

Global, regional and national burden of rheumatoid arthritis, and attributable risk factors from 1990 to 2019: update from the Global Burden of Disease 2019 study

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Abstract

Objective

Statistical data on the incidence, disability-adjusted life years (DALYs) and burden of rheumatoid arthritis (RA), and associated risk factors are essential for the development of effective treatment options. The Global Burden of Disease (GBD) study provides a unique opportunity to evaluate the aforementioned parameters.

Methods

The RA incidence rate, age-standardised incidence rate (ASR), DALYs and estimated annual percentage change (EAPC) between 1990 and 2019 were evaluated, using data from 204 territories and countries from the GBD 2019. Risk factors associated with DALYs in patients with RA were estimated using the comparative risk assessment framework of the GBD study.

Results

The results of the present study demonstrated that the incidence of RA increased from 567,462.89 to 1,074,390.80 cases, with an ASR of 13/100,000 patients between 1990 and 2019. The number of RA cases and DALYs were increased in all socio-demographic index quintiles during the study period. A significant negative association was found between EAPCs and age-standardised DALYs per 100,000 ($q = -0.60$; $p < 0.001$). Notably, females exhibited an increased ASRs and DALYs than males, at both global and regional levels during the study period. Globally, age-standardised DALYs increased in an age-dependent manner, with the highest rate in the 60–69 years age group. Moreover, smoking was the predominant contributor to RA-associated DALYs for males worldwide, and this trend decreased from 1990 to 2019.

Conclusion

The incidence rate of RA and associated DALYs are increasing worldwide, particularly among female patients. This trend is expected to increase, due an ageing population. Notably, smoking remained the predominant risk factor for RA-associated DALYs in males. Therefore, further investigations into the impact of smoking, and improvements in early diagnosis and treatment strategies for RA are required to reduce the global burden of RA.

Key words

rheumatoid arthritis, global burden, incidence, disability-adjusted life years, risk factors

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Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that is characterised by inflammation in joints, bone erosions and cartilaginous destruction (1). RA burden is high due to the significant influence on a patient's life, and the associated symptoms may cause the severe destruction of joints, long-term facet effects and a reduced life expectancy (2). The mechanisms of RA are yet to be fully elucidated. The results of a previous study demonstrated that RA involves multiple systems, and is developed through interactions between genetic and environmental factors (3). Notably, smoking is the primary environmental risk factor for RA, and accounts for ~20% of the environmental risk factors for RA (4). Patients who have smoked 1–10 packs/year may exhibit a 26% increased risk of developing RA (5). Further investigations into the associated global trends and attributable risk factors are required, as RA exerts a high impact on public health at present. In recent years, more and more research has been carried out on the incidence and mortality rates associated with RA. The results of these previous studies present an inclusive picture (6–8). However, specific investigations into the burden of RA at a global level and the associated risk factors are lacking. A previous study reported the global burden of musculoskeletal disease using the World Health Organization Burden of Diseases Database for 2000, 2010 and 2015, but it did not specifically focus on RA (9). In addition, the worldwide burden of RA was reported using the Global Burden of Disease (GBD) 2017 study, but the attributable risk factors were not reported, and the overall RA burden estimates still rely on data obtained in 2017 (10).

The present study aimed to provide comprehensive, comparable and current information on the burden of RA. This was assessed using the temporal trends of RA incidence, age-standardised incidence rates (ASRs) and disability-adjusted life years (DALYs) from the GBD 2019 study. This study included data spanning from 1990 to 2019, at global, regional and national levels. Cases of RA were stratified by age and sex of patients, risk factors and the so-

cio-demographic index (SDI; a composite of sociodemographic factors). The present study may exhibit potential as an extension of the previous study.

Materials and methods

Overview and definitions

The GBD 2019 study was conducted by The Institute of Health Metrics and Evaluation and has been updated annually. It contains data on 369 human diseases and 87 risk factors spanning 204 countries and regions worldwide, and this data has been collected since 1990 (11). RA burden was calculated each year from 1990 to 2019 worldwide using data from the GBD 2019 study. In the GBD 2019 study, the extra-articular effects on internal organ injuries in RA were not factored into the disability weights used. Case definitions for RA were based on the 1987 guidelines by The American College of Rheumatology (ACR 1987) (12). A comprehensive systematic review of the population-based incidence of RA was conducted in the GBD 2017 study, and this was updated in 2019. The following studies were excluded: i) non-representative of the national population; ii) non-population-based; iii) exhibiting inadequate primary data on epidemiological parameters; iv) studying a specific type of RA, for example, seropositive RA; and v) reviews. The present study was approved by the Human Research Ethics Committee of the Second Affiliated Hospital of Nanchang University.

Data sources

Data on the annual incidence rate, DALYs and ASRs of RA were derived from the GBD 2019 dataset. Using available epidemiological data, the online Global Health Data Exchange (GHDx) query tool (<http://ghdx.health-data.org/gbd-results-tool>; accessed 11/07/22), was used to evaluate the burden of RA. The results of a previous study detailed the methods of the GBD 2017 study, and the methods used for estimations of disease burden in RA (10). A total of 204 countries and territories were subsequently categorised into five SDI quintiles, including high, high-middle, middle, low-middle and low (11). The 95% uncertainty inter-

vals (UIs) for all estimates in the GBD Study were applied using the DisMod-MR 2.1 tool. The RA-associated DALYs were calculated as the sum of years of life lost due to disability and the years of life lived with disability.

Statistical analysis

The ASR and estimated annual percentage change (EAPC) were used to quantify the RA incidence trends. The ASR (per 100,000 population) was calculated using the sum of the products of the age-specific rates [α_i : the age class, and the number of persons (or weight) (w_i) in the identical age subgroup i of the selected reference standard population] (13).

$$ASR = \frac{\sum_{i=1}^A \alpha_i w_i}{\sum_{i=1}^A \alpha_i} \times 100,000$$

Moreover, trends in ASR may serve as suitable substitutes for reflecting the alterations in human disease patterns and risk factors. The concept of EAPC was introduced to describe the trends in ASR within a specified time interval, as it is assumed that the natural logarithm of ASR corresponds with time. The following formula was used to determine the EAPCs in the ASRs of RA within a specific time frame (14):

$$Y = \alpha + \beta X + \varepsilon$$

[Y, ln (ASR); X, calendar year; ε , error term; β , positive or negative age-standardised rate trend]

$$EAPC = 100 \times (\exp(\beta) - 1)$$

The 95% confidence interval (CI) can also be obtained from the linear regression model. When the EAPC and CI lower boundary are both >0 , the ASR will present an increasing trend. Conversely, when the EAPC and CI upper boundary are both <0 , the ASR will display a downward trend. All statistical analyses were carried out using R software (v. 4.2.1; the R Foundation for Statistical Computing; Vienna, Austria). $p < 0.05$ was considered to indicate a statistically significant difference.

Results

Analysis of changes in RA incidence

- Global burden

The global incidence rate of RA in-

creased from 567,462.89 (95% UI, 519,417.45–621,414.74) to 1,074,390.80 (95% UI, 975,501.75–1,179,332.46) with an ASR of 13/100,000 patients (95% UI, 11.83–14.27) between 1990 and 2019 (Table I). The EAPC was 0.30% (95% CI, 0.26–0.34) from 1990 to 2019, which increased by 0.89% (95% CI, 0.86–0.93). The ASR of RA increased in both males and females (male EAPC, 0.30%; 95% CI, 0.28–0.33; female EAPC, 0.28%; 95% CI, 0.23–0.33). However, the ASR of RA was markedly increased in females compared with males from 1990 to 2019, as demonstrated by the female:male ratio of 2.32 (Table I). Notably, the number of RA cases increased in all SDI quintiles during the study period. The highest ASR of RA was detected in the high-SDI group (17.13 per 100,000; 95% UI, 15.77–18.61), followed by the low-middle SDI group (15.31 per 100,000; 95% UI, 13.9–16.84). The high-middle SDI group demonstrated the lowest ASR (11.24 per 100,000; 95% UI, 10.24–12.38).

