Predictions of rheumatoid arthritis burden in 204 countries and territories by 2044: based on the Global Burden of Disease Study 2021

W. Zhang[1,2,3], D. Zhuang[4], H. Lu[5], Z. Lv[2], L. Huang[2], H. Du[2], J. Chang[2], M. Xiao[2], M. Chen[2], W. Ying[2], H. Lei[2], X. Li[1,2,]

[1]Department of Psychiatry, Chaohu Hospital of Anhui Medical University, Hefei, China; [2]Department of Medical Psychology, School of Mental Health and Psychological Science, Anhui Medical University, Hefei, China; [3]Department of Clinical Medical, First Clinical Medical College, Anhui Medical University, Hefei, China; [4]Suzhou Hospital of Anhui Medical University, Suzhou, China; [5]The Second Affiliated Hospital of Bengbu Medical University, Bengbu, China.

Abstract

Objective
We conducted a comprehensive analysis of the spatiotemporal dynamics of rheumatoid arthritis (RA), including age-standardised prevalence (ASPR), incidence (ASIR), and disability-adjusted life years (DALYs, ASDR), from 1990 to 2021, and projected trends through 2044 using data from the Global Burden of Disease (GBD) 2021 to inform and strengthen global prevention, control strategies, and public health policy for RA.

Methods
ASPR, ASIR, and ASDR estimates for 204 countries and territories (1990-2021) were retrieved from GBD 2021. We quantified temporal trends by the estimated annual percentage change (EAPC) and average annual percentage change (AAPC). We examined gender-age-specific differences in ASPR, ASIR, and ASDR and the relationships between RA-related DALYs and risk factors across strata. Moreover, we employed AutoRegressive Integrated Moving Average (ARIMA) and the Nordpred age-period-cohort model to forecast prevalence and incidence through 2044. All statistical analyses were performed in R 4.4.1 and Joinpoint Trend Analysis Software.

Results
Between 1990 and 2021, global ASPR and ASIR rose (AAPC: 0.44 and 0.40, respectively), while ASDR declined modestly (AAPC: -0.03). In 2021, Ireland exhibited the highest ASPR (529.08) and ASIR (35.08), whereas Mexico recorded the highest ASDR (87.45). Although higher sociodemographic index (SDI) regions bore a greater RA burden overall, lower SDI regions experienced more rapid increases. Across all metrics, women – particularly those aged ≥60 years – demonstrated higher rates than men. 'Smoking' emerged as a vital risk of DALYs across age groups, genders, and regions. Projections from Nordpred and ARIMA model indicate continued rapid growth in prevalence and incidence cases through 2044, with more gradual increases in ASPR and ASIR.

Conclusion
Global prevalence and incidence of RA are projected to rise further. Detailed knowledge of these trends and their drivers is essential to inform targeted interventions and mitigate the worldwide impact of RA.

Key words
global burden disease, rheumatoid arthritis, cross-sectional study, Nordpred, ARIMA, smoking

Wenhao Zhang, MD*
Dongmei Zhuang, MD*
Huan Lu, MD*
Ziyan Lv, MS
Limin Huang, MS
He Du, MS
Jin Chang, MS
Mengmeng Xiao, MS
Mingyu Chen, MS
Wenjie Ying, MS
Haoyang Lei, MS
Xiaoming Li, PhD

*Contributed equally.

Please address correspondence to:
Xiaoming Li
Department of Psychiatry,
Chaohu Hospital of Anhui
Medical University,
150 Meishan Road,
230032 Hefei (Anhui), China.
E-mail: psyxiaoming@126.com

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease marked by symmetric polyarthritis (1). Early manifestations often include joint pain, swelling and morning stiffness, initially affecting the small joints of the hands and feet before progressing to involve multiple synovial joints. Without prompt and effective treatment, RA can precipitate progressive joint destruction and deformity, ultimately resulting in substantial disability and a marked decline in quality of life (2, 3). In addition to articular damage, RA frequently presents with extra-articular complications – most notably involving the heart, lungs and kidneys – which are more common in patients with severe, high-activity disease (4, 5). Pulmonary involvement, reported in approximately 60% of individuals with RA, encompasses conditions such as pleural effusion and interstitial lung disease (ILD). And RA-associated ILD is a leading contributor to increased morbidity and mortality in this population (6, 7).

RA is a prevalent condition worldwide, affecting approximately 0.5–1% of adults and with a notably higher prevalence in women. The incidence in women is 2–3 times greater than that in men, and its prevalence increases with age, peaking between 60 and 70 years (8-10). Despite the availability of non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and biologic therapies, the global burden of RA continues to rise annually, which underscores the necessity of rigorous, large-scale epidemiological investigations to elucidate regional differences in RA prevalence and to guide targeted prevention and control strategies (11).

The Global Burden of Disease (GBD) 2021 study delivers the most comprehensive, up-to-date estimates of morbidity, mortality, and disease burden for 204 countries and territories (12). By synthesising data contributed by researchers, policymakers, clinicians, and local partners, GBD 2021 ensures high levels of accuracy and completeness. It integrates secondary sources and primary field studies to furnish robust evidence for comparing health outcomes, forecasting disease trends, and optimising policy decisions and resource allocation. The GBD conceptual framework, analytical methods, and detailed protocols have been published elsewhere, and all data visualisation and retrieval tools are accessible at http://ghdx.healthdata.org/gbd-results-tool without permission.

We systematically assessed the spatiotemporal trends in RA prevalence, incidence, and disability-adjusted life years (DALYs) across 204 countries and territories from 1990 to 2021, exploring their associations with the sociodemographic index (SDI). We further examined sex-age-specific variations in these metrics and quantified the influence of key risk factors on RA-related DALYs across demographic and regional subgroups. To project future trajectories, we applied the AutoRegressive Integrated Moving Average (ARIMA) model and the Nordpred age-period-cohort (APC) framework to forecast RA incidence and prevalence through 2044. By filling critical knowledge gaps regarding cross-country burden disparities, SDI correlations, and risk-factor impacts, our findings provide essential evidence to inform ongoing epidemiological surveillance and public health policymaking (13).

Methods and materials

Case definition and data collection

According to GBD 2021, RA is defined as a systemic autoimmune disorder marked by joint pain, swelling, and deformity, often accompanied by systemic manifestations. Although RA can involve internal organs, extra-articular manifestations are not yet quantified within the GBD framework. As the reference diagnostic standard, GBD 2021 applied the 1987 American College of Rheumatology (ACR) classification criteria: RA was diagnosed when at least four of seven criteria – such as morning stiffness, arthritis in three or more joint areas, hand-joint involvement, and symmetrical arthritis – persisted for over six weeks (14). Data sources using alternative diagnostic definitions, such as those under the 2010 ACR/EULAR criteria, where individuals scoring ≥6 points were classified as RA cases

(Supplementary Table S1), were harmonised using the Meta-Regression-Bayesian Regularized Trimmed (MR-BRT) method (15).

We extracted GBD 2021 estimates of RA prevalence, incidence, and DALYs, along with their 95% uncertainty intervals (UIs) (accessible at http://ghdx. healthdata.org/gbd-results-tool without permission), which encompass all age groups across 204 countries and territories from 1990 to 2021. A comprehensive account of data collection procedures and adjustments for potential confounders is provided in the online Supplementary file. Detailed methodological descriptions appear in the official GBD 2021 Methods Appendices (https://www.healthdata.org/gbd/methods-appendices-2021) (12).

Social development index
We analysed the relationship between SDI and age-standardised prevalence (ASPR), incidence (ASIR), and DALYs (ASDR) rate in various regions. The SDI is a composite measure of socioeconomic conditions that assesses health outcomes in a region, with higher values indicating higher educational levels, greater per capita income, and lower fertility rates categorised as low, lower-middle, middle, high-middle, and high.

Non-fatal disease modelling
The methodology for non-fatal disease modelling in GBD 2021 has been comprehensively described in previous studies (16). GBD 2021 employed DisMod-MR 2.1, a Bayesian, geospatial disease-modelling tool that integrates epidemiological parameters, associations, and spatial covariates, to estimate RA incidence, prevalence, and DALYs (17). All available high-quality inputs (incidence, prevalence, and DALYs) were synthesised to characterise the non-fatal burden of RA.

DALYs combine years of life lost (YLLs) due to premature mortality and years lived with disability (YLDs) to quantify total health loss from disease onset to death (18). YLLs represent the years of life lost because of premature death from disease or injury, calculated as the difference between the expected life expectancy and actual age of death. YLDs reflect the years lived with disability due to disease or injury, considering the severity and duration of the disability to quantify its impact on the quality of life. The total DALYs are the sum of the YLLs and YLDs, providing a comprehensive measure of health loss from the onset of disease to death (see Suppl. Fig. S1). Further details of the modelling can be found in the Supplementary file.

Risk factors
The classification of risk factors and the methods for their attribution in GBD 2021 are detailed in the Supplementary Materials. We quantified the contribution of "smoking" to RA-related DALYs across 28 GBD super-regions and 20 five-year age bands (<5, 5–9, 10–14, …, 90–94, ≥95 years), stratified by sex. Our primary analyses focused on 14 age groups (30–34, 35–39, 40–44, ..., 90–94, and ≥95 years) for both males and females because smoking-related DALYs were negligible in populations under 30.

Statistical methods
- Age-standardised rate
In GBD 2021, the age-standardised rate (ASR) denotes the value of a health metric after adjustment for differences in age structure, using a uniform standard population. By neutralising the impact of demographic variation, ASRs enable valid comparisons of disease burden across countries, regions, and time periods, thereby furnishing critical evidence to inform public health policy decisions (19). The detailed computational formulas for ASR estimation are provided in Supplementary Figures 1 and 2. GBD 2021 applies the custom GBD standard population developed by the Institute for Health Metrics and Evaluation (IHME) as the W_i in the ASR calculation, which fixed reference population underpins all estimates in the database, serving as a consistent hypothetical framework across years. In epidemiological investigations, ASRs not only facilitate cross-population comparisons but also aid in elucidating disease-specific risk factors and temporal trends (20).

