density per 1000 inhabitants	3.87	2.47	4.43	4.02	3.24	3.48	2.96	2.83	
Health expenditure per capita Intl$	3183	9536	2661	3351	4542	5313	5335	4144	

Proportions are calculated by taking the total number of patients of all centres within the same country. Proportion of missing data per variable: symptom duration 23%, ACPA 43%, rheumatoid factor 15%, gender 0.4%, smoking 31%.
ACPA, anticitrullinated protein antibodies; GDP, gross domestic product; Intl$, international dollars; RF, rheumatoid factor.



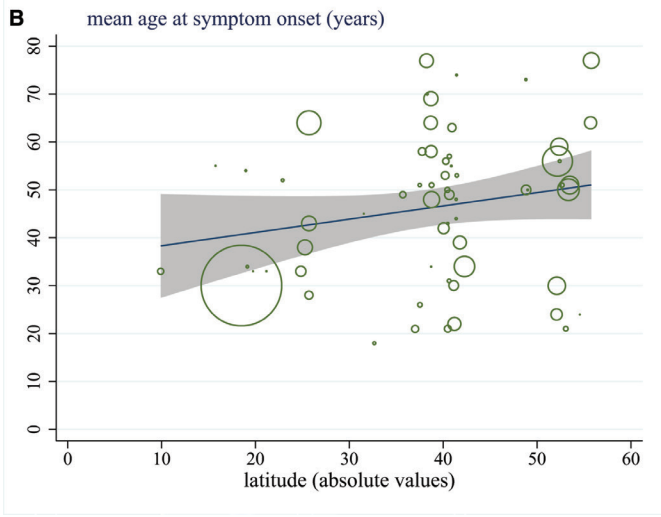


Figure 1 Association between hospital latitude and mean age at diagnosis (A) and mean age at symptom onset (B) per hospital. Green circles indicate the average age per hospital. The circle size indicates the number of patients per hospital. The blue line indicates a fitted linear regression line for the association between latitude and age at diagnosis. The grey zone indicates the 95% CI.

turned out that it only occurred at the country level, but not at the hospital level; per degree increase in average country latitude, the average age at diagnosis per country increased by 0.23 years (95% CrI 0.095 to 0.38). If we consider the range of latitudes that is evaluated in this study (Δ45.9°), this would relate to a difference in age at onset of 10.6 years. At the hospital-level within a country, however, this effect was negligible: β=−0.091 (−0.38 to 0.20). Thus, a difference in hospital latitude within a country did not further affect age at diagnosis.

If country latitude increases with 1 SD, age at diagnosis increases with 0.70 SDs (95% CrI 0.35 to 0.91). At the hospital level, the standardised effect was only −0.082 (−0.36 to 0.18) (14 times less). We will use standardised effects to further describe the output of model A and model B.

Model A: patient-level variables

In model A, we added all patient-level variables to the main model, to evaluate whether these can explain the total effect between latitude and age at diagnosis. Details regarding the associations included in this model are displayed in figure 2.

The direct effect at one measurement level can only be explained by mediation at the same measurement level (ie, only country-level mediation can explain the country-level direct effect between latitude and age at diagnosis). Since associations between latitude and several patient-level variables only occurred at the country level, whereas associations between patient-level variables and age at diagnosis only occurred at the patient level. This means that patient-level variables could not explain (ie, mediate) the association between latitude and age at diagnosis at the country level. Indeed, the main country-level effect between latitude and age at diagnosis only changed from a standardised effect of 0.70 before to 0.59 (95% CrI −0.83 to 3.10) after inclusion of patient-level variables. The hospital-level effect between latitude and age at diagnosis was still negligible (−0.022 (95% CrI −0.28 to 0.20)).

Model B: country-level variables

In contrast, the inclusion of the set of country-level variables in model B (figure 3) reduced the country-level association between latitude and age at diagnosis from a standardised effect of 0.70 to almost zero: β=0.051 (95% CrI (−0.37 to 0.38)). The hospital-level association between latitude and age at diagnosis remained small (−0.12 (−0.37 to 0.15)). This suggests that country-level indicators, but not patient-level indicators, explain the country-level association between latitude and age at diagnosis.