- Regional and national level

At the regional level, the incidence rates and ASR of RA increased in all regions between 1990 and 2019. The largest increase in ASR of RA in 2019 was observed in the high-income North America group (21.46 per 100,000; 95% UI, 20.02–23.09), followed by Central Latin America (21.12 per 100,000; 95% UI, 19.29–23.07) and Australasia (20.89 per 100,000; 95% UI, 18.75–23.34). On the other hand, the lowest increase in ASR in 2019 was observed in Oceania, followed by Western Sub-Saharan Africa and Southeast Asia. From 1990 to 2019, the largest increase in ASR of RA was observed in Andean Latin America (EAPC, 1.39%; 95% CI, 1.32–1.45), followed by Southern Latin America (EAPC, 1.01%; 95% CI, 0.92–1.1; Table I).

The ASR of RA varied considerably worldwide, with the highest ASR observed in Ireland (30.03 per 100,000; 95% UI, 26.97–33.31), followed by Finland and Kazakhstan. Moreover, the lowest ASR of RA in 2019 was in Kiribati (3.47 per 100,000; 95% UI, 2.96–

4.1), followed by Yemen and Saudi Papua New Guinea (Fig. 2A). The most pronounced increase in ASR of RA from 1990 to 2019 was observed in Qatar (895.15%; 95% CI, 826.12–969.24%), followed by United Arab Emirates and Bahrain (Fig. 1B). The largest increase in ASR of RA was observed in Equatorial Guinea (EAPC, 1.78; 95% CI, 1.60–1.96), followed by Bhutan and Peru (Fig. 2C). The global EAPCs in ASRs of RA in 204 countries and territories are displayed in Supplementary Table S1.

Analysis of changes in

DALYs associated with RA

The results of the present study demonstrated that DALYs associated with RA increased by 96.23% from 1,662,621.95 (95% UI, 1,273,128.91–2,077,289.55) to 3,262,589.14 (95% UI, 2,510,208.35–4,091,554.9) between 1990 and 2019 (Table II), with an age-standardised DALY rate of 39.57 (95% UI, 30.51–49.53). In addition, the age-standardised DALY rate was higher in females than in males, as demonstrated by the female:male ratio of 2.14.

The results of the present study demonstrated that the total DALYs increased in all five SDI regions, with the highest increase in the low-middle region and the lowest increase in the high-middle region in 2019. From 1990 to 2019, the age-standardised DALYs associated with RA increased in all SDI regions except the high region, with an EAPC of -0.12% (95% CI, -0.15 to -0.09). The highest increase occurred in the low-middle SDI regions, where the EAPC was greatest (0.41%; 95% CI, 0.38–0.44). The highest age-standardised DALYs associated with RA were observed in Central Latin America (68.69 per 100,000; 95% UI, 52.71–86.7), followed by Southern Sub-Saharan Africa (56.76 per 100,000; 95% UI, 43.29–71.95) and high-income North America (53.53 per 100,000; 95% UI, 39.82–68.25) in 2019. Among the 21 GBD regions, the age-standardised DALYs increased in 13 regions and decreased in 9 GBD regions from 1990 to 2019. During this period, the age-standardised DALYs increased at the highest rate in Andean Latin America (EAPC, 0.94%; 95% CI, 0.83–1.04), followed by West-

Table I. Incidence of RA in 1990 and 2019 for both sexes and all locations, with EAPC from 1990 to 2019.