- Estimated annual percentage change
We utilised the estimated annual percentage change (EAPC) to describe the trends in the ASPR, ASIR and ASDR across 204 countries and territories worldwide, which helps researchers understand the dynamic shifts in the disease burden (21). EAPC is a widely adopted statistical measure used to quantify the annual trend of a specific indicator over a given period. It was estimated using a logarithmic linear regression (LLR) model to calculate the annual percentage change rate for the specified period, with 95% confidence intervals (CIs) determined by the standard error of the regression coefficient and a z-value of 1.96. The EAPC is particularly useful for long-term trend analysis, as it smoothens short-term fluctuations and provides a clearer depiction of the overall trend. In epidemiology and public health, especially within the GBD framework, the EAPC is widely applied to assess the dynamic trends of diseases, injuries, and risk factors (22). The EAPC and its 95% CI entirely below 0 denote a statistically significant decline; entirely above 0 signifies a significant rise, whereas inclusion of 0 within the CI indicates a stable trend. The detailed computation is illustrated in Supplementary Figure S2.

- Joinpoint regression analysis
We applied the Joinpoint regression analysis programme (https://surveillance.cancer.gov/joinpoint)) to delineate temporal trends in ASPR, ASIR and ASDR globally and across 56 GBD regions. The same approach was used to evaluate smoking-attributable ASDR for RA at global and regional levels. Joinpoint regression is a robust epidemiological tool that detects statistically significant inflection points in longitudinal data and quantifies changes in trend segments, thereby enabling precise characterisation of shifts in disease burden over time (23).

To comprehensively characterise long-term trends, we computed the average annual percentage change (AAPC) from 1990 to 2021. Statistically, the AAPCs and entire 95%CIs lie above 0 signifies a significant upward trend in disease burden. Conversely, values and
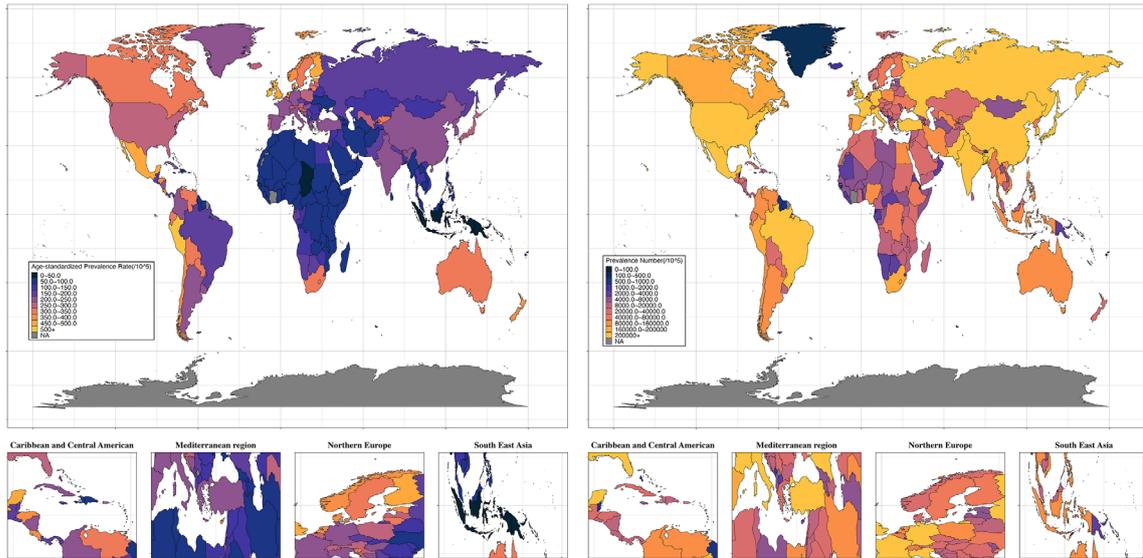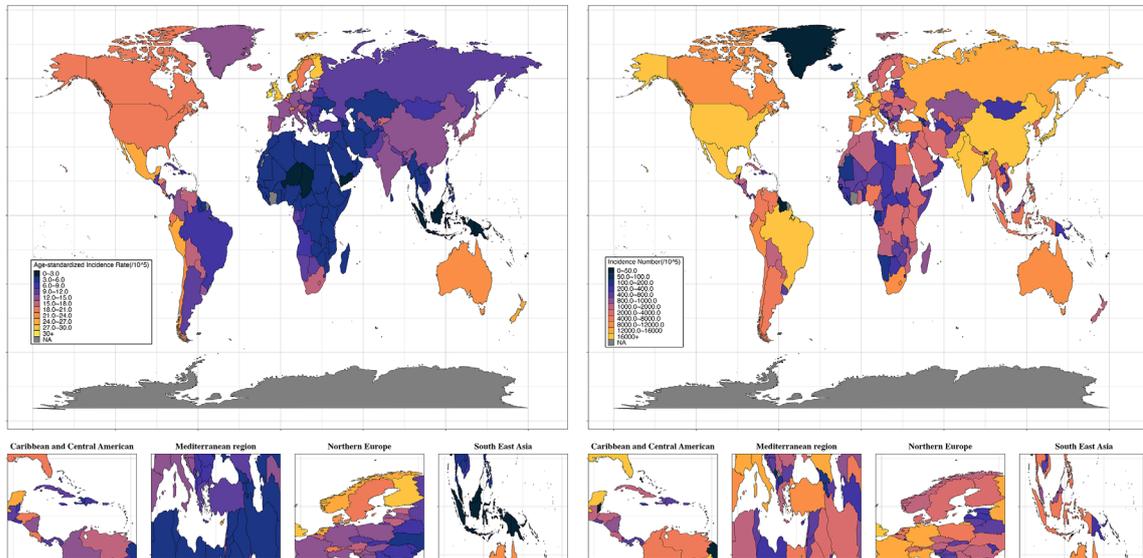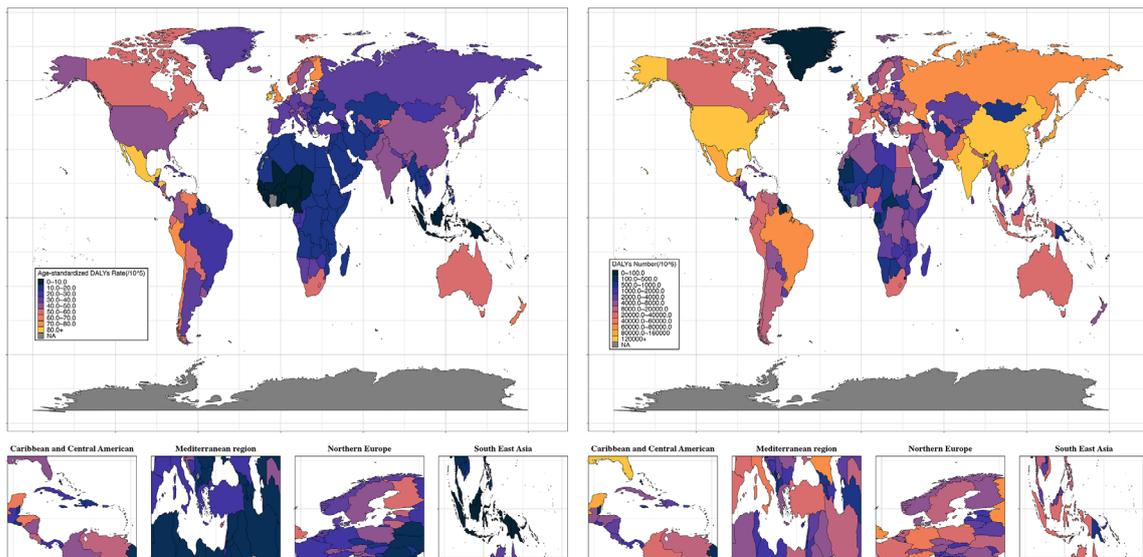
Fig. 1. The global ASRs and all ages number of prevalence, incidence, and DALYs burden of RA in 204 countries and territories.
A: The ASPR and all ages number of incidence burden of RA in 2021. **B**: The ASIR and all ages number of incidence burden of RA in 2021. **C**: The ASDR and all ages number of DALYs burden of RA in 2021.

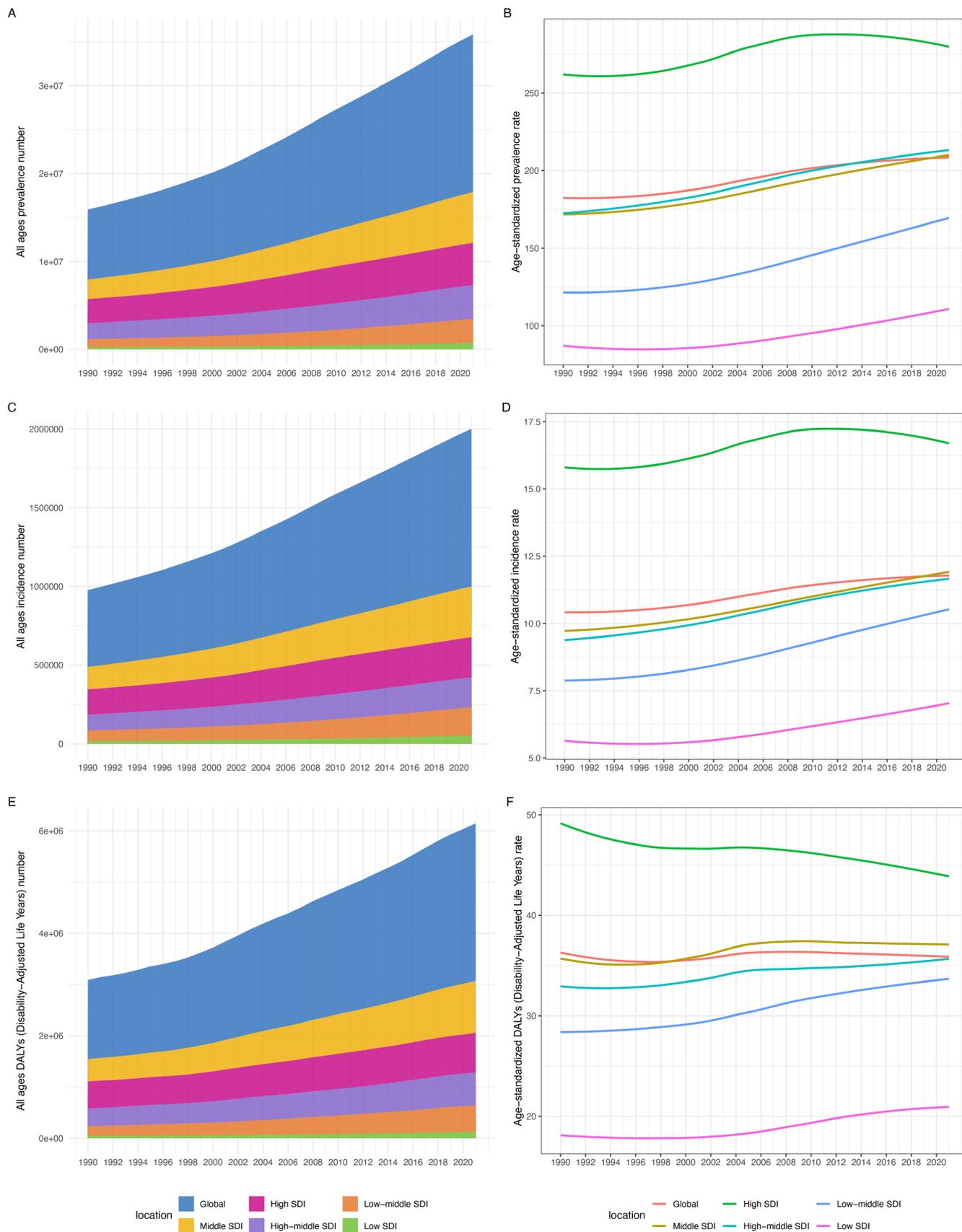**Fig. 2.** The global ASRs and all ages number of prevalence, incidence, and DALYs burden of RA in 5 SDI regions from 1990 to 2021.
A: The ASPR and all ages number of prevalence burden of RA in 5 SDI regions from 1990 to 2021. **B**: The ASIR and all ages number of incidence burden of RA in 5 SDI regions from 1990 to 2021. **C**: The ASDR and all ages number of DALYs burden of RA in 5 SDI regions from 1990 to 2021.

