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ORIGINAL ARTICLE

Latitude gradient influences the age of onset of rheumatoid arthritis: a worldwide survey

GEO-RA Group

Abstract The age of onset of rheumatoid arthritis (RA) is an important outcome predictor. Northern countries report an age of RA onset of around 50 years, but apparently, variability exists across different geographical regions. The objective of the present study is to assess whether the age of onset of RA varies across latitudes worldwide. In a proof-of-concept cross-sectional worldwide survey, rheumatologists from preselected cities interviewed 20 consecutive RA patients regarding the date of RA onset (RAO, when the patient first noted a swollen joint). Other studied variables included location of each city, rheumatologist settings, latitudes (10° increments, south to north), longitudes (three regions), intracountry consistency, and countries' Inequality-adjusted Human Development Index (IHDI). Data from 2481 patients (82% females) were obtained from 126 rheumatologists in 77 cities of 41 countries. Worldwide mean age of RAO was 44 ± 14 years (95% CI 44–45). In 28% of patients, RA began before age 36 years and before age 46 years in 50% of patients. RAO was 8 years earlier around the Tropic of Cancer when compared with northern latitudes ($p < 0.001$, 95% CI 3.5–13). Multivariate analysis showed that females, western cities, and latitudes around the Tropic of Cancer are associated with younger age of RAO (R^2 0.045, $p < 0.001$). A positive correlation was found between the age of RAO and IHDI ($r = 0.7$, $p < 0.01$, R^2 0.5). RA often begins at an early age and onset varies across latitudes worldwide. We postulate that countries'

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developmental status and their geographical and geomagnetic location influence the age of RAO.

Introduction

Rheumatoid arthritis (RA) is a disease of unknown cause and variable clinical presentation. Its prevalence and incidence vary across populations [1–3] and time [4–6]. Patients with RA may have a variable course, and their response to treatment is oftentimes unpredictable. Because of this variability, RA has been described as one of modern medicine's greatest enigmas [7].

The complete etiologic picture of this disease remains unclear because the genetic contribution to RA has been estimated to be 12–60% [8, 9], and environmental factors contribute to up to half of the variation in disease susceptibility [10]. Variations in the reported figures on genetic and environmental factors across populations can be partially explained by differences in study design, the time when studies were performed, and that the data often come from historical studies that are restricted to specific regions or ethnic groups. Nevertheless, it is recognized that there are differences in the rates of occurrence of RA between countries and areas of the world [3].

The age of RA onset (RAO) is recognized as one of the most important predictors of disease outcome [11]. When RA starts at an early age, the economic burden imposed upon the patient, their family, and health services may be devastating. However, variability in the age of RAO is often neglected in studies of RA patterns. Some reports involving patients of

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European descent from developed countries found that the mean age of RAO is around 50 years [2, 12–14] with epidemiologic studies from these countries consistently reporting incidence rates that increase with age into the 70s [1]. Conversely, some studies from African and Asian countries have observed a significantly earlier peak in the mean age of RAO, which can be as young as the 20s or 30s [1]. Significant variations in the age of RAO have been reported in regional studies at different latitude gradients, both in terms of the mean age of onset and the frequency distribution by age groups [15, 16].

Latitude gradients have been used in geoepidemiology as a surrogate to study the influence of environment on disease incidence and risks across different geographic areas, so as to generate hypotheses for further investigation [17]. For example, diseases such as systemic lupus erythematosus, dermatomyositis, and Crohn's disease are geographically associated with northern latitudes [17].

The objective of this proof-of-concept cross-sectional survey was to assess whether the age of RAO varies across latitudes worldwide.

Subjects and methods

In a proof-of-concept survey, rheumatologists working at preselected cities around the world interviewed consecutive RA patients regarding their disease onset. Major cities were selected by 15° quadrants (latitude and longitude) worldwide. Rheumatologist contact information for these cities was obtained using regional or local rheumatology association open databases, the web site of the US National Library of Medicine (PubMed), and direct recommendation from selected rheumatologists. An individualized invitation letter, which included information about the study but not its hypothesis, was sent electronically to each identified rheumatologist. A reply confirming the rheumatologists' interest in participating and confirmation of whether they treated RA patients and were board certified in rheumatology, the type of clinical practice (private, university, or other), and the city and country where the rheumatologist worked was requested. No compensation was offered. A second electronic communication, with detailed instructions that included guidelines on how to gather patient information in the data log sheet format, was sent to rheumatologists who agreed to participate. Participants were to provide data by directly interviewing 20 consecutive RA patients as per the 1987 criteria of the American Rheumatism Association [18]. This information was limited to nonsensitive data, in compliance with local regulations, and included nontraceable patient identification (e.g., consecutive numbers, letters, or initials), date

of birth (month and year), sex, date of RA diagnosis (month and year), and date of RAO, defined as the month and year when the patient first noticed a swollen joint.