We observed a positive and statistically significant country-level association between latitude and several of the country-level indicators (ie, higher latitude associated with better socioeconomic status). Since none of the separate country-level variables were significantly associated with age at diagnosis at the country level, we could not distinguish one particular country-level indicator mediating the total effect between latitude and age at diagnosis.

Sensitivity analyses

We repeated all analyses with age at symptom onset as outcome. Per degree increase in latitude, age at symptom onset increased by 0.27 years (95% CrI 0.19 to 0.34). The models provided similar results as the models with age at diagnosis as outcome (online supplemental figures 3 and 4)

In another sensitivity analysis, 21 hospitals contributing with <20 patients were excluded, and the results were also similar (online supplemental figures 5 and 6). Analyses excluding India also provided very similar results (online supplemental figures 7–9)

DISCUSSION

It has been previously observed that RA starts at a younger age in people living at lower latitudes (ie, closer to the equator).[8] We hypothesised that latitude is a proxy for differences in genetic and environmental risk factors for RA, and investigated to what extent patient characteristics and country socioeconomic factors explain this association. In a study with 17 countries and large geographical spread, we confirmed that on average the age at diagnosis increased by increasing geographical latitude. This effect mainly occurred at the country level: in a country at 10° lower geographical latitude, the average age at diagnosis was 2.3 years lower. For hospitals within a country, there was no further latitude gradient, even though some hospitals within one country spanned 20° of latitude. This implies that not latitude in the strict sense, but rather country-associated factors explain age at diagnosis.