95%CIs entirely below 0 denote a significant decline. If the 95% CI spans 0, it indicates that no statistically significant change occurred over the study period.

- Predictive analysis
We conducted ARIMA model to capture time-series dynamics in RA prevalence and incidence from 2022 to 2044, stratified by sex. To assess the accuracy of the predictions, we conducted an additional analysis by the Nordpred APC model, which is based on a power5 APC framework for forecasting (24). A detailed description of the Nordpred APC and ARIMA model is provided in the Supplementary file. All statistical analyses were conducted in R 4.4.1, with *p*<0.05 denoting statistical significance.

Results

Global burden of RA
By 2021, the global burden of RA remained substantial, with pronounced regional disparities (Fig. 1). From 1990 to 2021, the ASPR, ASIR and ASDR all trended upward worldwide. Specifically, the ASPR rose from 182.45 (95% UI: 161.59–207.48) in 1990 to 208.90 (95% UI: 186.34–236.33) in 2021, corresponding to an AAPC of 0.44 (95% CI: 0.44–0.45). Similarly, the ASIR increased from 10.42 (95% UI: 9.32–11.64) in 1990 to 11.80 (95% UI: 10.64–13.12) in 2021, with an AAPC of 0.40 (95% CI: 0.40–0.41). While the ASDR declined modestly over the same period, from 36.42 (95% UI: 28.71–46.00) in 1990 to 35.89 (95% UI: 26.95–46.46) in 2021, with an AAPC of -0.03 (95% CI: -0.05 to -0.02) (Suppl. Table S2).

Global trends by GBD regions and socio-demographic index
From 1990 to 2021, all five SDI regions experienced upward trajectories in both the ASPR and ASID of RA, with the most pronounced increases observed in low-middle SDI regions, with an AAPC of 1.07 (95% CI: 1.06–1.08) for ASPR and 0.93 (95% CI: 0.92–0.94) for ASIR (Suppl. Table S2). Although high SDI regions consistently exhibited ASPR, ASIR, and ASDR above the global mean, their growth was the slowest. Moreover, only the high SDI regions

Fig. 3. Trends in the ASPR, ASIR, and ASDR of RA in 204 countries and territories from 1990 to 2021 in relation to changes in the SDI.
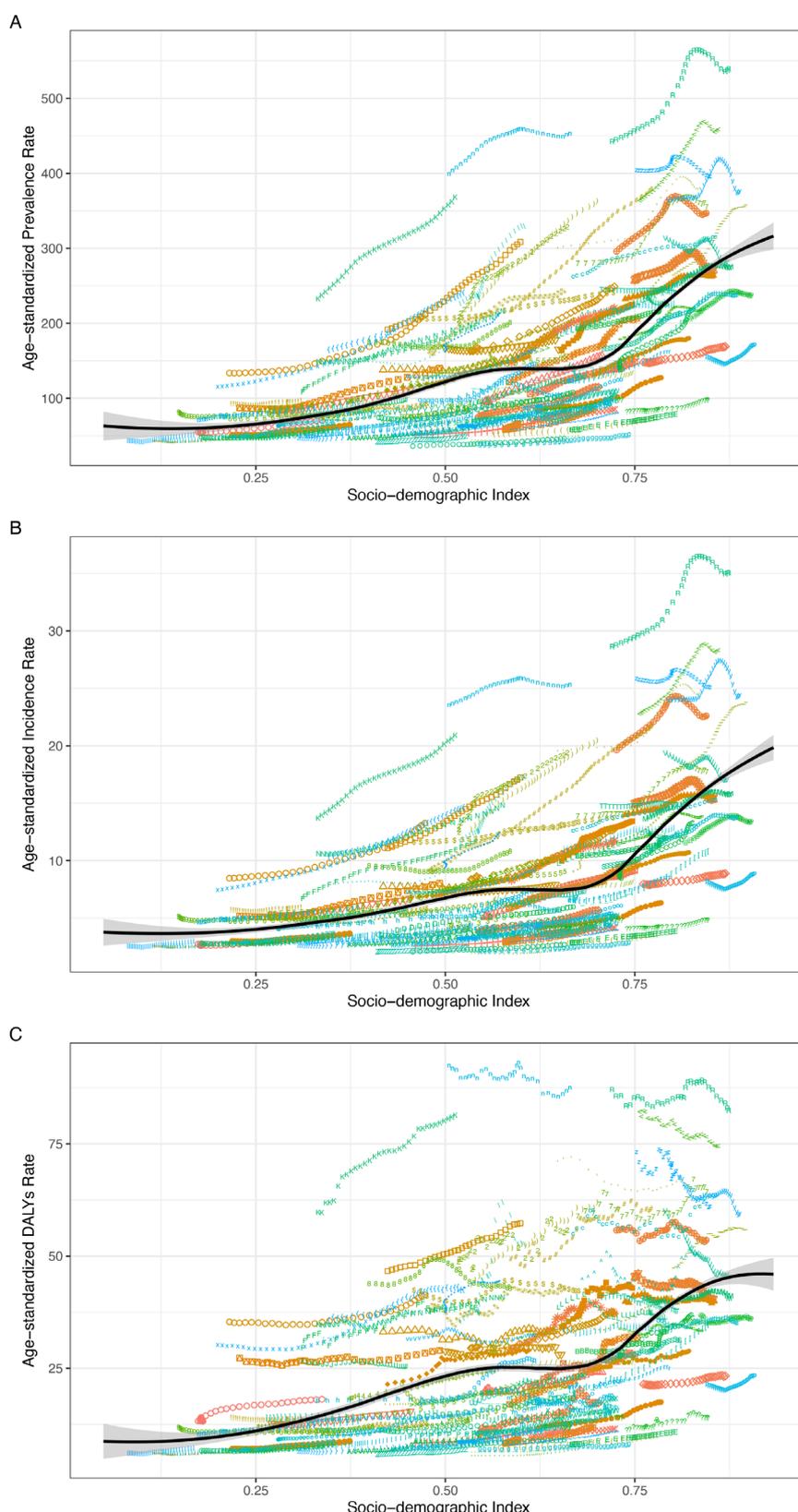**A**: Trends in the ASPR of RA in 204 countries and territories from 1990 to 2021 in relation to changes in the SDI. **B**: Trends in the ASIR of RA in 204 countries and territories from 1990 to 2021 in relation to changes in the SDI. **C**: Trends in the ASDR of RA in 204 countries and territories from 1990 to 2021 in relation to changes in the SDI.
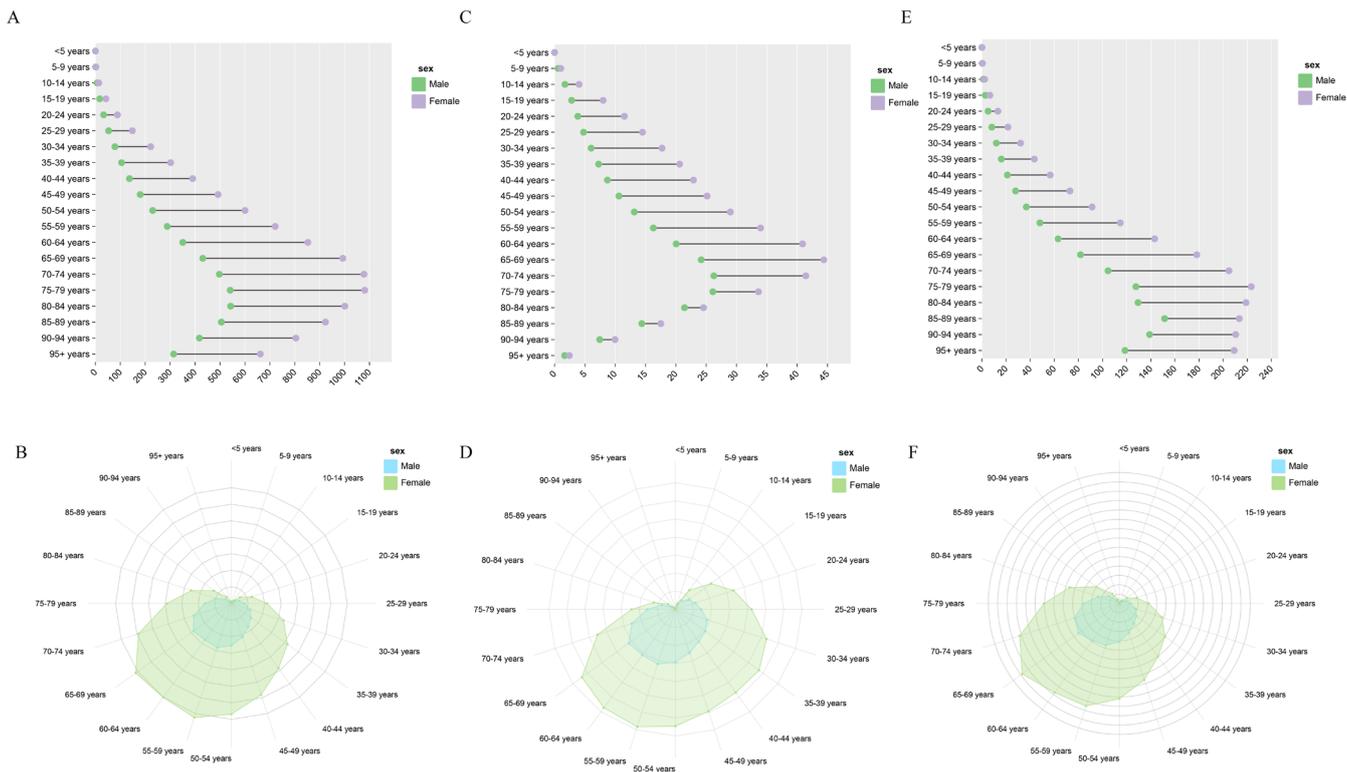
Fig. 4. The global ASRs and all ages number of prevalence, incidence, and DALYs burden of RA in males and females in different age groups in 2021. **A**: The ASPR and all ages number of prevalence of RA in males and females in different age groups in 2021. **B**: The ASIR and all ages number of incidence of RA in males and females in different age groups in 2021. **C**: The ASDR and all ages number of DALYs of RA in males and females in different age groups in 2021.