Data from data log sheets were extracted by two medical students, and the precise latitude and longitude of each city were obtained using Google Earth (Google Inc., Mountain View, CA, USA). For cases in which the data log sheet included errors or inconsistencies for up to three patients, the participating rheumatologist was asked to review the data. If there were four or more patients with inconsistent data or submitted data from less than 18 patients, the complete set was excluded; no substitutions were allowed. Summary data and manuscript drafts were shared with all participants.

Statistical analysis

Data handling was based on the following assumptions: (a) rheumatologists would have easy access to 20 RA patients in their clinical practice over a short period of time, to assure their compliance; (b) comparing data from two or more rheumatologists in the same city would allow us to assess the intracity consistency of the main variable (age of RAO) using nonparametric Mann–Whitney U or Kruskal–Wallis tests; and (c) comparing data from two or more cities located at the same latitude in each country would allow us to assess intracountry consistency of the main variable using parametric tests (Student's t test or one-way ANOVA). The age of RAO was examined as both a continuous variable and a categorical variable (age groups, 10-year increments).

Differences in age of RAO according to latitudes worldwide (10° increments, south to north) were examined using one-way ANOVA for continuous variables (with a post hoc Schaffé for multiple comparisons), whereas a Pearson's chi-square or Fisher's exact test was used for categorical variables. Thereafter, the world map was arbitrarily divided by longitudes into three regions: region 1 (30° W to 134° W) that includes countries of the Americas; region 2 (29° W to 104° E) that includes countries of Europe, Africa, and Western Asia; and region 3 (105° E to 180° E) that includes countries of East Asia and Oceania. This division was made to assess whether significant differences in the age of RAO, detected according to latitudes worldwide, persisted by region (using one-way ANOVA and Pearson's chi-square or Fisher's exact test). A p of ≤0.05 was set as the level of statistical significance, and confidence intervals were reported at 95% (95% CI).

Stepwise multiple linear regression analysis was performed to assess the effects of sex (binary), northern cities (binary), western cities (binary, from the Greenwich parallel), cities

grouped per longitude (categorical variable, three regions), and cities grouped per latitude code (categorical variable, each 10°) on age of RAO. A backward regression was run for all significant variables ($p < 0.1$) identified by univariate analysis.

After reviewing the results, a post hoc analysis was performed to explore whether the age of RAO is correlated with the developmental status of participating countries (Pearson's correlation coefficient). The countries' developmental status was obtained from the United Nations Development Programme report [19] on the 2015 Human Development Index (HDI) (years 2010–2014) and on the Inequality-adjusted HDI (year 2014).

This being a nonintervention study, and the collected information precludes individual patient identification (nonsensitive data), no informed consent was required as per local regulations at each site.

Results

Figure 1 shows the distribution of rheumatologists invited to participate and those who accepted our invitation. Figure 2
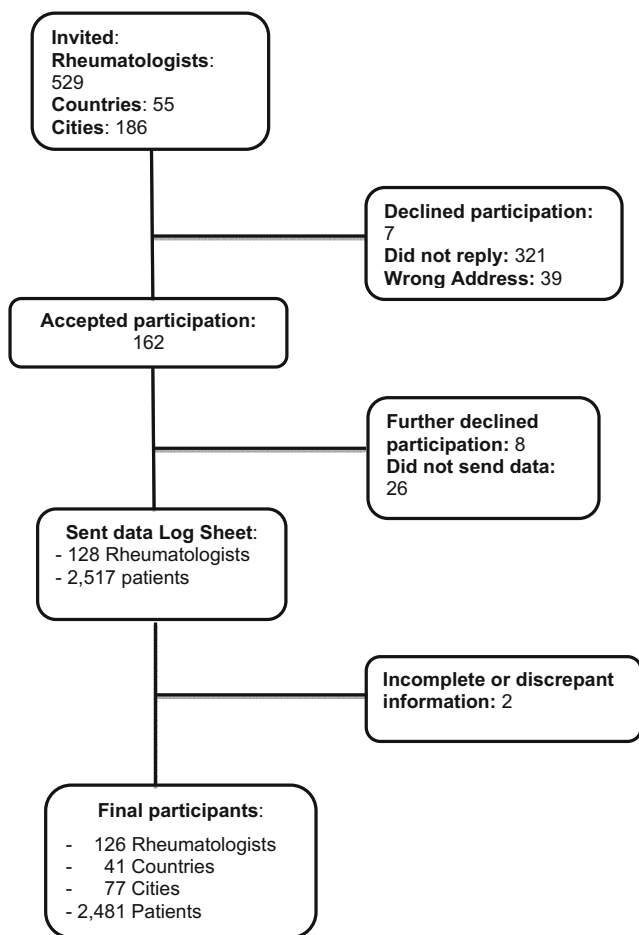

Fig. 1 Flow chart of study participants (rheumatologists, countries, and cities)

shows the distribution of the mean age of RAO by participating country, with the number of sites (rheumatologists) and cities per country. We obtained data of 2481 patients (82% females) from 126 rheumatologists in 77 cities of 41 countries.