Location	1990			2019			1990-2019	
	Count (95%UI)	ASR per 100,000 No. (95%UI)	F/M	Counts (95%UI)	ASR per 100,000 No. (95%UI)	F/M	Change in No. (95%UI)	EAPC No. (95%UI)
Global	567,462.89 (519,417.45 to 621,414.74)	12.21 (11.13 to 13.38)	2.32	1,074,390.80 (975,501.75 to 1,179,332.46)	13.00 (11.83 to 14.27)	2.25	0.89% (0.86 to 0.93)	0.30% (0.26 to 0.34)
Sex								
Male	171,151.72 (155,988.16 to 188,597.53)	7.59 (6.9 to 8.34)	NA	330,460.59 (298,856.18 to 364,426.1)	8.13 (7.38 to 8.94)	NA	0.93% (0.89 to 0.97)	0.30% (0.28 to 0.33)
Female	396,311.17 (362,913.15 to 432,831.42)	16.79 (15.35 to 18.34)	NA	743,930.21 (678,043.92 to 817,225.02)	17.8 (16.22 to 19.52)	NA	0.88% (0.84 to 0.92)	0.28% (0.23 to 0.33)
Sociodemographic index								
High	149,343.70 (138,368.15 to 161,539.61)	15.95 (14.73 to 17.25)	2.64	232,587.21 (214,481.50 to 252,314.67)	17.13 (15.77 to 18.61)	2.41	0.56% (0.53 to 0.58)	0.38% (0.32 to 0.45)
High-middle	118,140.58 (107,392.53 to 130,450.79)	10.17 (9.26 to 11.23)	2.65	199,083.82 (179,889.11 to 219,047.46)	11.24 (10.24 to 12.38)	2.60	0.68% (0.64 to 0.73)	0.45% (0.4 to 0.51)
Middle	152,154.4 (137,556.6 to 168,805.91)	10.65 (9.63 to 11.76)	2.31	305,363 (275,478.85 to 337,878.17)	11.48 (10.41 to 12.69)	2.34	0.96% (0.89 to 1.02)	0.31% (0.27 to 0.35)
Low-middle	109,205.61 (99,110.57 to 119,978.03)	13.89 (12.63 to 15.29)	2.01	242,444.25 (219,998.63 to 266,778.47)	15.31 (13.9 to 16.84)	2.11	1.21% (1.17 to 1.25)	0.36% (0.34 to 0.38)
Low	38,402.61 (34,586.69 to 42,429.4)	12.01 (10.85 to 13.21)	1.48	94,502.79 (85,248.69 to 104,581.97)	13.27 (12.06 to 14.56)	1.52	1.34% (1.31 to 1.37)	0.41% (0.39 to 0.44)
Region								
Andean Latin America	3,037.54 (2,651.28 to 3,509.52)	10.01 (8.93 to 11.31)	2.84	9,218.46 (8,173.27 to 10,464.32)	14.74 (13.16 to 16.62)	2.94	2.03% (1.84 to 2.22)	1.39% (1.32 to 1.45)
Australasia	4,246.51 (3,843.15 to 4,702.71)	19.12 (17.25 to 21.24)	2.58	7,968.43 (7,148.8 to 8,850.94)	20.89 (18.75 to 23.34)	2.48	0.88% (0.76 to 1.01)	0.43% (0.32 to 0.55)
Caribbean	2,922.31 (2,560.18 to 3,361.07)	8.84 (7.78 to 10.03)	2.92	5,322.72 (4,719.72 to 6,013.78)	10.77 (9.55 to 12.17)	2.86	0.82% (0.72 to 0.93)	0.72% (0.67 to 0.77)
Central Asia	7,949.96 (7,202.58 to 8,839.41)	13.57 (12.47 to 14.89)	2.48	1,6171.95 (1,4695.17 to 1,7910.49)	17.33 (15.91 to 18.97)	2.34	1.03% (0.94 to 1.12)	1.00% (0.9 to 1.09)
Central Europe	14,738.49 (13,204.34 to 16,365.9)	10.82 (9.73 to 11.99)	2.61	16,227.94 (14,513.11 to 18,043.97)	11.44 (10.2 to 12.72)	2.50	0.10% (0.08 to 0.13)	0.35% (0.26 to 0.44)
Central Latin America	24,316 (22,122.96 to 26,694.18)	20.35 (18.54 to 22.23)	3.09	53,797.19 (49,153.46 to 58,879.03)	21.12 (19.29 to 23.07)	2.81	1.21% (1.15 to 1.28)	0.08% (0.05 to 0.11)
Central Sub-Saharan Africa	3,221.25 (2,855.72 to 3,680.98)	9.18 (8.12 to 10.32)	1.53	9,346.93 (8,255.18 to 10,701.82)	10.57 (9.39 to 11.92)	1.48	1.9% (1.8 to 2)	0.57% (0.51 to 0.62)
East Asia	129,318.67 (116,794.38 to 143,092.36)	11.41 (10.31 to 12.65)	2.42	229,076.27 (204,355.58 to 254,751.08)	11.68 (10.56 to 12.89)	2.49	0.77% (0.69 to 0.86)	0.21% (0.12 to 0.3)
Eastern Europe	17,426.23 (15,654 to 19,402.48)	7.19 (6.45 to 8)	3.19	17,769.46 (15,895.58 to 19,888.1)	7.61 (6.83 to 8.47)	3.13	0.02% (0 to 0.04)	0.24% (0.23 to 0.25)
Eastern Sub-Saharan Africa	15,629.44 (14,046.4 to 17,360.76)	15.05 (13.6 to 16.61)	0.93	41,084.97 (36,922.21 to 45,823.8)	17.02 (15.4 to 18.77)	0.91	1.63% (1.58 to 1.68)	0.52% (0.48 to 0.56)
High-income Asia Pacific	29,395.87 (26,394.61 to 32,482.59)	14.5 (13.05 to 15.99)	2.55	37,154.58 (33,401.66 to 41,233.27)	14.19 (12.75 to 15.65)	2.30	0.26% (0.23 to 0.3)	0.11% (0.02 to 0.2)
High-income North America	56,815.47 (53,011.07 to 61,122.91)	18.12 (16.98 to 19.4)	2.55	104,526.8 (96,438.64 to 113,262.61)	21.46 (20.02 to 23.09)	2.37	0.84% (0.8 to 0.88)	0.72% (0.66 to 0.79)
North Africa and Middle East	13,508.68 (11,860.33 to 15,455.18)	4.68 (4.15 to 5.30)	2.53	36,548.39 (32,078.13 to 41,602.94)	5.86 (5.18 to 6.63)	2.37	1.71% (1.56 to 1.84)	0.85% (0.82 to 0.88)
Oceania	218.17 (185.79 to 258.64)	3.69 (3.2 to 4.26)	2.04	498.5 (427.71 to 583.31)	3.92 (3.4 to 4.51)	2.13	1.28% (1.18 to 1.39)	0.13% (0.1 to 0.17)
South Asia	121,146.99 (109,681.52 to 133,792.19)	16.66 (15.08 to 18.36)	2.02	290,965.5 (262,697.56 to 320,812.16)	18.09 (16.35 to 19.94)	2.22	1.4% (1.36 to 1.44)	0.29% (0.28 to 0.30)
Southeast Asia	20,114.81 (17,806.5 to 22,783.89)	5.05 (4.47 to 5.68)	2.02	40,268.74 (35,540.55 to 45,593.86)	5.54 (4.92 to 6.24)	2.04	1.00% (0.91 to 1.1)	0.42% (0.38 to 0.46)

Location	1990			2019			1990-2019	
	Count (95%UI)	ASR per 100,000 No. (95%UI)	F/M	Counts (95%UI)	ASR per 100,000 No. (95%UI)	F/M	Change in No. (95%UI)	EAPC No. (95%UI)
Southern Latin America	5,214.41 (4,662.63 to 5,860.93)	10.93 (9.78 to 12.24)	3.09	10,666.62 (9,723.92 to 11,790.86)	14.51 (13.16 to 16.09)	3.46	1.05% (0.95 to 1.16)	1.01% (0.92 to 1.1)
Southern Sub-Saharan Africa	7,288.52 (6,575.61 to 8,103.12)	17.51 (15.69 to 19.48)	1.48	13,131.76 (11,765.55 to 14,690.76)	17.16 (15.35 to 19.11)	1.32	0.80% (0.75 to 0.85)	0.03% (-0.01 to 0.08)
Tropical Latin America	16,894.12 (15,152.05 to 18,947.69)	11.25 (10.07 to 12.59)	2.43	28,859.54 (25,679.92 to 32,359.69)	12.00 (10.74 to 13.41)	2.36	0.71% (0.64 to 0.78)	0.23% (0.2 to 0.25)
Western Europe	69,384.65 (63,394.9 to 75,649.88)	14.94 (13.64 to 16.35)	2.75	92,644.46 (84,750.59 to 101,324.82)	15.76 (14.35 to 17.32)	2.51	0.34% (0.3 to 0.36)	0.28% (0.22 to 0.35)
Western Sub-Saharan Africa	4,674.8 (4,135.33 to 5,319.65)	3.90 (3.45 to 4.4)	1.15	13,141.57 (11,576.75 to 14,995.65)	4.63 (4.09 to 5.23)	1.25	1.81% (1.75 to 1.86)	0.54% (0.49 to 0.59)

ASR: age-standardised rate; F/M: Female counts/ Male counts ratio; EAPC: estimated annual percentage change; CI: confidence interval; NA: not applicable; UI: uncertainty interval.