demonstrated a declining ASDR over this period, with an AAPC of -0.39 (95% CI: -0.41 to -0.37) (Fig. 2).

We examined the temporal patterns of RA burden and its relationship with the SDI across 204 countries and territories from 1990 to 2021. Our findings indicate that as both calendar year and SDI increased, the ASPR, ASID and ASDR generally rose. Specifically, when the SDI was below approximately 0.70, these measures increased gradually in parallel with incremental SDI gains. Once the SDI surpassed 0.70, the RA burden escalated sharply, with markedly accelerated rises in ASPR, ASIR, and ASDR (Fig. 3).

Detailed information on the GBD regional analysis can be found in the Supplementary file.

Global trends by genders and age groups
From 1990 to 2021, the ASPR, ASIR, and ASDR increased for males and females globally (see Suppl. Fig. S3). In males, ASPR and ASIR rose from 101.91 (95% UI: 89.65 to 117.83) and

6.39 (95% UI: 5.66–7.22) in 1990 to 119.68 (95% UI: 105.95–137.45) and 7.33 (95% UI: 6.56–8.26) in 2021, with AAPCs of 0.52 (95%CI: 0.51–0.52) and 0.44 (95%CI: 0.44–0.45), respectively. The ASDR in males climbed steadily as well, with an AAPC of 0.07 (95% CI: 0.05–0.10). During the same period, females experienced an increase in ASPR and ASIR from 257.98 (95% UI: 229.32–292.43) and 14.43 (95% UI: 12.95–16.01) in 1990 to 293.66 (95% UI: 263.52–331.33) and 14.43 (95% UI: 12.95–16.01) in 2021, with AAPCs of 0.52 (95% CI: 0.48–0.56) and 0.38 (95%CI: 0.38–0.39). In contrast to males, females experienced a slight decline in ASDR, with an AAPC of -0.06 (95% CI: -0.07 to -0.04) (Suppl. Table S2).

More detailed analyses stratified by age group, gender and GBD super-regions are available in the Supplementary file.

Risk factors analysis
We evaluated all identified RA risk factors, stratifying by age, sex, and 56 GBD regions. Figure 5 depicts the

2021 contribution of these factors to DALYs across sex and age groups. Individuals younger than 30 years experienced almost negligible DALYs, and risk factor burdens in this cohort were effectively 0.

Across all age brackets, males bore a consistently greater share of risk-attributable DALYs than females. The 55–59 year group was most affected: males accrued 18,190.67 DALYs (95% UI: 12,188.75–26,352.89), compared with 12,042.42 DALYs in females (95% UI: 8,127.01–17,449.34). In terms of DALYs rates, the highest impact occurred in males aged 75–79 years (15.04, 95% UI: 10.76–20.23) and females aged 65–69 years (6.94, 95% UI: 4.78 to 9.64) (Suppl. Table S6).

We also analysed the trajectory of smoking-related ASDR from 1990 to 2021 across GBD regions. Globally, smoking-related ASDR declined markedly, with an AAPC of -1.05 (95% CI: -1.06 to -1.03). Among SDI regions, high SDI regions experienced the steepest reduction (AAPC = -1.42; 95% CI: -1.45 to -1.40). Among the 56 GBD re-
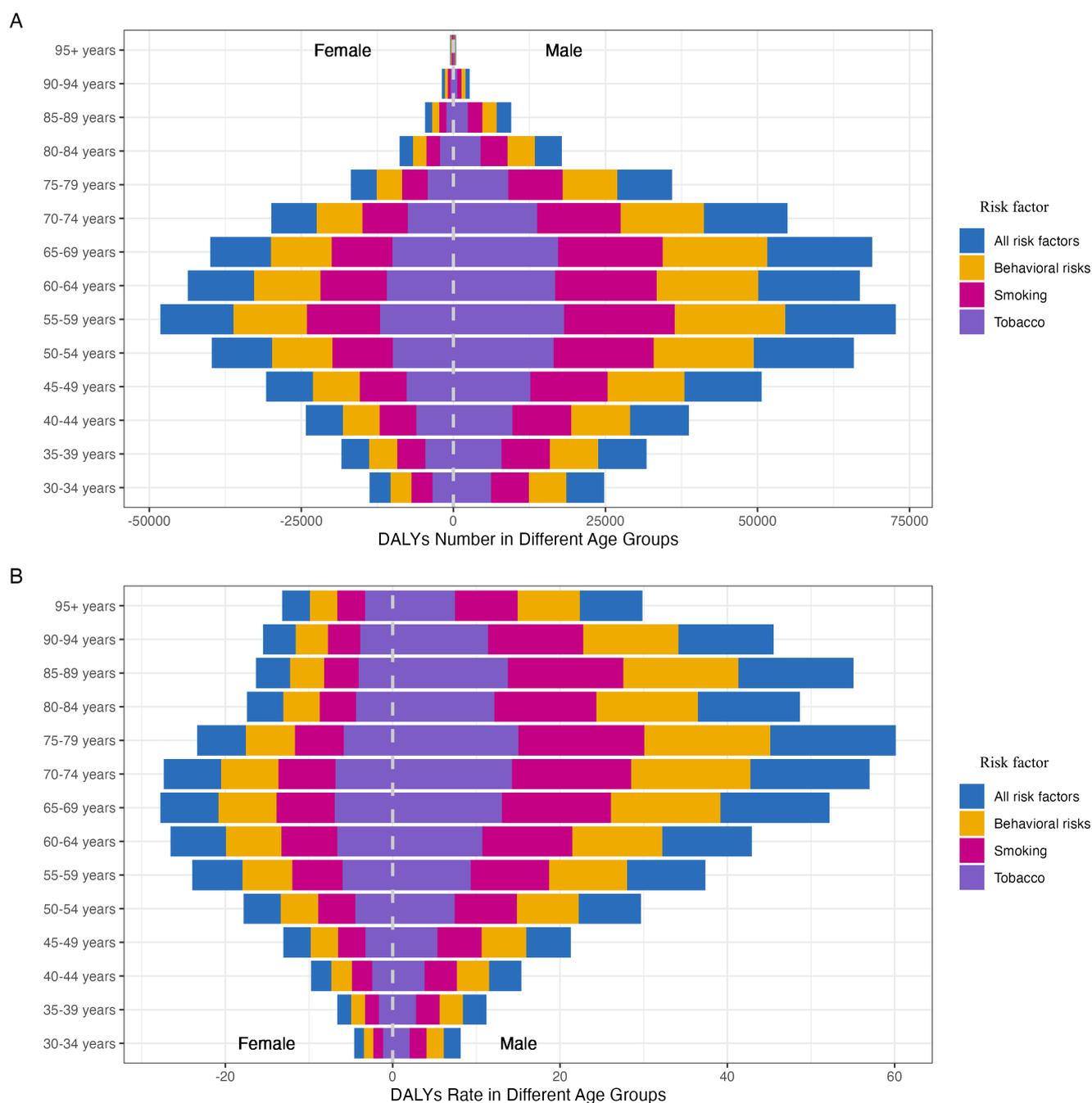
A

B

Fig. 5. RA-related DALYs number and rate in males and females in different age groups attributable to risk factors.
A: RA-related DALYs number in males and females in different age groups attributable to risk factors. **B**: RA-related DALYs rate in males and females in different age groups attributable to risk factors.

gions, most showed downward trends, a small subset of regions continued to exhibit an upward trajectory, with Central Asia demonstrating the most rapid rate of increase, with an AAPC at 1.34 (95% CI: 1.19–1.48) (Table I).

Predictive analysis
We applied an ARIMA forecasting model to project RA prevalence and in-cidence from 2022 through 2044, with Nordpred to validate our estimates. The ARIMA projections reveal a steady rise in global disease burden: by 2044, prevalent cases are anticipated to reach 26,048,902.68 (95% CI: 22,574,293.73–29,523,511.62), corresponding to an ASPR of 216.64 (95% CI: 188.55–244.72). Incident cases are forecasted at 1,347,410.19 (95% CI: 1,169,540.31–1,525,280.08), with an ASIR of 12.10 (95% CI: 11.01–13.18) (Table II). Over the 2022–2044 period, both raw case counts and ASRs of RA prevalence and incidence are projected to increase steadily, underscoring a mounting global burden (Fig. 6).

Detailed information on the Nordpred APC model analysis can be found in the Supplementary file.

Table I. Global and regional trends in smoking-related DALYs of RA from 1990 to 2021.