Table 1 shows the mean age of RAO and the frequency distribution by age group according to latitude in 10° intervals from south to north. The worldwide overall mean age of RAO was 44.4 ± 14 years (95% CI 44–45). The overall frequency distribution by age group shows that 28% of patients had an RAO before the age of 36 years and between the ages of 16 and 45 years in 50% of patients. Analysis of age of RAO by latitude showed significant differences in both, as mean and as distribution by age groups. Age of RAO for latitude code 8 (20° N to 29° N) was on average 8, 8, 5, and 6 years younger when compared with latitude codes 11, 10, 3, and 2, respectively ($p < 0.001$, 95% CI for differences of 3.5–13, 2–13, 0.1–10, and 2–10 years, respectively). Latitude codes 8 and 9 (around the Tropic of Cancer) had a higher proportion of patients with an RAO before age 35 years compared with northern or southern latitudes ($p < 0.001$). Intracity variability could be assessed in 29 (38%) cities, and consistency was confirmed in 79% of them (supplementary Table 1). Intracountry variability could be assessed for 19 (46%) countries, and consistency was ascertained in 16 (84%) (supplementary Table 2).

The results of subanalysis by region (longitudes) are shown in Table 2 as the mean age of RAO and in Table 3 as the frequency distribution by age group, both by latitude in 10° intervals south to north. Similar trends were observed in region 1 (the Americas), where 12 countries participated and provided data on a total of 1062 patients. No rheumatologists from the USA replied to our electronic communications. The overall mean age of RAO was 44 ± 14 years (95% CI 43–45). Disease onset was on average 8 and 14.5 years younger for latitude code 8 compared with northern latitude codes 11 and 10, respectively ($p < 0.01$), and 7 years younger than southern latitude code 2 (31°–40° S) ($p = 0.01$). The frequency distribution by age group showed that in latitude code 8, nearly half of patients had RAO before the age of 36 years, which was significantly different when compared with latitude codes 2 (24.8%) and 6 (27.8%) ($p < 0.001$). In region 2 (Europe, Africa, and Western Asia), 24 countries participated, yielding data on 1126 total patients. The overall mean age of RAO was 44 ± 14 years (95% CI 43–45). For latitude code 8, RAO was on average 8.5 and 7.5 years younger when compared with northern latitude codes 11 and 10, respectively ($p < 0.01$). For latitude codes 8 and 9, there were a significantly higher proportion of patients with RAO before age 36 years compared with latitudes 10 and 11 ($p = 0.01$). However, there is no land in latitude code 1 (>40° S). In addition, in latitude code 4 (11° S–
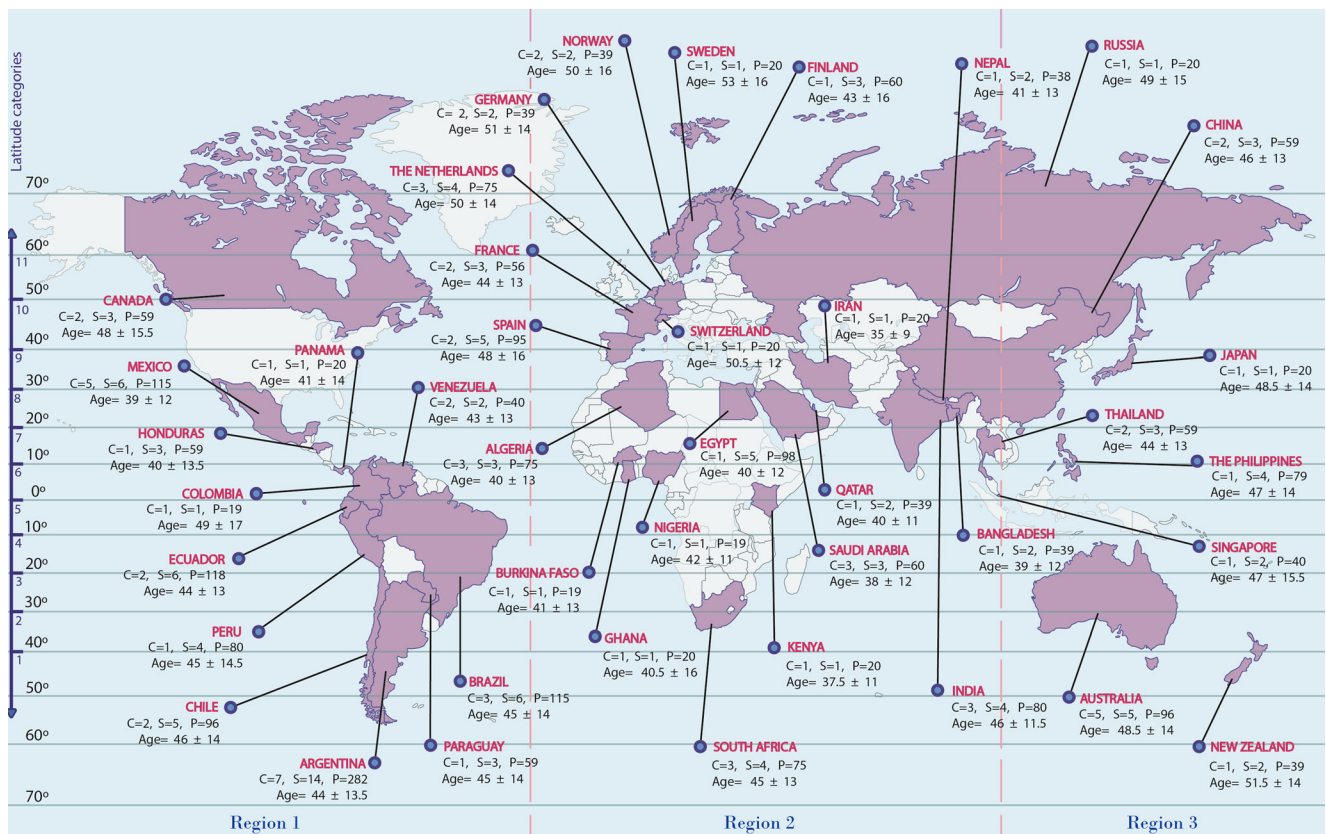
Latitude categories