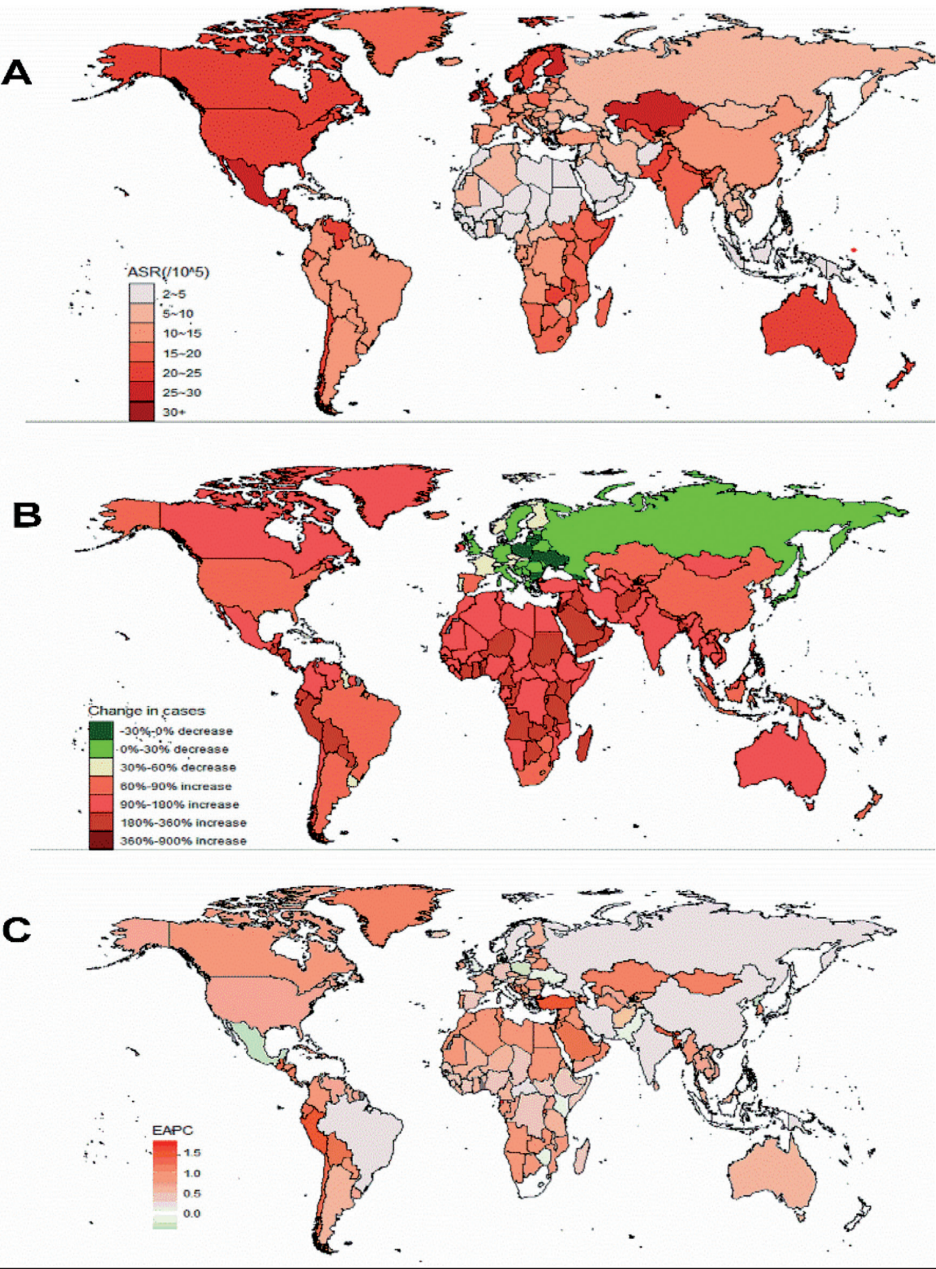


Fig. 1. The global disease burden of RA for both sexes in 204 countries and territories.
A: The ASR of RA in 2019.
B: The relative change in incidence cases of RA between 1990 and 2019.
C: The EAPC of RA ASR from 1990 to 2019.
ASR: age-standardised rate;
EAPC: estimated annual percentage change.

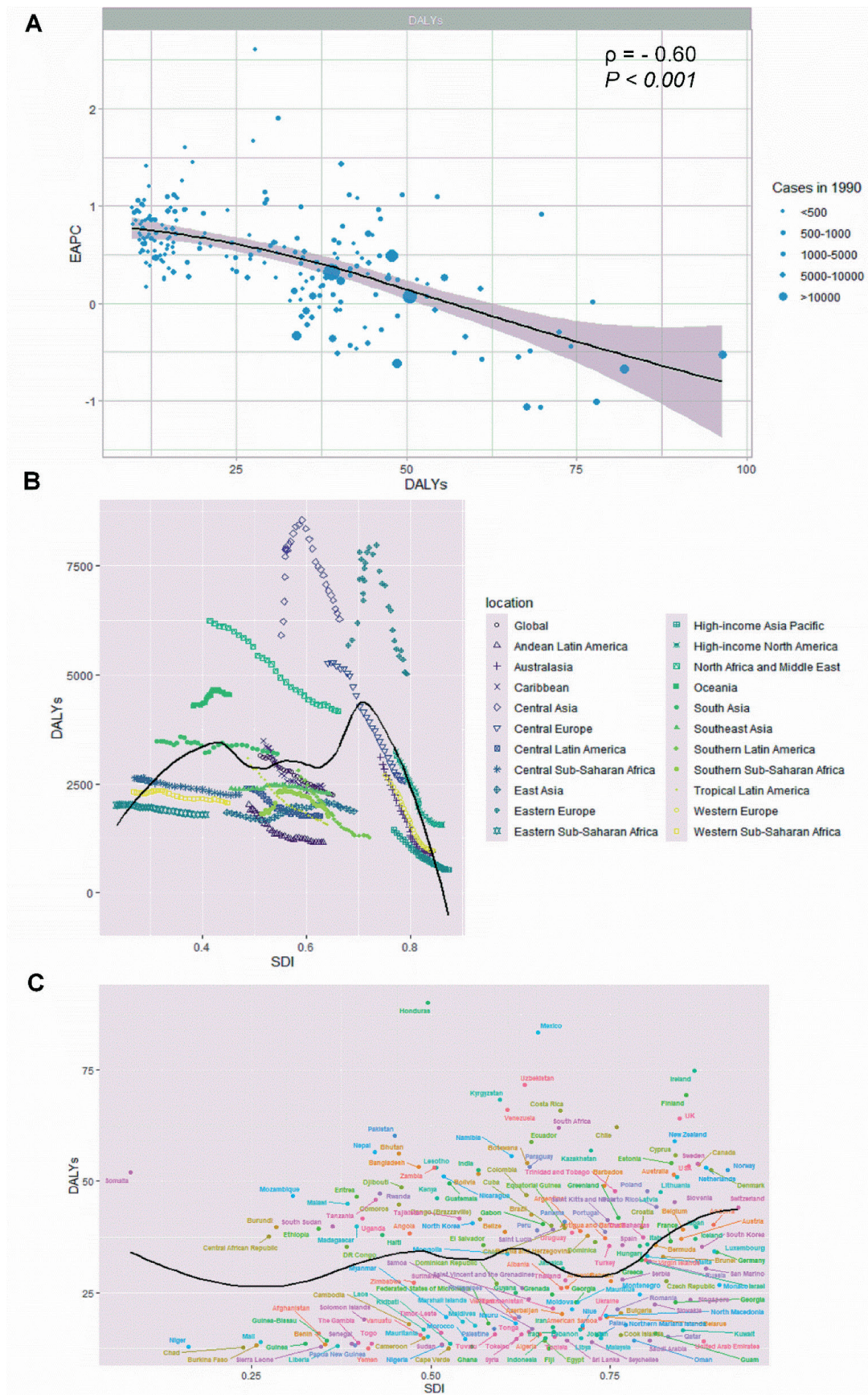


Fig. 2. Correlation analyses of EAPC- age-standardised DALYs rate per 100,000 in 1990 (A) and age-standardised DALYs rate per 100,000-socio-demographic index (SDI) for 21 regions from 1990 to 2019 (B) and 204 countries or territories in 2019 (C).

Table II. The DALYs of RA in 1990 and 2019 and its temporal trends.