Characteristics	Smoking-related age-standardised DALYs rate per 100,000 population		
	1990 no. (95%UI)	2021 no. (95%UI)	AAPC no. (95%CI)
Global	0.43 (0.28 to 0.66)	0.39 (0.25 to 0.59)	-1.05 (-1.06 to -1.03)
SDI quintile			
High SDI	0.57 (0.38 to 0.84)	0.68 (0.44 to 1.02)	-1.42 (-1.45 to -1.40)
High-middle SDI	3.72 (2.61 to 5.20)	1.76 (1.20 to 2.55)	-0.02 (-0.05 to 0.00)
Low SDI	0.84 (0.58 to 1.21)	0.54 (0.35 to 0.80)	-0.46 (-0.50 to -0.41)
Low-middle SDI	1.14 (0.72 to 1.67)	1.00 (0.64 to 1.46)	-0.43 (-0.47 to -0.38)
Middle SDI	10.08 (7.17 to 13.89)	5.31 (3.58 to 7.66)	-0.91 (-0.93 to -0.89)
All GBD regions			
Advanced Health System	0.49 (0.29 to 0.78)	0.56 (0.33 to 0.88)	-0.96 (-0.98 to -0.94)
Africa	4.03 (2.86 to 5.57)	3.60 (2.48 to 4.96)	-1.44 (-1.46 to -1.41)
African Region	3.44 (2.43 to 4.73)	2.48 (1.69 to 3.46)	-1.86 (-1.89 to -1.83)
America	1.12 (0.77 to 1.57)	1.08 (0.73 to 1.53)	-1.38 (-1.42 to -1.36)
Andean Latin America	4.70 (3.30 to 6.54)	3.65 (2.39 to 5.33)	0.46 (0.41 to 0.51)
Asia	0.96 (0.60 to 1.45)	1.50 (0.95 to 2.23)	-0.77 (-0.80 to -0.75)
Australasia	2.11 (1.44 to 2.98)	2.94 (2.01 to 4.19)	-1.38 (-1.41 to -1.36)
Basic Health System	5.19 (3.69 to 7.13)	2.88 (1.90 to 4.21)	-0.61 (-0.63 to -0.59)
Caribbean	6.23 (4.34 to 8.80)	4.04 (2.58 to 5.88)	-0.56 (-0.61 to -0.51)
Central Africa	3.86 (2.65 to 5.31)	4.12 (2.74 to 5.95)	-0.28 (-0.30 to -0.27)
Central Asia	6.13 (4.18 to 8.60)	4.31 (2.83 to 6.36)	1.34 (1.19 to 1.48)
Central Europe	6.01 (4.19 to 8.43)	4.38 (2.98 to 6.21)	-0.83 (-0.86 to -0.79)
Central Latin America	1.88 (1.29 to 2.62)	1.56 (1.06 to 2.23)	-2.09 (-2.15 to -2.04)
Central Sub-Saharan Africa	4.07 (2.97 to 5.54)	2.12 (1.45 to 2.98)	0.19 (0.18 to 0.20)
Commonwealth High Income	1.61 (1.12 to 2.29)	1.86 (1.19 to 2.74)	-2.08 (-2.14 to -2.03)
Commonwealth Low Income	1.00 (0.70 to 1.42)	1.02 (0.67 to 1.48)	-0.34 (-0.39 to -0.30)
Commonwealth Middle Income	3.57 (2.40 to 5.10)	1.84 (1.23 to 2.61)	-0.92 (-0.95 to -0.89)
East Asia	4.53 (3.13 to 6.32)	3.66 (2.45 to 5.29)	-0.36 (-0.38 to -0.34)
East Asia & Pacific - WB	0.39 (0.25 to 0.60)	0.42 (0.26 to 0.63)	-0.70 (-0.73 to -0.67)
Eastern Africa	1.96 (1.32 to 2.75)	1.53 (1.04 to 2.18)	-0.33 (-0.35 to -0.32)
Eastern Europe	0.16 (0.09 to 0.24)	0.16 (0.09 to 0.24)	1.12 (1.06 to 1.18)
Eastern Mediterranean Region	0.46 (0.30 to 0.69)	0.40 (0.26 to 0.60)	-0.92 (-0.94 to -0.90)
Eastern Sub-Saharan Africa	3.68 (2.62 to 5.08)	2.96 (2.03 to 4.09)	-0.41 (-0.42 to -0.40)
Europe	5.84 (4.08 to 8.14)	2.64 (1.80 to 3.81)	-0.66 (-0.69 to -0.64)
Europe & Central Asia - WB	3.46 (2.43 to 4.80)	2.17 (1.46 to 3.08)	-0.68 (-0.70 to -0.66)
European Region	0.97 (0.67 to 1.39)	0.54 (0.36 to 0.81)	-0.68 (-0.71 to -0.67)
High-income Asia Pacific	0.39 (0.25 to 0.59)	0.53 (0.34 to 0.78)	-1.89 (-1.93 to -1.85)
High-income North America	1.91 (1.29 to 2.67)	1.50 (1.02 to 2.14)	-1.02 (-1.05 to -0.99)
Latin America & Caribbean - WB	1.89 (1.31 to 2.61)	1.42 (0.96 to 2.01)	-1.51 (-1.56 to -1.47)
Limited Health System	0.15 (0.09 to 0.23)	0.15 (0.09 to 0.23)	-0.64 (-0.69 to -0.61)
Middle East & North Africa - WB	4.84 (3.39 to 6.78)	3.14 (2.13 to 4.44)	0.57 (0.57 to 0.58)
Minimal Health System	3.01 (2.13 to 4.16)	2.37 (1.63 to 3.27)	-0.07 (-0.08 to -0.05)
North Africa and Middle East	4.84 (3.39 to 6.78)	3.14 (2.13 to 4.44)	0.07 (0.05 to 0.08)
North America	4.65 (3.21 to 6.49)	3.78 (2.54 to 5.47)	-1.02 (-1.05 to -0.99)
Northern Africa	1.64 (1.11 to 2.28)	1.38 (0.94 to 1.96)	1.00 (0.98 to 1.02)
Oceania	0.96 (0.67 to 1.38)	0.54 (0.36 to 0.80)	0.42 (0.41 to 0.43)
Region of the Americas	4.52 (3.12 to 6.30)	3.65 (2.45 to 5.27)	-1.38 (-1.42 to -1.36)
South Asia	1.29 (0.86 to 1.85)	0.96 (0.62 to 1.40)	-0.78 (-0.82 to -0.74)
South Asia - WB	4.09 (2.91 to 5.65)	3.31 (2.26 to 4.57)	-0.78 (-0.81 to -0.75)
Southeast Asia	1.70 (1.18 to 2.36)	1.48 (1.02 to 2.06)	-0.12 (-0.13 to -0.11)
South-East Asia Region	0.89 (0.62 to 1.24)	0.77 (0.53 to 1.10)	-0.56 (-0.59 to -0.52)
Southern Africa	3.11 (2.15 to 4.32)	3.08 (2.10 to 4.36)	-2.41 (-2.46 to -2.36)
Southern Latin America	5.99 (4.19 to 8.36)	3.87 (2.61 to 5.55)	0.18 (0.11 to 0.27)
Southern Sub-Saharan Africa	6.01 (4.19 to 8.43)	4.38 (2.98 to 6.21)	-2.53 (-2.58 to -2.48)
Sub-Saharan Africa - WB	0.32 (0.20 to 0.49)	0.29 (0.18 to 0.45)	-1.85 (-1.89 to -1.82)
Tropical Latin America	3.10 (2.20 to 4.24)	2.33 (1.60 to 3.22)	-2.13 (-2.20 to -2.07)
Western Africa	4.99 (3.49 to 6.94)	3.71 (2.51 to 5.31)	0.11 (0.11 to 0.12)
Western Europe	3.20 (2.26 to 4.40)	2.65 (1.83 to 3.68)	-1.16 (-1.20 to -1.13)
Western Pacific Region	1.63 (1.11 to 2.25)	1.32 (0.90 to 1.88)	-0.68 (-0.70 to -0.66)
Western Sub-Saharan Africa	0.28 (0.18 to 0.43)	0.28 (0.18 to 0.41)	0.05 (0.04 to 0.06)

Discussion

We utilised GBD 2021 to analyse the trends in the ASPR, ASIR, and ASDR of RA across 204 countries and territories globally, employing Joinpoint regression and LLR model. Furthermore, we examined the risk factors associated with RA-related ASDR across different regions, age groups, and genders. We used the ARIMA and Nordpred APC models to forecast the future prevalence and incidence trends through 2044.

Table II. Prediction of RA prevalence and incidence cases, ASPR and ASIR from 2022 to 2044 by the ARIMA model.