NORWAY
C=2, S=2, P=39
Age= 50 ± 16

SWEDEN
C=1, S=1, P=20
Age= 53 ± 16

FINLAND
C=1, S=3, P=60
Age= 43 ± 16

NEPAL
C=1, S=2, P=38
Age= 41 ± 13

RUSSIA
C=1, S=1, P=20
Age= 49 ± 15

GERMANY
C= 2, S=2, P=39
Age= 51 ± 14

CHINA
C=2, S=3, P=59
Age= 46 ± 13

THE NETHERLANDS
C=3, S=4, P=75
Age= 50 ± 14

FRANCE
C=2, S=3, P=56
Age= 44 ± 13

IRAN
C=1, S=1, P=20
Age= 35 ± 9

CANADA
C=2, S=3, P=59
Age= 48 ± 15.5

SWITZERLAND
C=1, S=1, P=20
Age= 50.5 ± 12

JAPAN
C=1, S=1, P=20
Age= 48.5 ± 14

SPAIN
C=2, S=5, P=95
Age= 48 ± 16

PANAMA
C=1, S=1, P=20
Age= 41 ± 14

MEXICO
C=5, S=6, P=115
Age= 39 ± 12

VENEZUELA
C=2, S=2, P=40
Age= 43 ± 13

THAILAND
C=2, S=3, P=59
Age= 44 ± 13

HONDURAS
C=1, S=3, P=59
Age= 40 ± 13.5

ALGERIA
C=3, S=3, P=75
Age= 40 ± 13

EGYPT
C=1, S=5, P=98
Age= 40 ± 12

THE PHILIPPINES
C=1, S=4, P=79
Age= 47 ± 14

COLOMBIA
C=1, S=1, P=19
Age= 49 ± 17

QATAR
C=1, S=2, P=39
Age= 40 ± 11

NIGERIA
C=1, S=1, P=19
Age= 42 ± 11

BANGLADESH
C=1, S=2, P=39
Age= 39 ± 12

SINGAPORE
C=1, S=2, P=40
Age= 47 ± 15.5

ECUADOR
C=2, S=6, P=118
Age= 44 ± 13

BURKINA FASO
C=1, S=1, P=19
Age= 41 ± 13

SAUDI ARABIA
C=3, S=3, P=60
Age= 38 ± 12

PERU
C=1, S=4, P=80
Age= 45 ± 14.5

GHANA
C=1, S=1, P=20
Age= 40.5 ± 16

KENYA
C=1, S=1, P=20
Age= 37.5 ± 11

INDIA
C=3, S=4, P=80
Age= 46 ± 11.5

AUSTRALIA
C=5, S=5, P=96
Age= 48.5 ± 14

CHILE
C=2, S=5, P=96
Age= 46 ± 14

BRAZIL
C=3, S=6, P=115
Age= 45 ± 14

NEW ZEALAND
C=1, S=2, P=39
Age= 51.5 ± 14

ARGENTINA
C=7, S=14, P=282
Age= 44 ± 13.5

PARAGUAY
C=1, S=3, P=59
Age= 45 ± 14

SOUTH AFRICA
C=3, S=4, P=75
Age= 45 ± 13

Region 1 · Region 2 · Region 3

Fig. 2 Mean age of onset of rheumatoid arthritis distributed by participating country, number of cities (*C*), number of sites (*S*) (rheumatologists), and number of patients (*P*)

20° S), we were unable to contact rheumatologists in Senegal, Guinea, Niger, Ethiopia, and Sudan. The number of patients varied per country, yielding a broad 95% CI for latitude codes 3 and 5. In region 3 (East Asia and Oceania), five countries participated and provided data on 293 patients. We were unable to contact

Table 1 Worldwide distribution of mean age of onset of rheumatoid arthritis (RA) and frequency distribution by age group per every 10° of latitude, south to north