Location	1990		2019		1990-2019	
	Count (95%UI)	Age-standardised DALY rate per 100,000 no. (95%UI)	Counts (95%UI)	Age-standardised DALY rate per 100,000 no. (95%UI)	Change in no. (95%UI)	EAPC no. (95%UI)
Global	1,662,621.95 (1,273,128.91 to 2,077,289.55)	39.12 (30.13 to 48.56)	3,262,589.14 (2,510,208.35 to 4,091,554.9)	39.57 (30.51 to 49.53)	0.96% (0.87 to 1.04)	0.12% (0.08 to 0.17)
sex						
Male	493,996.34 (384,815.18 to 616,199.04)	24.67 (19.47 to 30.57)	980,812.84 (759,988.78 to 1,234,948.74)	24.94 (19.42 to 31.31)	0.99% (0.89 to 1.08)	0.16% (0.1 to 0.22)
Female	1,168,625.6 (875,452.91 to 1,464,387.92)	52.37 (39.43 to 65.39)	2,281,776.3 (1,727,389.39 to 2,875,227.64)	53.26 (40.2 to 67.08)	0.95% (0.82 to 1.07)	0.12% (0.08 to 0.16)
Sociodemographic index						
High	473,819.78 (362,070.5 to 592,072.83)	47.62 (36.29 to 59.68)	705,955.96 (525,042.85 to 897,160.63)	45.02 (33.28 to 57.74)	0.49% (0.42 to 0.57)	0.12% (-0.15 to -0.09)
High-middle	380,320.15 (287,140.56 to 480,211.74)	34.02 (25.74 to 42.78)	675,069.15 (508,138.3 to 859,496.72)	35.01 (26.33 to 44.52)	0.78% (0.68 to 0.85)	0.18% (0.13 to 0.24)
Middle	428,690.47 (324,833.31 to 538,480.37)	35.69 (27.56 to 44.59)	966,741.26 (743,565.39 to 1,219,446.23)	37.61 (29.11 to 47.14)	1.26% (1.1 to 1.37)	0.31% (0.22 to 0.39)
Low-middle	285,669.87 (220,749.26 to 354,753.92)	43.47 (34.07 to 53.54)	691,109.87 (535,276.39 to 858,365.36)	48.38 (37.95 to 59.54)	1.42% (1.25 to 1.6)	0.41% (0.38 to 0.44)
Low	93,460.15 (71,500.62 to 119,646.3)	35.2 (27.49 to 44.42)	222,421.67 (169,707.17 to 283,475.75)	38.07 (29.29 to 47.88)	1.38% (1.21 to 1.53)	0.29% (0.26 to 0.32)
Region						
Andean Latin America	8,741.49 (6,589.91 to 11,168.18)	35.29 (27.27 to 44.28)	27,408.69 (20,251.53 to 35,421.57)	46.17 (34.27 to 59.1)	2.14% (1.86 to 2.4)	0.94% (0.83 to 1.04)
Australasia	13,132.45 (9,994.69 to 16,617.98)	56.49 (42.91 to 71.42)	22,917.73 (17,018.69 to 29,415.15)	52.75 (38.71 to 68.08)	0.75% (0.58 to 0.9)	-0.15% (-0.19 to -0.11)
Caribbean	9,085.12 (67,12.81 to 11,603.54)	31.67 (23.54 to 40.11)	18,374.25 (13,531.12 to 23,558.83)	36.11 (26.56 to 46.29)	1.02% (0.88 to 1.17)	0.5% (0.48 to 0.51)
Central Asia	21,942 (15,915.32 to 28,051.29)	41.29 (30.03 to 52.86)	44,277.55 (32,408.38 to 56,973.54)	51.16 (37.6 to 65.3)	1.02% (0.86 to 1.2)	0.69% (0.61 to 0.77)
Central Europe	52,380.46 (39,189.66 to 66,220.61)	36.09 (26.96 to 45.67)	60,375.99 (44,838.93 to 77,458.21)	34.08 (25.02 to 44.13)	0.15% (0.07 to 0.26)	-0.11% (-0.18 to -0.03)
Central Latin America	71,407.03 (55,554.22 to 90,299.87)	72.37 (56.77 to 90.73)	169,127.81 (128,800.2 to 213,662.79)	68.69 (52.71 to 86.7)	1.37% (1.21 to 1.5)	-0.17% (-0.22 to -0.12)
Central Sub-Saharan Africa	10,266.91 (7,616.45 to 13,160.29)	37.13 (27.5 to 47.02)	24,605.82 (18,091.55 to 31,842.14)	36.53 (26.88 to 47.19)	1.4% (1.02 to 1.76)	-0.11% (-0.17 to -0.06)
East Asia	383,314.75 (291,899.28 to 488,149.33)	38.92 (29.85 to 49.62)	798,558.78 (608,293.25 to 1,007,875.37)	39.3 (30.11 to 49.71)	1.08% (0.88 to 1.23)	0.31% (0.14 to 0.48)
Eastern Europe	77,750.48 (59,101.6 to 97,427.16)	28.97 (22.03 to 36.32)	85,413.3 (65,071.18 to 108,177.79)	29 (22.08 to 36.95)	0.1% (0.03 to 0.16)	-0.09% (-0.15 to -0.04)
Eastern Sub-Saharan Africa	36,674.86 (27,040.95 to 48,347.59)	42.38 (31.27 to 56.17)	84,024.06 (62,307.58 to 110,618.58)	43.79 (32.22 to 57.93)	1.29% (1.1 to 1.44)	0.14% (0.11 to 0.16)
High-income Asia Pacific	94,354.04 (70,822.8 to 118,762.43)	46.61 (35.04 to 58.57)	129,841.47 (96,933.84 to 166,909.33)	38.31 (28.14 to 49.8)	0.38% (0.27 to 0.53)	-0.63% (-0.71 to -0.56)
High-income North America	157,761.95 (119,062.61 to 198,712.72)	47.73 (35.95 to 60.34)	288,983.04 (217,344.68 to 36,7042.41)	53.53 (39.82 to 68.25)	0.83% (0.78 to 0.88)	0.47% (0.38 to 0.56)
North Africa and Middle East	36,482.99 (26,371 to 47,676.6)	16.05 (11.65 to 20.91)	103,572.32 (74,241.6 to 136,654.8)	19.04 (13.91 to 24.87)	1.84% (1.58 to 2.05)	0.66% (0.62 to 0.69)
Oceania	557.48 (390.29 to 746.67)	12.36 (8.8 to 16.43)	14,13.62 (1,005.1 to 1,906.47)	13.77 (9.89 to 18.4)	1.54% (1.31 to 1.82)	0.37% (0.34 to 0.39)
South Asia	294,203.31 (225,065.8 to 367,931.59)	49.99 (39.16 to 61.89)	770,841.33 (597,981.92 to 966,528.98)	53.36 (41.81 to 65.99)	1.62% (1.41 to 1.87)	0.18% (0.14 to 0.21)
Southeast Asia	53,297.3 (39,196.27 to 68,855.09)	16.17 (11.99 to 20.98)	125,279.28 (92,572.71 to 161,884.47)	18.48 (13.76 to 23.64)	1.35% (1.08 to 1.56)	0.54% (0.5 to 0.58)

Location	1990		2019		1990-2019	
	Count (95%UI)	Age-standardised DALY rate per 100,000 no. (95%UI)	Counts (95%UI)	Age-standardised DALY rate per 100,000 no. (95%UI)	Change in no. (95%UI)	EAPC no. (95%UI)
Southern Latin America	17,068.97 (12,873.48 to 21,575.21)	37.35 (27.96 to 47.1)	35,783.68 (26,772.28 to 45,755.86)	45.77 (34.05 to 58.57)	1.1% (0.95 to 1.26)	0.78% (0.73 to 0.84)
Southern Sub-Saharan Africa	22,777.72 (17,585.48 to 28,319.72)	66.91 (51.84 to 82.86)	37,444.82 (28,391.44 to 47,750.65)	56.76 (43.29 to 71.95)	0.64% (0.49 to 0.84)	-0.75% (-0.97 to -0.54)
Tropical Latin America	48,429.1 (35,404.19 to 62,343.25)	40.03 (29.04 to 51.63)	106,837.45 (78,061.45 to 137,943.15)	42.82 (31.44 to 55.05)	1.21% (1.07 to 1.31)	0.28% (0.26 to 0.3)
Western Europe	242,169.01 (184,513.5 to 306,336.7)	46.37 (35.1 to 58.69)	296,733.89 (219,394.32 to 379,185.51)	42.22 (30.83 to 54.67)	0.23% (0.15 to 0.31)	-0.27% (-0.3 to -0.24)
Western Sub-Saharan Africa	10,824.53 (7,957.74 to 14,062.99)	10.56 (7.97 to 13.59)	30,774.26 (22,062.85 to 40,005.83)	13.29 (9.8 to 17.09)	1.84% (1.53 to 2.18)	0.8% (0.77 to 0.83)