Year	Prediction of incidence number no. (95%CI)	Prediction of age-standardised incidence rate no. (95%CI)	Prediction of prevalence number no. (95%CI)	Prediction of Age-standardised prevalence rate no. (95%CI)
2022	1016689.3 (1015595.03 to 1017783.58)	11.82 (11.8 to 11.84)	18277622.79 (18257706.46 to 18297539.11)	209.52 (209.28 to 209.75)
2023	1031722.07 (1028456.38 to 1034987.76)	11.84 (11.79 to 11.89)	18627879.33 (18565594.99 to 18690163.68)	210.18 (209.41 to 210.94)
2024	1046754.84 (1039967.01 to 1053542.67)	11.86 (11.77 to 11.94)	18978480.51 (18851850.85 to 19105110.16)	210.77 (209.25 to 212.29)
2025	1061787.61 (1050654.6 to 1072920.61)	11.87 (11.76 to 11.99)	19330271.8 (19120623.05 to 19539920.55)	211.29 (208.89 to 213.7)
2026	1076820.37 (1060671.42 to 1092969.32)	11.89 (11.73 to 12.05)	19683099.73 (19375239.76 to 19990959.7)	211.79 (208.4 to 215.19)
2027	1091853.14 (1070101.69 to 1113604.59)	11.9 (11.71 to 12.1)	20036547.6 (19618041.74 to 20455053.47)	212.29 (207.81 to 216.77)
2028	1106885.91 (1079002.73 to 1134769.08)	11.92 (11.68 to 12.16)	20390262.93 (19850571.64 to 20929954.22)	212.76 (207.09 to 218.44)
2029	1121918.68 (1087417.33 to 1156420.02)	11.93 (11.65 to 12.22)	20744038.7 (20073834.08 to 21414243.31)	213.19 (206.24 to 220.14)
2030	1136951.44 (1095379.15 to 1178523.74)	11.95 (11.61 to 12.28)	21097787.64 (20288508.58 to 21907066.7)	213.58 (205.3 to 221.86)
2031	1151984.21 (1102915.62 to 1201052.81)	11.96 (11.58 to 12.35)	21451491.52 (20495090.8 to 22407892.25)	213.94 (204.28 to 223.6)
2032	1167016.98 (1110049.68 to 1223984.28)	11.97 (11.54 to 12.41)	21805160.54 (20693974.45 to 22916346.64)	214.28 (203.21 to 225.34)
2033	1182049.75 (1116800.9 to 1247298.59)	11.99 (11.5 to 12.47)	22158810.31 (20885494.17 to 23432126.45)	214.59 (202.09 to 227.08)
2034	1197082.52 (1123186.25 to 1270978.78)	12 (11.46 to 12.54)	22512452.63 (21069946.06 to 23954959.2)	214.87 (200.93 to 228.81)
2035	1212115.28 (1129220.6 to 1295009.96)	12.01 (11.42 to 12.6)	22866093.88 (21247597.13 to 24484590.63)	215.13 (199.74 to 230.52)
2036	1227148.05 (1134917.15 to 1319378.95)	12.02 (11.38 to 12.67)	23219736.49 (21418689.98 to 25020783)	215.36 (198.52 to 232.21)
2037	1242180.82 (1140287.69 to 1344073.94)	12.03 (11.33 to 12.73)	23573380.73 (21583445.55 to 25563315.92)	215.58 (197.28 to 233.87)
2038	1257213.59 (1145342.89 to 1369084.28)	12.04 (11.29 to 12.8)	23927026.13 (21742065.46 to 26111986.79)	215.78 (196.04 to 235.51)
2039	1272246.35 (1150092.41 to 1394400.3)	12.05 (11.24 to 12.86)	24280672.1 (21894734.14 to 26666610.07)	215.96 (194.79 to 237.12)
2040	1287279.12 (1154545.07 to 1420013.17)	12.06 (11.2 to 12.93)	24634318.28 (22041620.76 to 27227015.8)	216.12 (193.53 to 238.7)
2041	1302311.89 (1158708.99 to 1445914.79)	12.07 (11.15 to 12.99)	24987964.46 (22182881.13 to 27793047.79)	216.27 (192.28 to 240.25)
2042	1317344.66 (1162591.63 to 1472097.68)	12.08 (11.1 to 13.05)	25341610.58 (22318659.23 to 28364561.94)	216.4 (191.03 to 241.77)
2043	1332377.43 (1166199.93 to 1498554.92)	12.09 (11.06 to 13.12)	25695256.65 (22449088.64 to 28941424.65)	216.52 (189.79 to 243.26)
2044	1347410.19 (1169540.31 to 1525280.08)	12.1 (11.01 to 13.18)	26048902.68 (22574293.73 to 29523511.62)	216.64 (188.55 to 244.72)

RA has emerged as a major global health burden, with pronounced disparities in ASPR, ASIR and ASDR across countries and regions over the past three decades. Although ASIR and ASPR have risen in all five SDI regions, ASDR has declined markedly in high SDI regions, reflecting gains in disease management and outcomes (19). At the national level, high-income countries continue to record relatively high ASPR, ASIR, and ASDR, while their ASDR has stabilised or even decreased over the past 30 years – an achievement largely attributable to abundant healthcare resources, early diagnosis, and timely, effective interventions that preserve quality of life. However, regions with low SDI often suffer from delayed diagnoses and restricted treatment access, leading to inadequate disease control, progressive joint destruction, and severe deformities that profoundly compromise both physical and mental health, which may ultimately result in life-threatening complications (25). In 2021, we found that individuals aged 55–79 years exhibited particularly high prevalence, incidence, and DALY rates, and all age groups showed substantial increases in both prevalence and incidence since 1990. Ongoing advances in medical technology have yielded novel therapeutic approaches for RA. Traditional treatments, NSAIDs, corticosteroids, and DMARDs, remain effective at suppressing disease activity but are frequently accompanied by significant adverse effects (26). For example, aspirin, one of the earliest NSAIDs prescribed for joint pain, can induce tinnitus, hearing loss, and gastrointestinal discomfort at high doses. Selective COX-2 inhibitors deliver anti-inflammatory and analgesic efficacy comparable to non-selective COX inhibitors while markedly reducing gastrointestinal risk (26, 27). Corticosteroids, although more potent than NSAIDs, carry a higher burden of side effects: prolonged administration may precipitate Cushing's syndrome, osteoporosis, pathological fractures, and avascular necrosis of the femoral head (28-31). In recent years, biologic agents have revolutionised RA care. These therapies not only offer superior disease control but also present a more favourable safety profile than traditional agents, establishing them as foundational components of modern RA management (32, 33). In addition to pharmacologic innovations, enhanced patient education and structured self-management programmes, implemented in countries such as the USA, Germany, and Australia, have further mitigated the impact of RA. Although a definitive cure remains elusive, the combination of targeted therapies and comprehensive care strategies now enables effective, long-term disease control.

In our analysis, women consistently exhibit higher ASPR, ASIR and ASDR of RA. Hormones appear to underlie much of this disparity: oestrogen potentiates autoimmune activity, whereas androgens confer protective effects, resulting in a greater disease burden among women (34). Nevertheless, from 1990 to 2021, men experienced a more pronounced rise in ASPR, ASIR, and ASDR than women. One of the key drivers may be 'smoking', which contributes to multiple phases of RA pathogenesis (35). As global smoking prevalence has climbed, driven by population growth and the introduction of novel tobacco products, men have borne the brunt of this increase. By 2022, the WHO estimated that one-fifth of the adult population worldwide used tobacco, totaling approximately 1.245 billion smokers. In 2015, men accounted for over 80 percent of daily smokers, with an age-standardised daily smoking rate nearly five times that of women (36).
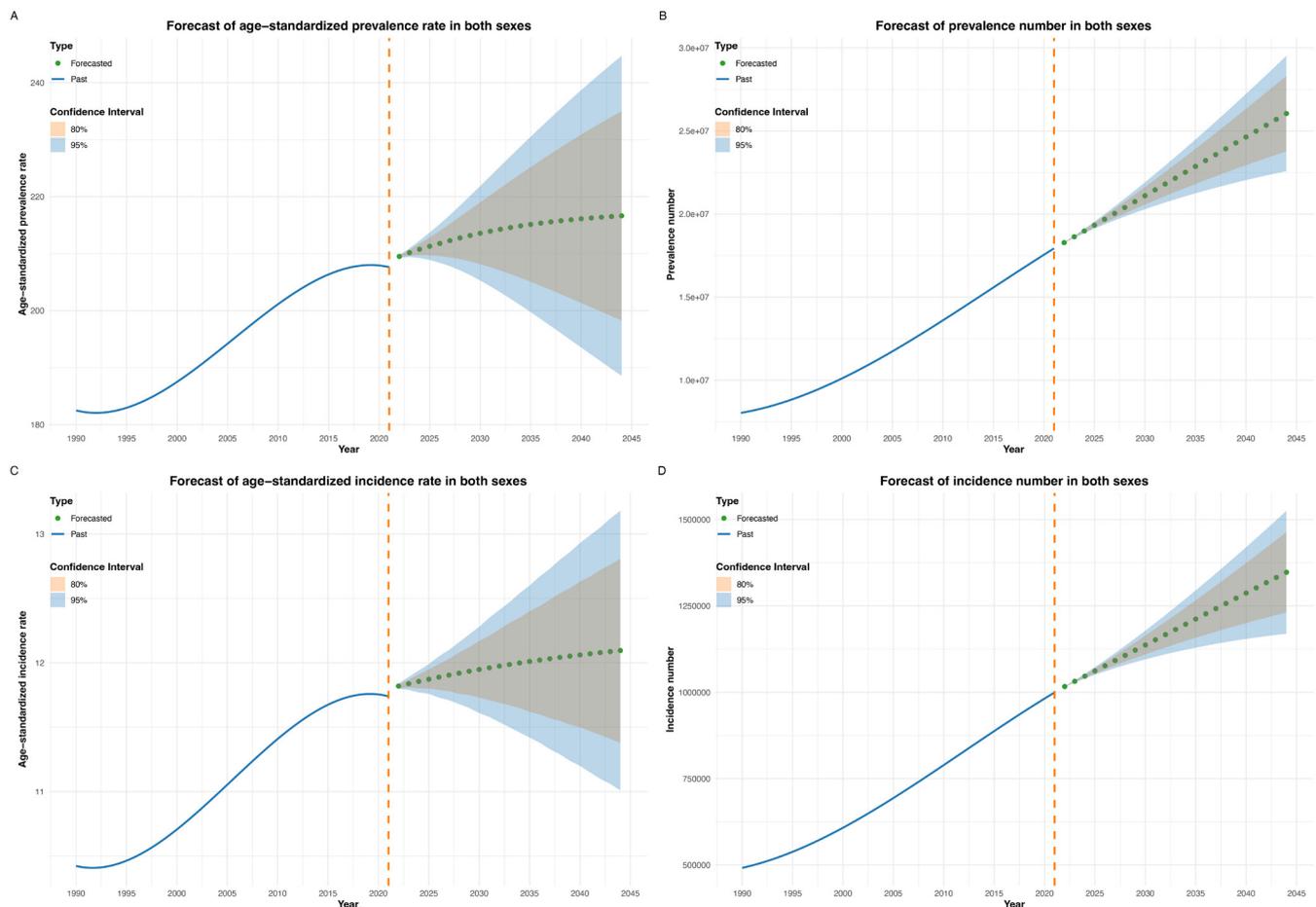
Fig. 6. Forecast of prevalence and incidence of RA for both sexes from 2022 to 2050 by the ARIMA model.
A: Forecast of ASPR of RA for both genders from 2022 to 2050 by the ARIMA model. **B**: Forecast of prevalence cases of RA for both genders from 2022 to 2050 by the ARIMA model. **C**: Forecast of ASIR of RA for both genders from 2022 to 2050 by the ARIMA model. **D**: Forecast of incidence cases of RA for both genders from 2022 to 2050 by the ARIMA model.

Consequently, the smoking-related RA burden among men has surged more rapidly than that among women.