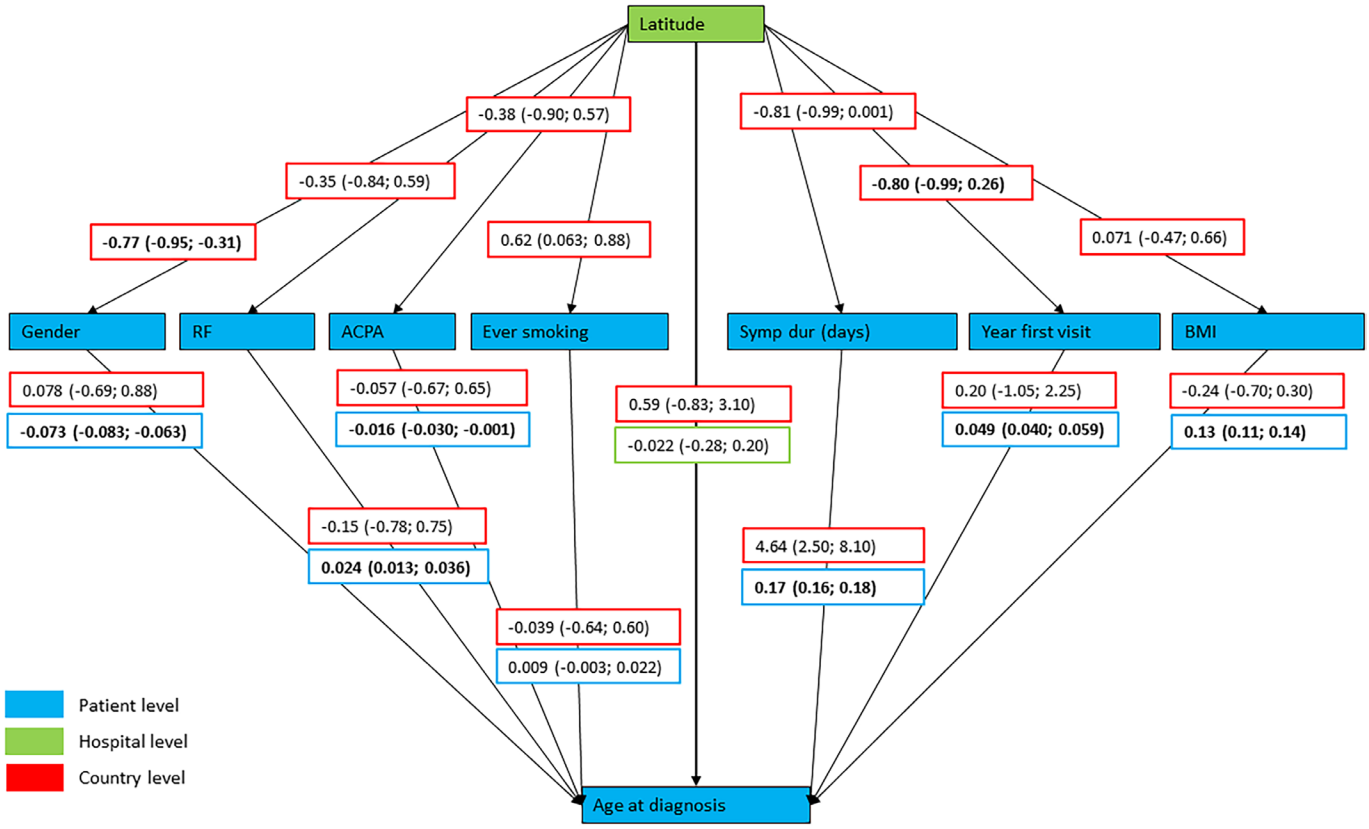


Figure 2 Model A, multilevel Bayesian structural equation model to study whether patient-level mediators explain the association between hospital latitude and age at diagnosis. All associations are deconflated to show separate effects at the country level, hospital level and patient level. Hospital coefficients for the potential mediators are hidden to simplify the figure, since the main model showed no direct effect at the hospital level. Hidden coefficients were non-significant, except for the association between gender and age at diagnosis: β=−0.45 95% CrI (−0.72 to −0.075). Standardised coefficients with 95% credibility intervals are shown. All variables, including dichotomous variables, are added as continuous variables. Gender is coded as 0=male, 1=female, ever smoking is coded as 0=never smoking, 1=ever smoking. Rheumatoid factor and ACPA are coded as 0=negative, 1=positive. Values in bold reflect statistically significant results. ACPA, anticitrullinated protein antibody; BMI, body mass index; RF, rheumatoid factor.

Both differences in genetic make-up and environmental exposition between countries and regions may in theory impact age at onset of a chronic autoimmune disease such as RA. Indeed, in previous studies, several isolated factors were suggested to be related to the age at onset of RA. Here, we have explored several patient-specific factors simultaneously and disentangled whether the latitude effect takes place at the individual patient level, or rather at the hospital level or country level. We confirmed most of the previously isolated factors (and added a few new ones) that were related with age at diagnosis at the patient level: a higher age at diagnosis was found in males, in patients with a longer symptom duration and in those with a higher BMI. A lower age at diagnosis was found in ACPA-positive patients.[11–13 16] In addition, we could not confirm a previously reported association with (ever) smoking and found a higher (rather than a lower) age at diagnosis in RF-positive patients.[11 14 15] The lack of association with smoking may be due to a low proportion of female smokers and the use of smokeless tobacco products (not captured in METEOR) in some of the included countries, such as India.[27 28]

Geographical latitude, in turn, was associated with several patient factors. Since these associations between latitude and patient factors occurred at the country level, and the associations between patient-factors and age at RA onset only occurred at the patient-level, we have proven here that none of the patient factors could satisfactorily explain the observed latitude gradient of age at onset. Instead, a set of country indicators of socioeconomic welfare fully explained this relationship. When comparing standardised effects of socioeconomic indicators, the effect of gross enrolment ratio for secondary education seems strongest—two times as strong as GDP per capita—but did not suffice as sole indicator. Physician density, a potential although poor indicator of access to healthcare, did not explain at all.

One may argue that other unmeasured country-specific factors play a role and could contribute to clarifying the complex relationship between country-level socioeconomic indicators and age at RA onset. Candidates are level of air pollution, dietary habits and exposure to certain (childhood) infections or agricultural pesticides, which have all been related to the onset of RA,[29–32] as well as social habits and beliefs about (musculoskeletal) healthcare, which may importantly differ between countries, and may affect the decision to consult a rheumatologist.[8] For example, in some countries musculoskeletal complaints may be considered a normal consequence of ageing, and only those patients who are particularly afflicted may consult a rheumatologist and receive a diagnosis of RA.