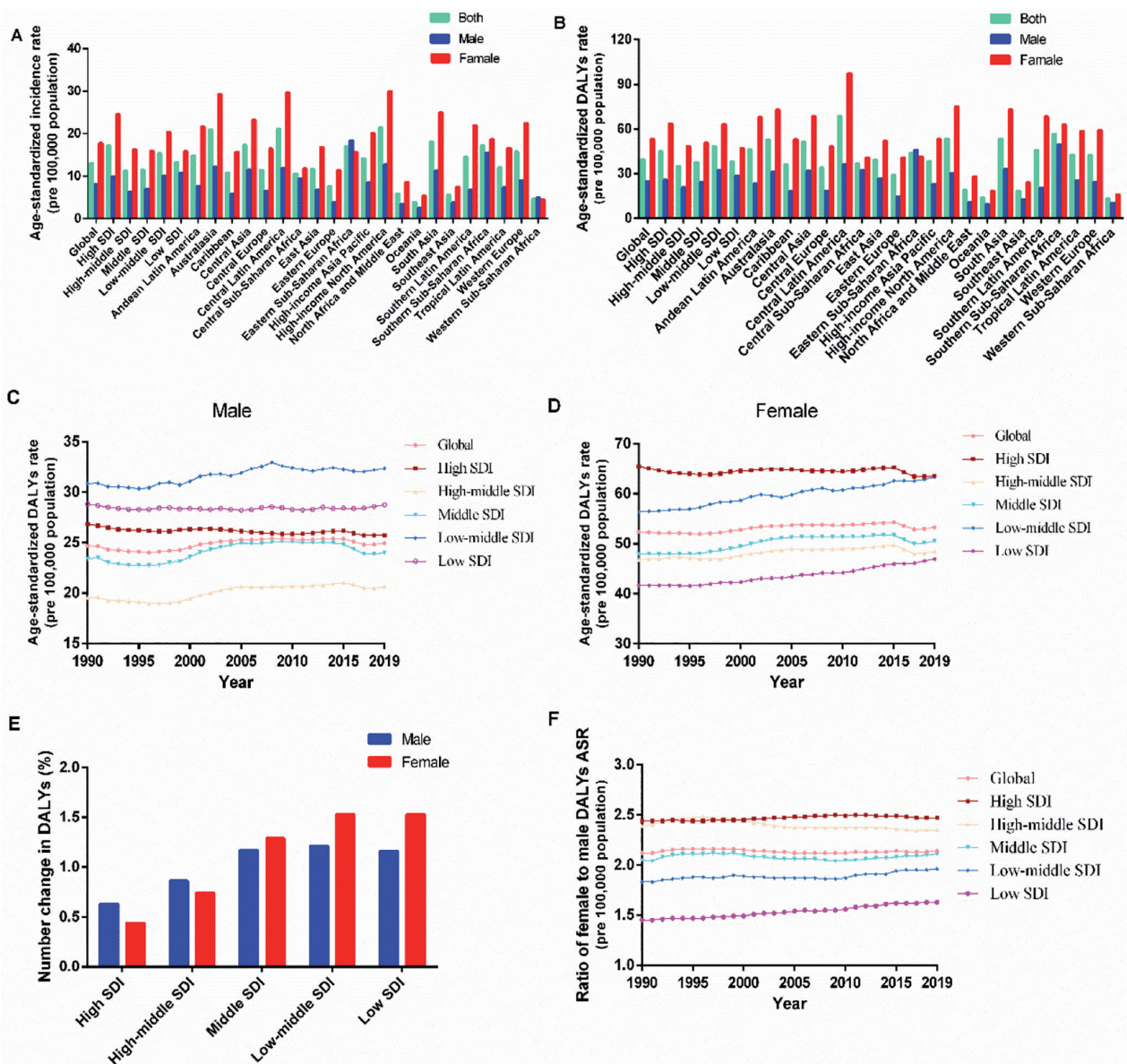


Fig. 3. Sex differences and trends in age-standardised DALYs rate of RA in different regions. A-B: The age-standardised incidence and DALYs Rate in males and females globally, in territories with low to high SDIs and in 21 GBD regions in 2019. The age-standardised DALYs rate of globally and territories with low to high SDIs in males (C) and females (D) between 1990 and 2019. E: The number changes in DALYs in males and females from 1990 to 2019. F: Female to male ratios of age-standardised DALYs rate globally and in all SDIs between 1990 and 2019.