Latitude, code (location)	Patients N=	Age of onset of RA, mean ± SD (years) (95% CI)	Age groups (years) n (%)**					
			16–25	26–35	36–45	46–55	56–65	>65
1 (>40° S)	96	45 ± 14 (42.5 to 48)	4 (4.2%)	22 (22.9%)	23 (24%)	23 (24%)	13 (13.5%)	11 (11.5%)
2 (31° to 40° S)	473	46 ± 14 (44 to 47)	32 (6.8%)	80 (16.9%)	125 (26.4%)	113 (23.9%)	84 (17.8%)	39 (8.2%)
3 (21° to 30° S)	213	45 ± 14 (43 to 47)	19 (8.9%)	32 (15%)	50 (23.5%)	58 (27.2%)	37 (17.4%)	17 (8%)
4 (11° to 20° S)	80	45 ± 14.5 (41.5 to 48)	8 (10%)	14 (17.5%)	16 (20%)	22 (27.5%)	12 (15%)	8 (10%)
5 (1° to 10° S)	138	43 ± 13 (41 to 45)	15 (10.9%)	24 (17.4%)	34 (24.6%)	40 (29%)	19 (13.8%)	6 (4.3%)
6 (0° to 9° N)	158	44 ± 15 (42 to 46.5)	21 (13.3%)	20 (12.7%)	40 (25.3%)	41 (25.9%)	24 (15.2%)	12 (7.6%)
7 (10° to 19° N)	316	44 ± 13 (42 to 45)	33 (10.4%)	54 (17.1%)	61 (19.3%)	107 (33.9%)	49 (15.5%)	12 (3.8%)
8 (20° to 29° N)	389	40 ± 12* (39 to 41)	41 (10.5%)	105 (27%)	104 (26.7%)	99 (25.4%)	29 (7.5%)	11 (2.8%)
9 (30° to 39° N)	193	43 ± 15 (41 to 45)	18 (9.3%)	48 (24.9%)	43 (22.3%)	46 (23.8%)	22 (11.4%)	16 (8.3%)
10 (40° to 49° N)	153	48 ± 14 (45 to 50)	6 (3.9%)	31 (20.3%)	30 (19.6%)	37 (24.2%)	30 (19.6%)	19 (12.4%)
11 (>50° N)	272	48 ± 15 (46 to 50)	18 (6.6%)	44 (16.2%)	52 (19.1%)	55 (20.2%)	63 (23.2%)	40 (14.7%)
Total	2481	44 ± 14 (44 to 45)	215 (8.7%)	474 (19.1%)	578 (23.3%)	641 (25.8%)	382 (15.4%)	191 (7.7%)

*Latitude code 8 is significantly different compared with latitude codes 2, 3, 10, and 11; *p* < 0.001

**Significant differences of age groups by latitudes, *p* < 0.001

Table 2   Mean age of onset of rheumatoid arthritis (RA) by region (longitude), according to latitude

	Regions by longitudes (longitude range) and participating countries					
	Region 1 (30° W to 134° W)		Region 2 (29° W to 104° E)		Region 3 (105° E to 180° E)	
	Argentina, Brazil, Canada, Chile, Colombia, Ecuador, Honduras, Mexico, Panama, Paraguay, Peru, Venezuela		Burkina Faso, Finland, France, Kenya, Netherlands, Nigeria, Norway, Saudi Arabia, South Africa, Spain, Sweden, Ghana, Russia, Egypt, Algeria, Germany, Switzerland, Qatar, Bangladesh, Iran, Singapore, Thailand, India, Nepal		China, Japan, New Zealand, Philippines, Australia	
Latitude (range)	Patients $N=$	RA age of onset Mean ± SD (95% CI)	Patients $N=$	RA Age of onset Mean ± SD (95% CI)	Patients $N=$	RA age of onset Mean ± SD (95% CI)
1 (>40° S)	57	41 ± 13 (38 to 44.5)	–	–	39	51.5 ± 14 47 to 56
2 (31°–40° S)	339	45 ± 14 (44 to 47)	57	46 ± 12 43 to 49	77	46.5 ± 14 43 to 50
3 (21°–30° S)	156	44 ± 13 (42 to 46)	38	43 ± 13 39 to 48	19	57 ± 11 51 to 62
4 (11°–20° S)	80	45 ± 14.5 (41.5 to 48)	–	–	–	–
5 (1°–10° S)	118	44 ± 13 (41 to 46)	20	37.5 ± 11 32 to 43	–	–
6 (0°–9° N)	79	44 ± 14 (41 to 47)	79	44 ± 15 41 to 48	–	–
7 (10°–19° N)	98	41 ± 13 (38 to 43)	139	44 ± 13 42 to 46.5	79	47 ± 14 44 to 50
8 (20°–29° N)	76	38 ± 11.5 (35 to 40)	274	39.5 ± 12 38 to 41	39	46 ± 13 42 to 50.5
9 (30°–39° N)	–	–	153	42 ± 15 40 to 44.5	40	47 ± 14 42 to 51
10 (40°–49° N)	20	52.5 ± 16 (45 to 60)	133	47 ± 14 45 to 49	–	–
11 (>50° N)	39	46 ± 15 (41 to 51)	233	48 ± 15 46 to 50	–	–
Total	1062	44 ± 14 (43 to 45)	1126	44 ± 14 43 to 45	293	48 ± 14 46 to 49.5

rheumatologists in latitudes 4 to 6 (the Republic of Indonesia and Papua New Guinea) or latitudes 10 and 11 (the Kuril Islands and the Kamchatka Peninsula). No significant differences were found in this region for mean age of RAO and frequency distribution by age group, probably incurring in a type II error.