The precise aetiology of RA remains incompletely understood while genetic predisposition, smoking, environmental exposures, and dysregulated immune responses are recognised as principal risk factors. Studies estimate that genetic factors account for over 50% of RA susceptibility (37, 38). Two hallmark autoantibodies, anti-citrullinated peptide/protein antibodies and rheumatoid factor, are detected in roughly 50–60% of patients and synergistically exacerbate bone erosion and disease progression (39, 40). In GBD 2021, 'smoking' stood as the sole behavioural risk factor for RA (41). Research has shown that the risk of developing RA is significantly higher among smokers than among non-smokers (42). Compared to non-smokers, individuals who smoked ≤10 pack-years had a 26% higher risk of developing RA, whereas those who smoked >21 pack-years had approximately twice the risk. Moreover, passive smokers have an increased prevalence (43, 44). Notably, the effect of smoking was particularly pronounced in individuals without family history of RA (44, 45). However, the risk did not increase significantly in individuals who had smoked previously. Compared with those who continue smoking, quitting after RA diagnosis is associated with a reduced risk of mortality (46). Studies have shown that smoking cessation within four years of RA diagnosis can significantly reduce the risk of subsequent death (47-49). From 1990 to 2021, smoking-related ASDR declined globally. Projections indicate that adult smoking prevalence (≥15 years) will fall from 2000 to 2025, while regional disparities persist (17).

In the Americas, smoking rates are expected to drop by 33% (from 21% in 2010 to 14% in 2025), with similar declines in Africa and Southeast Asia (32%). Europe and the Eastern Mediterranean anticipate more modest reductions (19% and 22%, respectively), while the Western Pacific region lags at an 8% decrease (50). These achievements reflect widespread adoption of the MPOWER measures Monitor (taxation), Protect (smoke-free laws), Offer (cessation services), Warn (health warnings), Enforce (advertising bans), and Raise (tobacco taxes) – integrated into comprehensive smoking control systems encompassing surveillance, legislation, clinical services, public education, enforcement, and fiscal policies (51). Economic analyses estimate that every dollar allocated to smoking control yields roughly twenty dollars in averted healthcare expenditures and

productivity losses. Over the past decade, more than ninety countries have enacted at least five MPOWER measures, driving global adult smoking prevalence down from 22.5% to 17.5%. It's reported that smoke-free regulations cover over half of the world's population, and upwards of eighty nations mandate graphic health warnings and levy tobacco taxes exceeding 65%, generating substantial funding for public health programmes. Moreover, the establishment of national implementation of behavioural support services have elevated cessation success rates by over 20%, contributing to a measurable reduction in both the incidence and severity of RA over the medium and long term (52).

Between 1990 and 2021, the ASPR, ASIR and ASDR of RA have risen steadily, exhibiting marked heterogeneity across countries with different sociodemographic profiles. Although advances in healthcare have attenuated the impact of RA on life expectancy, the condition continues to compromise quality of life and imposes a substantial socioeconomic burden. Forecasts extending to 2044 indicate that both prevalence and incidence cases will keep climbing, whereas the ASPR and ASIR are projected to increase at a more moderate pace. These patterns attest to the effectiveness of multi-pronged prevention and management strategies. Synergistic implementation of public health policies and clinical guidelines has successfully decelerated the upward trend in ASPR and ASIR. The MPOWER framework has helped lower smoking rates and curbed both incidence and ongoing disease burden. What's more, the 2019 EULAR/ACR recommendations for early RA diagnosis and 'treat-to-target' therapy advocate initiating DMARDs, notably methotrexate, within six weeks of symptom onset, which has substantially improved disease outcomes and forestalled progression (53). Furthermore, the inclusion of generic methotrexate in the WHO Essential Medicines List, coupled with the expansion of rheumatology services into lower income and remote regions, has substantially enhanced treatment accessibility. Integrating RA screening and chronic disease management into primary care networks, by community-based questionnaires and optimised referral pathways, facilitates early case detection and bolsters patient adherence (54). Collectively, these interventions have alleviated the social and economic burden of RA, improved long-term outcomes and quality of life, and supported the sustainable advancement of global health.

Limitation

This study has several limitations. First, the completeness and accuracy of GBD 2021 data vary markedly across regions. In many low-income countries, underdeveloped medical infrastructure, limited resources, and heterogeneous health-care systems may lead to under-reporting or biased estimates, thereby underestimating the true burden of RA. For instance, existing evidence suggests that increased estrogen levels, reduced progesterone levels, or sudden withdrawal can increase the risk of RA (55). Furthermore, certain lifestyle factors such as a diet high in red meat and sugar are associated with an increased risk (56). Low vitamin D levels are associated with the onset and severity (57). However, since GBD 2021 does not identify hormone use, genetic susceptibility, or lifestyle factors as independent risk factors for RA, it cannot quantify the precise contribution of these elements to RA prevalence, incidence, and DALYs, resulting in potential biases and confounding effects. Furthermore, incomplete surveillance of exposures such as 'smoking' can introduce additional errors in attributable burden estimates. In data sparse settings, GBD imputes values from neighboring regions with similar SDI, which may not accurately reflect local demographic or epidemiological contexts, therefore risking model transfer bias and undermining comparability and sensitivity in risk factor analyses (58). Second, our temporal trend and forecasting methods each carry inherent assumptions that may bias results. In Joinpoint analyses, we retained two decimal places for AAPCs, which leads to CIs abutting their point estimates in several regions, suggesting either a highly precise fit or an oversimplified model that masks true uncertainty and heterogeneity. The Nordpred APC framework rigidly extrapolates linear historical trends, over five-year intervals only, potentially overlooking inflection points caused by therapeutic advances or diagnostic shifts, and its fixed power5 link function may fail to capture non-linear dynamics (59). ARIMA forecasting likewise assumes stationarity and linearity; differencing to achieve stationarity can either strip meaningful patterns or leave spurious correlations, while p / d / q parameter selection remains subjective and prone to local optimum convergence (60). It is important to note that this study relied on GBD 2021, which presents a time lag and only reflects epidemiological estimates from 1990 to 2021, which limits the representation of the current situation. Variations in data quality, reporting timeliness, and SDI level coverage further complicate direct comparisons across regions and age groups. Although GBD 2021 offers valuable global estimates, it cannot substitute for real-time surveillance and should be complemented by future studies and updated datasets to validate and refine these findings.

Conclusion

We present a comprehensive analysis of RA burden measured by ASPR, ASIR and ASDR across 204 countries and territories from 1990 to 2021, stratified by sex, age and GBD regions. Our findings reveal a sustained global increase in RA burden, with the most pronounced rises observed in low SDI regions. Although females continue to bear a disproportionately higher ASPR, ASIR and ASDR, the increases among males have accelerated markedly in recent years. 'Smoking' emerges as the principal risk factor, exerting its significant effect on individuals aged 55–79 years. Projections to 2044 indicate that both the number of incidence and prevalence cases and their corresponding ASRs will continue to increase. These trends underscore an urgent need for targeted public health interventions and policy initiatives to mitigate the escalating global impact of RA.

Take-home messages

- The burden of RA increases at a faster rate in men than in women.
- It's expected that prevalence and incidence cases will increase rapidly by 2044, with ASPR and ASIR experiencing a slower rise.
- The main risk factor for RA is smoking, which significantly affects those aged 55–79.

References

1. SCHERER HU, HÄUPL T, BURMESTER GR: The etiology of rheumatoid arthritis. *J Autoimmun* 2020; 110: 102400. https://doi.org/10.1016/j.jaut.2019.102400
2. RADU AF, BUNGAU SG: Management of rheumatoid arthritis: an overview. *Cells* 2021;10(11). https://doi.org/10.3390/cells10112857
3. SYMMONS DP, GABRIEL SE: Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. *Nat Rev Rheumatol* 2011; 7(7): 399-408. https://doi.org/10.1038/nrrheum.2011.75
4. CONFORTI A, DI COLA I, PAVLYCH V *et al.*: Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. *Autoimmun Rev* 2021; 20(2): 102735. https://doi.org/10.1016/j.autrev.2020.102735
5. FIGUS FA, PIGA M, AZZOLIN I, MCCONNELL R, IAGNOCCO A: Rheumatoid arthritis: Extra-articular manifestations and comorbidities. *Autoimmun Rev* 2021; 20(4): 102776. https://doi.org/10.1016/j.autrev.2021.102776
6. KADURA S, RAGHU G: Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management. *Eur Respir Rev* 2021; 30(160). https://doi.org/10.1183/16000617.0011-2021
7. KIM Y, YANG HI, KIM KS: Etiology and pathogenesis of rheumatoid arthritis-interstitial lung disease. *Int J Mol Sci* 2023; 24(19). https://doi.org/10.3390/ijms241914509
8. FIRESTEIN GS: Evolving concepts of rheumatoid arthritis. *Nature* 2003; 423(6937): 356-61. https://doi.org/10.1038/nature01661
9. NGO ST, STEYN FJ, MCCOMBE PA: Gender differences in autoimmune disease. *Front Neuroendocrinol* 2014; 35(3): 347-69. https://doi.org/10.1016/j.yfrne.2014.04.004
10. SMOLEN JS, ALETAHA D, MCINNES IB: Rheumatoid arthritis. *Lancet* 2016; 388(10055): 2023-38. https://doi.org/10.1016/S0140-6736(16)30173-8
11. SINGH JA, SAAG KG, BRIDGES SL *et al.*: 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2016; 68(1): 1-26. https://doi.org/10.1002/acr.22783
12. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2024; 403(10440): 2133-61. https://doi.org/10.1016/S0140-6736(24)00757-8
13. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol* 2023; 5(10): e594-e610. https://doi.org/10.1016/S2665-9913(23)00211-4
14. ARNETT FC, EDWORTHY SM, BLOCH DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31(3): 315-24. https://doi.org/10.1002/art.1780310302
15. NAGY G, ROODENRIJS NMT, WELSING PM *et al.*: EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021; 80(1): 31-35. https://doi.org/10.1136/annrheumdis-2020-217344
16. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2023; 402(10397): 203-34. https://doi.org/10.1016/S0140-6736(23)01301-6
17. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990-2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet* 2021; 397(10292): 2337-60. https://doi.org/10.1016/S0140-6736(21)01169-7
18. SAFIRI S, KOLAHI AA, HOY D *et al.*: Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. *Ann Rheum Dis* 2019; 78(11): 1463-71. https://doi.org/10.1136/annrheumdis-2019-215920
19. MA Y, CHEN H, LV W *et al.*: Global, regional and national burden of rheumatoid arthritis from 1990 to 2021, with projections of incidence to 2050: a systematic and comprehensive analysis of the Global Burden of Disease study 2021. *Biomark Res* 2025; 13(1): 47. https://doi.org/10.1186/s40364-025-00760-8
20. Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet* 2024; 403(10440): 2162-203. https://doi.org/10.1016/S0140-6736(24)00933-4
21. HAO C, TING L, FENG G *et al.*: Global incidence trends of autoimmune diseases from 1990 to 2021 and projections to 2050: a systemic analysis of the global burden of disease study 2021. *Autoimmun Rev* 2024: 103621. https://doi.org/10.1016/j.autrev.2024.103621
22. SUN P, YU C, YIN L *et al.*: Global, regional, and national burden of female cancers in women of child-bearing age, 1990-2021: analysis of data from the global burden of disease study 2021. *EClinicalMedicine* 2024; 74: 102713. https://doi.org/10.1016/j.eclinm.2024.102713
23. CAO F, LIU YC, NI QY *et al.*: Temporal trends in the prevalence of autoimmune diseases from 1990 to 2019. *Autoimmun Rev* 2023; 22(8): 103359. https://doi.org/10.1016/j.autrev.2023.103359
24. HAN T, WANG T, YE Y, YING C, WANG X, LIU S: The global, regional, and national burden of paralytic ileus and intestinal obstruction, 1990 to 2021: a cross-sectional analysis from the 2021 global burden of disease study. *Int J Surg* 2025; 111(2): 1773-87. https://doi.org/10.1097/js9.0000000000002189
25. YANG W, XU Y, LIN J *et al.*: 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. *Clin Exp Rheumatol* 2023; 41(7): 1516-27. https://doi.org/10.55563/clinexprheumatol/h9lvvc
26. CHAPA-VILLARREAL FA, STEPHENS M, PAVLICIN R, BEUSSMAN M, PEPPAS NA: Therapeutic delivery systems for rheumatoid arthritis based on hydrogel carriers. *Adv Drug Deliv Rev* 2024; 208: 115300. https://doi.org/10.1016/j.addr.2024.115300
27. TUTTLE J, DRESCHER E, SIMÓN-CAMPOS JA *et al.*: A phase 2 trial of peresolimab for adults with rheumatoid arthritis. *N Engl J Med* 2023; 388(20): 1853-62. https://doi.org/10.1056/nejmoa2209856
28. WEINSTEIN RS: Glucocorticoid-induced osteonecrosis. *Endocrine* 2012; 41(2):183-90. https://doi.org/10.1007/s12020-011-9580-0
29. HALTON J, GABOURY I, GRANT R *et al.*: Advanced vertebral fracture among newly diagnosed children with acute lymphoblastic leukemia: results of the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) research program. *J Bone Miner Res* 2009; 24(7): 1326-34. https://doi.org/10.1359/jbmr.090202
30. WEINSTEIN RS, JILKA RL, PARFITT AM, MANOLAGAS SC: Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest* 1998; 102(2): 274-82. https://doi.org/10.1172/jci2799
31. FARDET L, CABANE J, LEBBÉ C, MOREL P, FLAHAULT A: Incidence and risk factors for corticosteroid-induced lipodystrophy: a prospective study. *J Am Acad Dermatol* 2007; 57(4): 604-9. https://doi.org/10.1016/j.jaad.2007.04.018
32. VAN DE PUTTE LB, ATKINS C, MALAISE M *et al.*: Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004; 63(5): 508-16. https://doi.org/10.1136/ard.2003.013052
33. JANI M, HIRANI N, MATTESON EL, DIXON WG: The safety of biologic therapies in RA-associated interstitial lung disease. *Nat Rev Rheumatol* 2014; 10(5): 284-94. https://doi.org/10.1038/nrrheum.2013.197
34. KLEIN SL, FLANAGAN KL: Sex differences in immune responses. *Nat Rev Immunol* 2016; 16(10): 626-38.