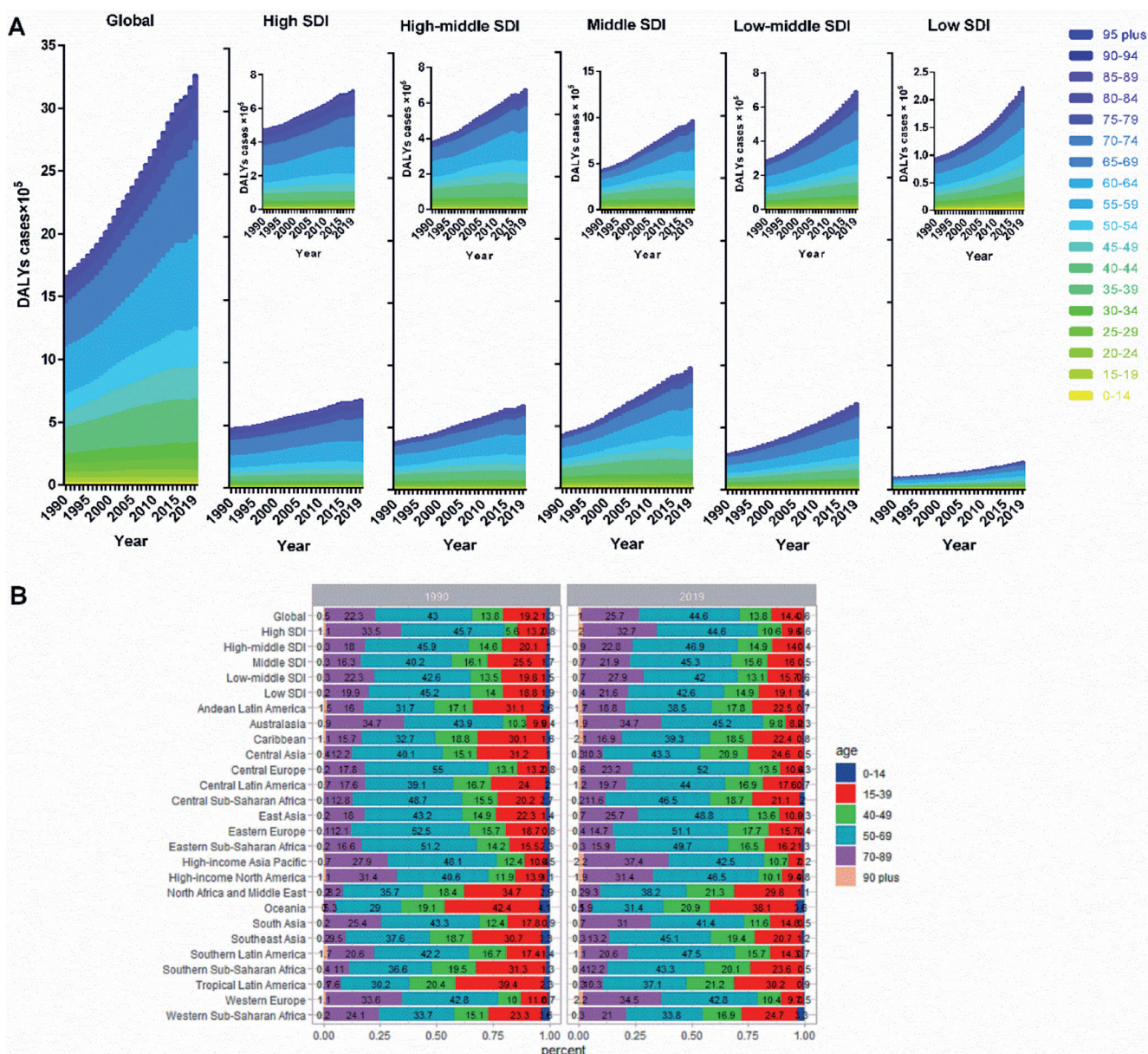


Fig. 4. DALYs cases of RA by age groups in different regions.

A: The contribution of each age group to total DALYs cases globally and in SDI regions from 1990 to 2019.

B: The 6 age groups as percentages of total DALYs globally, in territories with low to high SDIs and in 21 GBD regions in 1990 and 2019.

ern Sub-Saharan Africa and Southern Latin America. The age-standardised DALYs decreased at the highest rate in Southern Sub-Saharan Africa (EAPC, -0.75%; 95% CI, -0.97 to -0.54), high-income Asia Pacific (EAPC, -0.63%; 95% CI, -0.71 to -0.56) and Western Europe (EAPC, -0.27%; 95% CI, -0.3 to -0.24; Table II).

A significant negative association occurred between EAPCs and the age-standardised DALY rate per 100,000 ($\rho = -0.60$; $p < 0.001$), suggesting that RA cases increased more slowly in countries with high DALYs, than in coun-

tries with low DALYs (Fig. 2A). At the regional level, the age-standardised DALYs and the SDI demonstrated a non-linear association (Fig. 2B). The highest age-standardised DALYs were observed at an SDI of ~ 0.72 . The results of the present study demonstrated that age-standardised DALYs increased and decreased intermittently as SDI improved between 1990 and 2019. The results of the present study demonstrated a non-linear association between the age-standardised DALYs associated with RA and SDI for 204 countries and territories in 2019. The age-standard-

ised DALY rate was higher than the expected level for a number of the countries/territories, including Honduras, Mexico and Ireland (Fig. 2C).

Trends associated with age and sex

Females exhibited a higher age-standardised incidence rate and DALYs than males at both the global and regional levels in 2019 (Fig. 3A-B). The highest age-standardised DALYs in males (49.31 per 100,000) and females (97.37 per 100,000) were observed in Southern Sub-Saharan Africa and Central Latin America, while the lowest

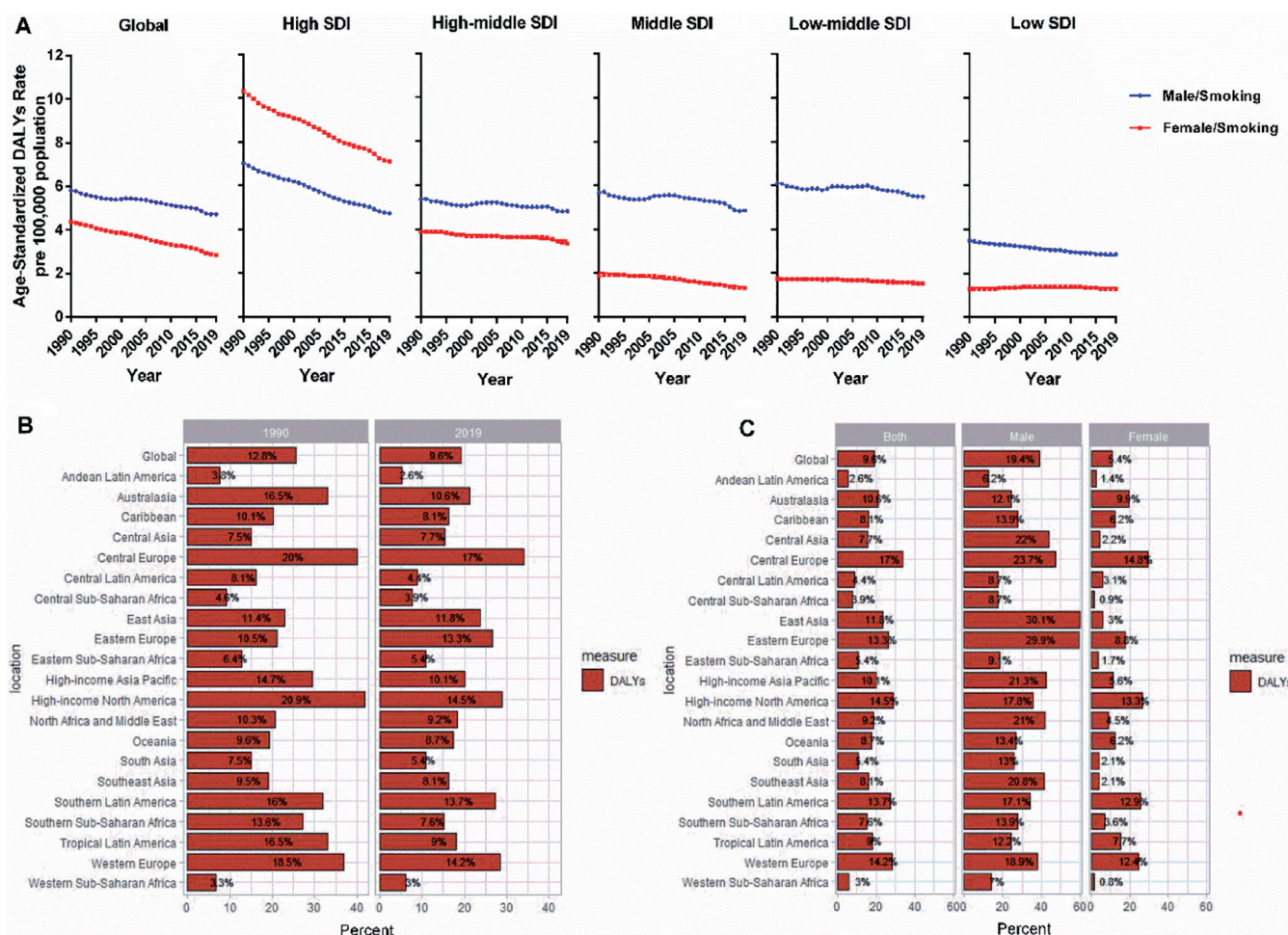


Fig. 5. Smoking risk factor contributing to RA-related DALYs.

A: The DALYs attributable to smoking risk factor by sex in SDI regions from 1990 to 2019. **B:** The percentage of DALYs by smoking risk factor in different regions in 1990 and 2019. **C:** The percentage of DALYs by smoking risk factor in different sex in 2019.