A younger age at onset of RA comes with personal, societal and economic consequences.[9 10] Based on the data presented here, this seems to be the case for lower-income versus higher-income countries, and the impact of lower age at onset will be augmented by the inherently limited resources available for healthcare and social support for these patients. This effect could not be explained by differences in life expectancy between countries, which was included in our models as a variable. As such, this model is an example of how mutually reinforcing factors work

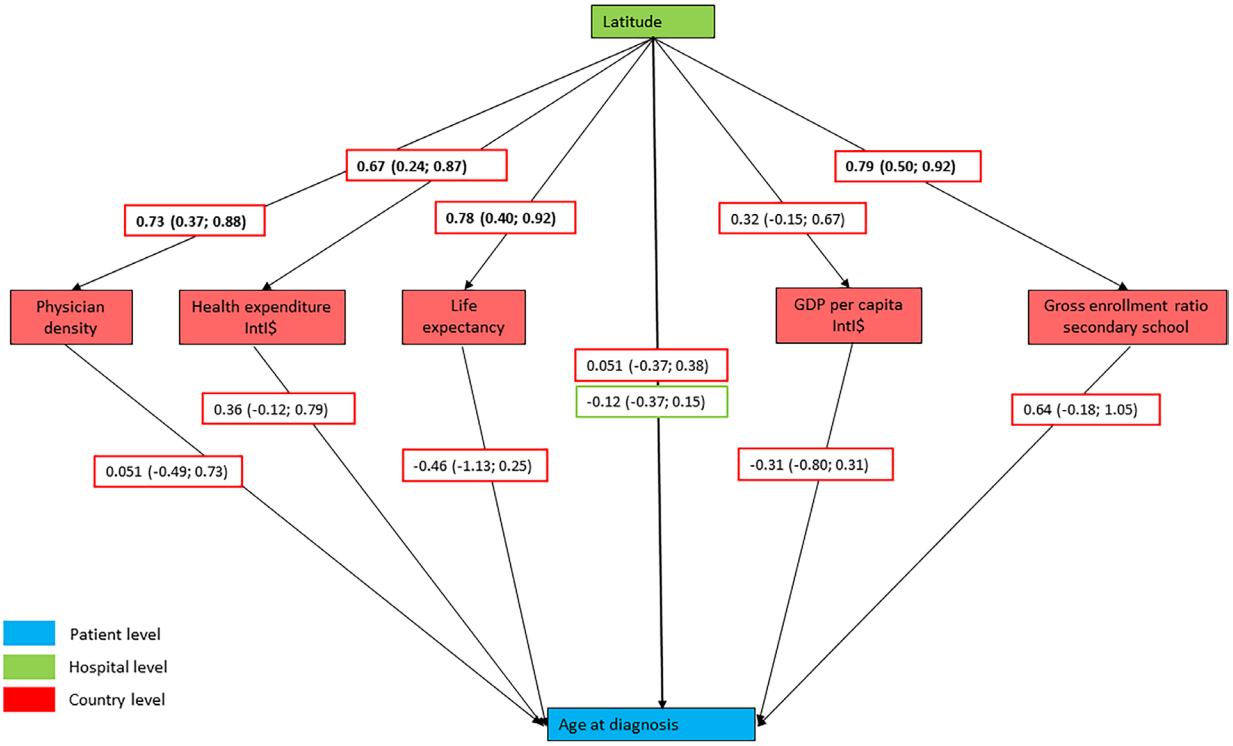


Figure 3 Model B, multilevel Bayesian structural equation model to study whether country-level mediators explain the association between hospital latitude and age at diagnosis. All associations are deconflated, to show separate effects at the country and hospital-level. Standardised coefficients with 95% credibility intervals are shown. Health expenditure and gross domestic product (GDP) per capita are shown per 10.000 international dollar (Intl$). Physician density refers to the number of physicians per 1000 inhabitants. Values in bold reflect statistically significant results.

toward inequity (a vicious circle). People living in high-income countries are relatively protected from getting RA at young age, but when contracting it 'the system' (access to healthcare and medicines, social security, etc) will take better care of them. People in low-income countries will not only get RA at a younger age, with an inherently longer disease course and a worse prognosis, but they also face poorer healthcare conditions and social support, which will further deteriorate their prognosis.

Here, we aimed to study age at RA onset, operationalised in two ways: the age at diagnosis and the age at symptom onset. While age at symptom onset is prone to recall bias, age at diagnosis is influenced by diagnostic delay, which may differ across countries, expectedly being largest in countries with the poorest socioeconomic conditions, usually at lower geographical latitudes. Interestingly, we found the opposite, a lower age at diagnosis in these countries, implying that—if a diagnostic delay plays a role—the true latitude effect would be even larger.