The final model in the stepwise multiple linear regression analysis included sex, latitude coded groups, and western cities. A significant regression equation was found (F (12, 2468) = 9.72, $p < 0.001$), with an R^2 of 0.045. The age of RAO was significantly younger among females and patients from western cities; age of RAO was older at northern latitudes (>50° N) (Table 4). We did not find significant differences between other variables, such as rheumatologist practice type or the number of years in rheumatology practice.

Post hoc analysis showed a positive correlation ($r = 0.58$, $p < 0.0001$) between the age of RAO and HDI by country for

the years 2010 to 2014, with a coefficient of determination (R^2) of 0.33. When the HDI was adjusted for inequality (year 2014), the positive correlation became stronger ($r = 0.71$, $p < 0.01$), with an R^2 of 0.50.

Discussion

Despite the importance of age of RAO as an outcome predictor, data on its variability in different populations are scarce and limited to specific geographical regions. In this proof-of-concept study, the age of RAO was evaluated in different regions of the world and its variability was analyzed per latitude gradients, as these are used as surrogates of environmental factors to posit hypotheses for further study.

Table 3 Frequency distribution of age groups for onset of rheumatoid arthritis by region (longitude), according to latitude

	Latitude codes[a]										
	1	2	3	4	5	6	7	8	9	10	11
Longitudes											
Region 1 (30° W to 134° W)											
Age groups, n (%)[b]											
16–25 years	4 (7)	24 (7)	15 (10)	8 (10)	12 (10)	8 (10)	12 (12)	9 (12)	–	1 (5)	3 (8)
26–35 years	18 (32)	60 (18)	25 (16)	14 (17.5)	19 (16)	14 (18)	23 (23.5)	25 (33)	–	3 (15)	7 (18)
36–45 years	12 (21)	85 (25)	39 (25)	16 (20)	27 (23)	21 (27)	23 (23.5)	20 (26)	–	2 (10)	9 (23)
46–55 years	13 (23)	79 (23)	40 (26)	22 (27.5)	36 (30.5)	19 (24)	29 (30)	16 (21)	–	5 (25)	6 (15)
56–65 years	8 (14)	64 (19)	27 (17)	12 (15)	18 (15)	12 (15)	6 (6)	5 (7)	–	5 (25)	10 (26)
>65 years	2 (3.5)	27 (8)	10 (6)	8 (10)	6 (5)	5 (6)	5 (5)	1 (1)	–	4 (20)	4 (10)
Total	57	339	156	80	118	79	98	76	–	20	39
Region 2 (29° W to 104° E)											
Age groups, n (%)[b]											
16–25 years	–	4 (7)	4 (10.5)	–	3 (15)	13 (16.5)	14 (10)	31 (11)	16 (10.5)	5 (4)	15 (6)
26–35 years	–	5 (9)	7 (18)	–	5 (25)	6 (8)	20 (14)	71 (26)	41 (27)	28 (21)	37 (16)
36–45 years	–	19 (33)	8 (21)	–	7 (35)	19 (24)	27 (19)	78 (28.5)	32 (21)	28 (21)	43 (18.5)
46–55 years	–	19 (33)	12 (32)	–	4 (20)	22 (28)	51 (37)	70 (25.5)	37 (24)	32 (24)	49 (21)
56–65 years	–	7 (12)	6 (16)	–	1 (5)	12 (15)	24 (17)	18 (7)	14 (9)	25 (19)	53 (23)
>65 years	–	3 (5)	1 (3)	–	0 (0)	7 (9)	3 (2)	6 (2)	13 (8.5)	15 (11)	36 (15.5)
Total	–	57	38	–	20	79	139	274	153	133	233
Region 3 (105° E to 180° E)											
Age groups, n (%)[b]											
16–25 years	0 (0)	4 (5)	0 (0)	–	–	–	7 (9)	1 (3)	2 (5)	–	–
26–35 years	4 (10)	15 (19.5)	0 (0)	–	–	–	11 (14)	9 (23)	7 (17.5)	–	–
36–45 years	11 (28)	21 (27)	3 (16)	–	–	–	11 (14)	6 (15)	11 (27.5)	–	–
46–55 years	10 (26)	15 (19.5)	6 (32)	–	–	–	27 (34)	13 (33)	9 (22.5)	–	–
56–65 years	5 (13)	13 (17)	4 (21)	–	–	–	19 (24)	6 (15)	8 (20)	–	–
>65 years	9 (23)	9 (12)	6 (32)	–	–	–	4 (5)	4 (10)	3 (7.5)	–	–
Total	39	77	19	–	–	–	79	39	40	–	–