DALYs in both sexes were observed in Western Sub-Saharan Africa (males, 10.31; females, 16.04; Fig. 3B). In males, the increase was mainly attributed to improvements in low-middle SDI regions, while the increase in females was mainly attributed to improvements in low-middle and low SDI regions from 1990 to 2019 (Fig. 3C and 3D). Moreover, during the study period, the numerical change in DALYs in females increased more significantly than in males (Fig. 3E). In SDI regions, the ratios of female:male of age-standardised DALYs were maintained between 1.83 and 2.50; however, in the low-SDI region, the ratio reduced to ~1.80 between 1990 and 2019 (Fig. 3F). Globally, age-standardised DALYs demonstrated an increasing trend with age, peaking in the 50–69-year age group. The 65–69-year age group exhibited the highest absolute number

of DALYs in all SDI regions in 2019. However, from 1990 to 2019, the increase in DALYs in all age groups was more rapid in lower-middle SDI regions than in all other regions. At the end of the study period, the middle-SDI region exhibited the highest DALYs compared with those in all other regions (Fig. 4A). The population was divided into six age groups: 0–14, 15–39, 40–49, 50–69, 70–89 and 90+ years. At the regional level, the largest increase in DALYs occurred in the 50–69-year group, except in Oceania and Tropical Latin America, from 1990 to 2019 (Fig. 4B).

Risk factors contributing to DALYs

The burden of RA is largely attributed to smoking. Smoking was the predominant contributor to RA-associated DALYs for males worldwide; however, this trend decreased between 1990 and 2019. In addition, during the study pe-

riod, the age-standardised DALYs for females was higher than for males in high SDI regions, compared with other regions (Fig. 5A). At the geographical level, Central Europe and high-income North America regions demonstrated the highest number of smoking-related DALYs from 1990 to 2019, while Tropical Latin America exhibited the highest decrease by 2019 (Fig. 5B). Compared with females who smoked, the percentage of DALYs was higher in males in all regions, particularly in East Asia and Eastern Europe in 2019 (Fig. 4C).

Discussion

The comprehensive analysis of the present study provides the current estimates of global, regional and national burdens of RA, and summarises the incidence rates and DALYs associated with RA from 1990 to 2019. The data spanned from 204 countries and terri-

tories. The results of the present study demonstrated that the incidence rates of RA increased from 567,462.89 in 1990 to 1,074,390.80 in 2019. The results of the present study also suggested that the number of RA cases increased in all SDI regions, while middle SDI regions exhibited the highest incidence rates of RA, with most cases occurring during the study period. The largest increase in ASR was in high-income North America. DALYs associated with RA increased by 96.23% from 1,662,621.95 to 3,262,589.14 between 1990 and 2019. For SDI regions, the total DALYs increased in all five SDI regions, with the highest increase in the low-middle region and the lowest increase in the high-middle region in 2019. Notably, the age-standardised incidence rate and DALYs were always higher in females than in males.

Previous studies analysed the global burden of RA using the GBD databases of 2015 and 2017 (7, 10); however, the results cannot be directly compared to those of the present study, due to different methods used and different data sources. For example, the GBD 2017 study demonstrated that the percentage change in age-standardised DALYs between 1990 and 2017 was -3.6%, but the percentage change in age-standardised DALYs increased by 0.12% from 1990 to 2019, according to the results of the GBD 2019 study. This difference may, in part, be explained by method optimisation and updates in the GBD 2019 study. In addition, the previous study did not report the association between DALYs and EAPCs, or female:male ratios of age-standardised DALYs.

The results of the present study demonstrated that the incidence and DALYs of RA increased with the temporal trend from 1990 to 2019, and these were higher than the GBD 2017 estimates. Similar results were obtained in previous studies (10) that predicted that RA may be one of the most common causes of YLDs worldwide, and that the prevalence would rise over time. The results of a previous study demonstrated that North America and the Eastern Mediterranean consistently demonstrate the highest rates of age-standardised incidence and DALYs (15) (16, 17). Moreo-

ver, the incidence rate and DALYs may differ within the same super-region. For example, Southern Sub-Saharan Africa, including Zambia, Mozambique and Madagascar, are among the regions with the highest incidence of RA, while North Africa and the Middle East, including Libya, Egypt and Sudan, are among the regions with the lowest incidence rates, globally. Therefore, further investigations into prevention measures, management and treatment of RA are required.

The present study predicted a negative correlation between the EAPC of DALYs and baseline DALYs in 1990. The age-standardised DALYs demonstrated a non-linear association with the SDI. The GBD 2019 data demonstrated that the association between the burden of RA and SDI is complex and non-linear. The global burden of RA is not limited to developed or less-developed countries, and differs hugely among regions with different SDIs, reflecting large discrepancies in medical facilities and healthcare.

As shown in the present study and in previous studies (6, 18, 19), females exhibit higher absolute incidence rates and DALYs than males at both global and regional levels. Low SDI and low-middle regions exhibited higher numerical changes in DALYs than other regions. Disease-associated knowledge of patients with RA was poor in low-SDI regions, which may be the main factor impacting the widespread occurrence of RA (20, 21). Although numerical changes in DALYs are lowest in males and females in the high-SDI region, numerical differences between males and females was highest in 2019. These differences may be explained by biological factors and behavioural risk factors, such as stress, obesity, infections and diet (22, 23). The results of previous observational studies demonstrated that smoking was associated with RA (4, 24, 25). The results of the present study demonstrated that the age-standardised DALYs decreased in females and males who smoked daily since 1990, globally. This decreasing trend was consistent with the results of the previous study (26). However, the age-standardised DALYs were higher in females than in

males in high-SDI regions. This indicates that females may possess a higher risk of smoke exposure than males in the high-SDI region, or males may possess an improved management of smoking. Therefore, an improved awareness of the impact of smoking is required in the high-SDI region.

Patients aged 50–69 years exhibited the highest number of DALYs. Globally, age-standardised DALYs increased with age, and this may be associated with advances in healthcare and an ageing population worldwide. Patients with RA with an increased age included a higher percentage of males, and there was high disease activity. These patients experienced complications, including cardiovascular disease, interstitial pneumonia and diabetes (27). The results of the present study demonstrated that the highest number of RA cases occurred in patients aged 50–69 years in the low-middle SDI region. Smoking-related DALYs demonstrated the lowest decrease in the low-middle SDI region from 1990 to 2019. Researchers now possess an improved understanding of the pathogenesis of RA, and an increasing number of therapeutics have been developed (28). The ultimate goal of RA treatment is to slow or inhibit disease progression. Development of novel medicines, particularly biological agents, and controlling risk factors, such as smoking, may aid in the management of this disease (28, 29).

To the best of our knowledge, the present study reported the latest data on the burden of RA at global, regional and national levels, and detected the impact of sex, age, SDI and associated risk factors. The present study systematically reviewed the latest GBD data to assess the incidence rates and DALYs of RA in various regions from 1990 to 2019. However, the present study exhibits certain limitations. Firstly, the reconstructed data may possess large discrepancies in terms of quality, comparability, accuracy and degrees of missing data in some countries, with sparse prior information, particularly in low-income countries. However, the robust estimation performed by the GBD study may alleviate this concern. In addition, there is a lack of data surround-

ing alternate attributions of risk factors associated with RA-related DALYs, such as hormones, stress, obesity, infections, gut bacteria and diet. Data was only available on smoking as a risk factor for RA; thus, further analyses into alternate risk factors are required in the future. Finally, the present analysis of the burden of RA does not include environmental factors, such as differences between urban and rural areas.

Conclusions

Globally, although there is variation between regions and nations in the incidence rates and DALYs associated with RA, the burden of RA continues in the majority of countries, particularly among females. This trend is expected to continue as ageing of the global population rises. Notably, smoking is the predominant contributor to RA-related DALYs in males. Therefore, an improved awareness of the impact of smoking may aid in improving early diagnosis and treatment strategies for RA, to reduce the global burden of RA.

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