This study has some strengths and many limitations. Strengths are: the large number of patients contributing with individual data from many countries with an unprecedentedly wide geographical spread; and the analytical approach of an SEM that allowed us to evaluate several indicators and associations at patient level, hospital level and country level simultaneously. One of the main limitations is that the number of patients per hospital/country strongly differs and it is impossible to determine to what extent the patients are representative to all patients with RA in a country, especially in large countries with a limited number of contributors. Some of these hospitals included only a small number of patients. Similar results after omitting all hospitals with less than 20 patients, and results that are in agreement with previous publications provided some reassurance.

Despite the wide geographical spread and the large variation in socioeconomic status of the included countries, still most patients and hospitals were from countries with high-income economies. We were unable to include patients from 1 of the 28 countries with low-income economies, according to the World Bank definition, probably since there is no infrastructure to collect data from these countries.[22] We had to assume that socioeconomic indicators of welfare were to some extent representative for an entire country, knowing that such indicators cannot reflect regional or personal differences in socioeconomic status. There were missing data in some patient-level variables. We assumed that these data were missing at random, since SEM is only considered unbiased under the missingness at random assumption, but this assumption cannot further be verified. The observational nature of our data always carries the possibility of residual bias and confounding as explanatory factors. Our data do not allow any causal interpretation, and our results and conclusions should therefore be considered as hypothesis generating. Nevertheless, they convey an important message, pointing at relevant differences between countries, which seem to be related to potentially influenceable socioeconomic factors related to the onset of RA, factors that go beyond individual patient characteristics (eg, genes, individual habits and circumstances).

Whether the results of this study can be generalised to other autoimmune diseases, which often share fundamental concepts about genetic predisposition and environmental factors of relevance for disease onset, or even to chronic diseases in general, remains to be seen. That patients with chronic diseases living in low-income countries have in general a worse prognosis than those in high-income countries is not disputed. That RA also starts earlier in low-income countries and that its time of onset is directly attributable to levels of socioeconomic welfare (environment) rather than to inherent patient-factors (eg, genes) has not been described before.

In conclusion, this analysis in a large worldwide prevalence cohort of patients with RA provides a direct link between countries' level of socioeconomic welfare and the onset of RA.

Author affiliations
[1]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[2]Universidade Nova de Lisboa, NOVA Medical School, Lisbon, Portugal
[3]Centre for Rheumatic Diseases, Pune, India
[4]University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa
[5]Hospital General de Zona No. 17, Instituto Mexicano del Seguro, Monterrey, Mexico
[6]University of Massachusetts Chan School of Medicine, UMass Memorial Health Rheumatology Center, Worcester, Massachusetts, USA
[7]Amsterdam Rheumatology Center, Amsterdam Medical Center, Amsterdam, The Netherlands
[8]Rheumatology, Zuyderland Medical Centre Heerlen, Heerlen, The Netherlands

Twitter Alexandre Sepriano @AlexSepriano

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Contributors SAB and RBML contributed to the conception and design of the work. SAB, XMEM and AS analysed the data. SAB, XMEM, AS and RBML interpreted the data and drafted the manuscript. AC, L-LW, DV-M and KS-E contributed to data acquisition. All authors critically revised and approved the final version of the paper. All authors accepted responsibility to submit the manuscript for publication. SAB acts as guarantor and accepts full responsibility for the conduct of the study, had access to the data and controlled the decision to publish.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. This study was non-protocolised and only contained anonymised data which could not be linked to individual patients. Exemption from Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that have been used for the current study, which are by definition deidentified, are available upon reasonable request to the corresponding author. Data shall only be made available after approval by the individual study contributors of a submitted research proposal, with investigator support and after a signed data access agreement. A data dictionary and the syntaxes that have been used for the analyses are also available upon reasonable request to the corresponding author.

ORCID iDs
Sytske Anne Bergstra http://orcid.org/0000-0002-7136-5248
Alexandre Sepriano http://orcid.org/0000-0003-1954-0229
David Vega-Morales http://orcid.org/0000-0003-0651-2202
Robert BM Landewé http://orcid.org/0000-0002-0577-6620

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