[a] Latitude codes: 1 = >40° S; 2 = 31° S–40° S; 3 = 21° S–30° S; 4 = 11° S–20° S; 5 = 1° S–10° S; 6 = 0°–9° N; 7 = 10° N–19° N; 8 = 20° N–29° N; 9 = 30° N–39° N; 10 = 40° N–49° N; and 11 = >50° N

[b] Rounded numbers

Our first important finding is that, in general, RA is not a disease of older adulthood. Based on the sample size of 2481 patients from 41 countries and the narrow 95% CI of the mean, we believe that our data are quite robust. The fact that half of RA patients worldwide have disease onset at a young age has several implications. First, RA may have a greater individual and familial impact than previously believed because its onset is before individuals reach their peak life roles. Second, the general perception that RA occurs mainly in older adulthood, which is based on older data from developed northern countries [1], may mislead local policy makers when allocating resources and developing health care strategies for a disease that can last as long as 40 years in many cases. Third, it is possible that the age of RAO

has changed over the past five decades, together with temporal trends in the occurrence of RA [1, 4–6, 20–23].

Our second finding is that the age of RAO is significantly different along latitude gradients. We have shown that at latitudes around the Tropic of Cancer (latitude codes 8 and 9), RA starts at a younger age, with a higher proportion of patients developing the disease before age 36 years as compared with northern and southern latitudes. When analyzed by region (longitudes), similar trends were observed for region 1. Region 2 also showed significant trends, but the data are not as robust as for the Americas. Region 3 lacked data at several latitudes, and the broad 95% CI observed for the available data indicates a possible type II error. However, multiple linear regression models showed that RA starts at a significantly

Table 4 Stepwise linear regression, variables associated with age of onset of rheumatoid arthritis

Variable	Univariable β coefficient 95% CI)	p value	Multivariable β coefficient (95% CI)	p value
Sex (female)	−4.4 (−5.8; −2.9)	<0.01	−3.9 (−5.4; −2.6)	<0.01
Latitude code[a]				
1 (>40° S)	−2.7 (−5.9; 0.5)	0.09	−1.4 (−4.7; 1.8)	0.37
2 (31° to 40° S)	−2.3 (−4.4; −0.3)	0.02	−0.9 (−3.1; 1.3)	0.42
3 (21° to 30° S)	−2.9 (−5.5; −0.5)	0.02	−1.5 (−4.1; 1.1)	0.25
4 (11° to 20° S)	−3.3 (−6.7; 0.1)	0.05	−1.2 (−4.7; 2.4)	0.53
5 (1° to 10° S)	−5.1 (−7.9; −2.2)	<0.01	−3.2 (−6.2; −0.3)	0.03
6 (0° to 9° N)	−3.8 (−6.5; −1.1)	<0.01	−2.4 (−5.2; 0.3)	0.08
7 (10° to 19° N)	−4.2 (−6.4; −1.9)	<0.01	−3.3 (−5.5; −1.0)	<0.01
8 (20° to 29° N)	−8.2 (−10.3; −6.0)	<0.01	−7.6 (−9.7; −5.4)	<0.01
9 (30° to 39° N)	−4.9 (−7.5; −2.4)	<0.01	−4.3 (−6.8; −1.8)	<0.01
10 (40° to 49° N)	−0.4 (−3.2; 2.3)	0.8	−0.0 (−2.7; 2.7)	0.99
Cities above the equator	−1.1 (−2.3; −0.02)	0.04	*	
Longitude regions[b]				
Europe, Africa, West Asia[c]	1.9 (0.1; 3.6)	0.04	**	
Americas (30° W to 134° W)	−1.6 (−3.2; 0.07)	0.06	**	
Western cities[d]	−0.9 (−2.0; 0.2)	0.10	−1.6 (−2.9 ; −0.3)	0.01

[a] Group 11 (>50° N) is the referent group

[b] East Asia, Australia, and New Zealand (105° E to 180° E) is the referent group

[c] Europe, Africa, Western Asia; 29° W to 104° E

[d] Starting from the Greenwich parallel

*Nonsignificant in the second step

**Nonsignificant in the third step

younger age among females; in patients from latitude codes 5, 7, 8, and 9; and in those from countries in the Western Hemisphere (west of the Greenwich parallel).

Although we found no similar reports with which to compare our results, these are in concert with other studies conducted at regional level. In 2007, our group reported that the mean age of RAO was significantly younger among Mexicans than among Canadians [15], with figures similar to those reported here. Abdel-Nasser et al. [1] reported that Egyptian patients, especially women, had a significantly younger age of RAO than Dutch patients. Studies from India and Pakistan have a higher RA prevalence in the age groups of 25–29 years [24] and 16–29 years [25], respectively. Studies from the USA have found that the incidence of RA varies by geographic coordinates [26, 27].

Therefore, it seems plausible that latitude gradients play a major role in triggering those mechanisms responsible for RA initiation among genetically predisposed subjects. We posit that this happens because of two characteristics that are shared among countries located near the Tropic of Cancer, which may differentiate them from nations at northern latitudes: the developmental status of these countries (developing countries around the Tropic of Cancer versus developed northern nations) and the latitude gradient per se.