https://doi.org/10.1038/nri.2016.90

35. BERNARD NJ: Rheumatoid arthritis: where there's smoke, there's altered transcription. *Nat Rev Rheumatol* 2014; 10(4): 197. https://doi.org/10.1038/nrrheum.2014.40

36. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015. *Lancet* 2017; 389(10082): 1885-906. https://doi.org/10.1016/s0140-6736(17)30819-x

37. PETROVSKÁ N, PRAJZLEROVÁ K, VENCOVSKÝ J, ŠENOLT L, FILKOVÁ M: The pre-clinical phase of rheumatoid arthritis: From risk factors to prevention of arthritis. *Autoimmun Rev* 2021; 20(5): 102797. https://doi.org/10.1016/j.autrev.2021.102797

38. MACGREGOR AJ, SNIEDER H, RIGBY AS *et al.*: Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum* 2000; 43(1): 30-37. https://doi.org/10.1002/1529-0131(200001)43:1<30::aid-anr5>3.0.co;2-b

39. HECHT C, ENGLBRECHT M, RECH J *et al.*: Additive effect of anti-citrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA. *Ann Rheum Dis* 2015; 74(12): 2151-56. https://doi.org/10.1136/annrheumdis-2014-205428

40. ORR C, NAJM A, BINIECKA M *et al.*: Synovial immunophenotype and anti-citrullinated peptide antibodies in rheumatoid arthritis patients: relationship to treatment response and radiologic prognosis. *Arthritis Care Res* (Hoboken) 2017; 69(11): 2114-23. https://doi.org/10.1002/art.40218

41. GUAN SY, ZHENG JX, FENG XY *et al.*: Global burden due to modifiable risk factors for autoimmune diseases, 1990-2021: Temporal trends and socio-demographic inequalities. *Autoimmun Rev* 2024; 23(12): 103674.m https://doi.org/10.1016/j.autrev.2024.103674

42. RUZZON F, ADAMI G: Environment and arthritis. *Clin Exp Rheumatol* 2024; 42(7): 1343-49. https://doi.org/10.55563/clinexprheumatol/z7lkua

43. DI GIUSEPPE D, DISCACCIATI A, ORSINI N, WOLK A: Cigarette smoking and risk of rheumatoid arthritis: a dose-response meta-analysis. *Arthritis Res Ther* 2014; 16(2): R61. https://doi.org/10.1186/ar4498

44. HEDSTRÖM AK, KLARESKOG L, ALFREDSSON L: Exposure to passive smoking and rheumatoid arthritis risk: results from the Swedish EIRA study. *Ann Rheum Dis* 2018; 77(7): 970-72. https://doi.org/10.1136/annrheumdis-2018-212973

45. HUTCHINSON D, SHEPSTONE L, MOOTS R, LEAR JT, LYNCH MP: Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. *Ann Rheum Dis* 2001; 60(3): 223-27. https://doi.org/10.1136/ard.60.3.223

46. HEDSTRÖM AK, STAWIARZ L, KLARESKOG L, ALFREDSSON L: Smoking and susceptibility to rheumatoid arthritis in a Swedish population-based case-control study. *Eur J Epidemiol* 2018; 33(4): 415-23. https://doi.org/10.1007/s10654-018-0360-5

47. JOSEPH RM, MOVAHEDI M, DIXON WG, SYMMONS DP: Smoking-related mortality in patients with early rheumatoid arthritis: a retrospective cohort study using the clinical practice research Datalink. *Arthritis Care Res* (Hoboken) 2016; 68(11): 1598-606. https://doi.org/10.1002/acr.22882

48. NARANJO A, KHAN NA, CUTOLO M *et al.*: Smoking cessation advice by rheumatologists: results of an international survey. *Rheumatology* (Oxford) 2014; 53(10): 1825-29. https://doi.org/10.1093/rheumatology/keu213

49. AIMER P, TREHARNE GJ, STEBBINGS S *et al.*: Efficacy of a rheumatoid arthritis-specific smoking cessation program: a randomized controlled pilot trial. *Arthritis Care Res* (Hoboken) 2017; 69(1): 28-37. https://doi.org/10.1002/acr.22960

50. Forecasting the effects of smoking prevalence scenarios on years of life lost and life expectancy from 2022 to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Public Health* 2024; 9(10): e729-e44. https://doi.org/10.1016/s2468-2667(24)00166-x

51. HUSAIN MJ, DATTA BK, NARGIS N *et al.*: Revisiting the association between worldwide implementation of the MPOWER package and smoking prevalence, 2008-2017. *Tob Control* 2021; 30(6): 630-37. https://doi.org/10.1136/tobaccocontrol-2020-055758

52. MOSQUERA I, ILBAWI A, MUWONGE R, BASU P, CARVALHO AL: Cancer burden and status of cancer control measures in fragile states: a comparative analysis of 31 countries. *Lancet Glob Health* 2022; 10(10): e1443-e52. https://doi.org/10.1016/s2214-109x(22)00331-x

53. SMOLEN JS, LANDEWÉ R, BIJLSMA J *et al.*: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017; 76(6): 960-77. https://doi.org/10.1136/annrheumdis-2016-210715

54. CAO F, HE YS, WANG Y *et al.*: Global burden and cross-country inequalities in autoimmune diseases from 1990 to 2019. *Autoimmun Rev* 2023; 22(6): 103326. https://doi.org/10.1016/j.autrev.2023.103326

55. CUTOLO M, GOTELLI E: Complex role of oestrogens in the risk and severity of rheumatoid arthritis in menopause. *RMD Open* 2023; 9(2). https://doi.org/10.1136/rmdopen-2023-003176

56. PHILIPPOU E, NIKIPHOROU E: Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis. *Autoimmun Rev* 2018; 17(11): 1074-77. https://doi.org/10.1016/j.autrev.2018.05.009

57. HERLY M, STENGAARD-PEDERSEN K, VESTERGAARD P *et al.*: Impact of season on the association between vitamin D levels at diagnosis and one-year remission in early Rheumatoid Arthritis. *Sci Rep* 2020; 10(1): 7371. https://doi.org/10.1038/s41598-020-64284-x

58. KATZMARZYK PT, FRIEDENREICH C, SHIROMA EJ, LEE IM: Physical inactivity and non-communicable disease burden in low-income, middle-income and high-income countries. *Br J Sports Med* 2022; 56(2): 101-6. https://doi.org/10.1136/bjsports-2020-103640

59. LI CJ, WANG YK, ZHANG SM, REN MD, HE SX: Global burden of inflammatory bowel disease 1990-2019: A systematic examination of the disease burden and twenty-year forecast. *World J Gastroenterol* 2023; 29(42): 5751-67. https://doi.org/10.3748/wjg.v29.i42.5751

60. CHEN Y, MA L, HAN Z, XIONG P: The global burden of disease attributable to high body mass index in 204 countries and territories: Findings from 1990 to 2019 and predictions to 2035. *Diabetes Obes Metab* 2024; 26(9): 3998-4010. https://doi.org/10.1111/dom.15748