Post hoc analysis showed a significant relationship between the age of RAO and countries' HDI, which became even stronger when adjusted for inequality. Developmental status takes into account life expectancy, education, per capita income, and inequality. These variables can in turn act as surrogates for population health, lifestyle, environmental pollutants, and exposure to infections. Therefore, air pollution, local environmental policies, social inequalities, the age of exposure to infections and how they are treated, changes in the microbiome because of infection or seasonal variation in diet [28], oral contraceptive use, age at first pregnancy, and breastfeeding practices may be related to differences between developing and developed countries. For instance, air pollution—a mixture of suspended particulate matter mainly from vehicular traffic, industry, stationary fuel burners, and solid fuel combustion—has recently been found to be associated with RA [29]. A study in Sweden found that the risk of developing RA was increased with exposure to gaseous pollutants (NO_2 and SO_2) in the 10th year before disease onset [30]. Lower socioeconomic status has been associated with RA [31], and there is an increased risk of exposure to atmospheric

pollution and greater smoking consumption compared with individuals at higher income levels [32, 33]. A variable also to consider is oral contraceptive use, which may delay the onset of RA [34] and have a protective effect [35]. Use of oral contraceptives is less common at an early age in developing countries than in developed ones [36]. Having more than one pregnancy, young age at first pregnancy, and breastfeeding patterns are other possible factors [37–39]. A delay in the age of RAO in developed countries may be related to an increased tendency to postpone first pregnancies or a tendency not to breastfeed [40]. Exposure to infections may have a dual effect on the initiation of RA in susceptible individuals. Some infections may produce a protective effect [41, 42], whereas others, such as periodontal disease, may increase the risk of triggering RA [31]. Hence, exposure to specific infectious agents and how they are treated, with consequent changes in the microbiome [43], may be related to socioeconomic status, health care characteristics, and inequality, which may in turn be related to a country's developmental status.

Several of these variables can be modified by non-medical means that depend more on public health measures than on pharmacologic interventions. If our hypothesis is correct, the age of RAO could be modified to affect fewer years in the lives of RA patients from developing countries, analogous to the decline in infectious diseases during the 19th and 20th centuries before the extended use of antibiotics, thereby reducing disease burden and health care costs [44].

The second characteristic that differentiates countries around the Tropic of Cancer from those at northern latitudes is the gradient of latitudes where countries are located. The incidence and periodicity of RA have been found to be related to increasing geographic latitudes, which determine the magnitude of exposure to variables such as solar cycles, auroral electrojets, extreme ultraviolet radiation, substorms, and magnetic field perturbations [45]. Unfortunately, these variables have only been studied in limited geographic areas over short time spans. Future studies with larger data sets that cover several countries and organized by geomagnetic and geographic coordinates would be necessary, to assess the biologic disturbance and magnitude that these variables may cause [46] on the incidence and age of RAO.

We chose a proof-of-concept study for feasibility reasons; however, this design has inherent limitations such as the fact that chance (random), bias, and confounders cannot be controlled. Our approach to decrease issues of RA ascertainment and selection bias included the recruitment of rheumatologists listed in rheumatology association registers as well as their self-reporting of board certification and that they had patients with RA under their care. Instructions for determining patient age of RAO were clearly stated, and participants were not informed of the primary aim of the study at the time of data collection. The wide standard deviation in the mean age of RAO observed in

each data set suggests that participants maintained a typical rheumatology practice. Unfortunately, it was possible to assess intracity consistency in only one third of participating cities, and inconsistencies were found in some of them. Chance is the most viable explanation based on the small sample of patients that we requested of each rheumatologist, the broad 95% CI of each data set, and the nonsignificance of other variables such as length or type of practice.

Intracountry consistency could be assessed for nearly half of participating countries, but some significant differences were observed. We retrieved the mean age of RAO reported in other studies (referent studies), to gain some insight into how much of our data from these countries are different from those reported previously, although the definitions of age of onset in these referent studies were different from ours. Mean ages of RAO in referent studies from Brazil (44.9 ± 14.5 years) [47] and Australia (49.6 ± 11 years) [48] were similar to our data from these countries; we did not find any published data from Ecuador. However, the main limitation of our study lies in the 11 (27%) countries where only one rheumatologist participated. Referent studies from Switzerland (mean age of RAO 51.5 years) [49], Japan (49 years) [50], Kenya (41 ± 17 years) [51], Nigeria (42 years) [52], Sweden (58 ± 18 years) [14], Russia (53 years) [53], Colombia (44 ± 12 years) [54], Burkina Faso (35 years) [55], and Iran (41 ± 13 years) [56] reported figures similar to ours. We did not find referent studies from Ghana or Panama.

In summary, RA often begins at an early age and its onset varies across latitudes throughout the world. From this observation, it can be hypothesized that countries' developmental status and location influence the age of RAO. These features warrant further studies on the precise magnitude of this phenomenon and the possible causality of diverse factors such as pollution, pregnancy-related patterns, and infection exposures, all adjusted for inequality, as well as atmospheric variables adjusted by geographical and geomagnetic coordinates.

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