



Rheumatoid Arthritis Burden in Middle-Aged Adults (40–59 Years): Evidence from the Global Burden of Disease 2021

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Background: Rheumatoid arthritis (RA) is a leading cause of disability worldwide. Although global assessments of RA have been reported, age-specific estimates focusing on middle-aged adults [middle-aged adults (MAA); 40–59 years] remain limited.

Aims: To quantify the global, regional, and temporal burden of RA among MAA from 1990 to 2021 and project age-standardized trends through 2050.

Study Design: A population-based descriptive epidemiological study using Global Burden of Disease (GBD) 2021 estimates.

Methods: GBD 2021 data (1990–2021) were used to estimate age-standardized incidence (ASIR), prevalence (ASPR), mortality (ASMR), and disability-adjusted life-year rates (ASDR) per 100,000 population among MAA. Temporal trends were assessed using joinpoint regression and expressed as the average annual percentage change (AAPC). Projections to 2050 were generated using a Bayesian age–period–cohort model. Burden

patterns were summarized across sociodemographic index quintiles and 21 GBD regions.

Results: In 2021, the global ASIR, ASPR, ASMR, and ASDR among MAA were 19.53, 368.73, 0.19, and 56.74 per 100,000 population, respectively. From 1990 to 2021, ASIR and ASPR increased (AAPC = 0.24% and 0.43%), ASMR decreased (AAPC = -1.70%), and ASDR showed minimal net change (AAPC = 0.05%). Substantial variation was observed across SDI quintiles and GBD regions; SDI was positively correlated with ASIR and ASPR and negatively correlated with ASMR. Projections to 2050 indicated an ASIR of 19.22, an ASPR of 367.47, an ASMR of 0.111, and an ASDR of 52.18 per 100,000, with widening credible intervals over time.

Conclusion: Between 1990 and 2021, the RA burden among MAA was characterized by increasing ASIR and ASPR, declining ASMR, and relatively stable ASDR. Projections suggest that ASIR and ASPR will remain near recent levels, whereas ASMR and ASDR will show lower median values over time.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and long-term functional impairment.¹ It is a major contributor to years lived with disability globally and represents a sustained burden on individuals, healthcare systems, and societies.¹ The clinical course of RA is typically prolonged, and its cumulative impact is influenced not only by disease severity but also by the age at onset and the duration of disease.

Although RA can occur at any age, epidemiological evidence indicates that incidence rates increase markedly during midlife,

with a substantial proportion of diagnoses occurring between 40 and 59 years of age.¹ This stage of life represents a critical period in which individuals often experience peak occupational engagement and social responsibilities. Consequently, the onset of RA in middle-aged adults (MAA) may lead to prolonged health service utilization, productivity loss, and sustained disability over subsequent decades.² Despite this, most global epidemiological assessments have focused on the general population or older adults, and age-specific analyses targeting MAA remain limited.³

Over the past decades, advances in early diagnosis and treatment—including treat-to-target strategies and the expanded use of biologic and targeted synthetic disease-modifying antirheumatic drugs—



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have improved disease control and survival.⁴ Nevertheless, the global number of RA cases has continued to increase, largely driven by demographic transitions, such as population growth and aging.⁴ Substantial regional and sociodemographic disparities also persist.⁵ However, comprehensive evaluations of long-term temporal trends and future projections specifically among MAA remain limited, constraining age-targeted planning and accurate assessment of disease burden in this economically and socially active population.

In this study, we conducted a comprehensive assessment of the burden of RA among MAA using data from the Global Burden of Disease (GBD) 2021 study,^{6,7} which provides standardized estimates for 369 diseases and injuries across 204 countries and territories from 1990 to 2021. Joinpoint regression was used to quantify temporal trends in age-standardized incidence (ASIR), prevalence (ASPR), mortality (ASMR), and disability-adjusted life years (DALY) rates (ASDR),⁸ and a Bayesian age–period–cohort (BAPC) model was applied to project these trends through 2050. This analysis provides an updated global overview of the RA burden among MAA and offers age-specific evidence to support epidemiological monitoring and health planning.

MATERIALS AND METHODS

Data source

Data were obtained from the GBD 2021 study conducted by the Institute for Health Metrics and Evaluation, University of Washington. GBD 2021 provides comprehensive epidemiological estimates for 369 diseases and injuries across 204 countries and territories from 1990 to 2021. RA was defined according to the GBD cause hierarchy based on ICD-10 codes M05–M06. Age-standardized rates (ASRs) were calculated using the GBD standard world population to allow comparability across time and regions. In this study, incidence, prevalence, mortality, and DALYs for individuals aged 40–59 years were extracted using the GBD Results Tool. Estimates were reported as counts and ASRs per 100,000 population, with corresponding 95% uncertainty intervals (UIs). Countries were categorized into five sociodemographic index (SDI) quintiles and 21 GBD regions.

Joinpoint regression analysis

Joinpoint regression was used to evaluate temporal trends in ASRs from 1990 to 2021. Analyses were conducted using the Joinpoint Regression Program (National Cancer Institute, USA). A maximum of five joinpoints was allowed, and the optimal model was identified using Monte Carlo permutation tests (overall two-sided $\alpha = 0.05$). Log-transformed ASRs were modeled under the assumption of a log-linear relationship. Variance was estimated using the default settings of the Joinpoint software for rate data. The analysis followed the default independent error assumption implemented in the Joinpoint Regression Program, and no additional autoregressive error structure was specified. For each time segment, the annual percentage change (APC) and its 95% confidence interval (CI) were estimated as $APC = (e^{\hat{\beta}} - 1) \times 100\%$, where $\hat{\beta}$ is the slope coefficient. The average APC (AAPC) was calculated as the weighted geometric mean of the segment-specific APCs across the entire study period, with weights proportional to the length of each segment.

Bayesian age–period–cohort models

Future projections of the RA burden through 2050 were estimated using a BAPC model applied to ASRs, implemented using the BAPC package. The model incorporates temporal effects to capture historical patterns and generate future projections. A Poisson likelihood was assumed, and parameter estimation was conducted within the Integrated Nested Laplace Approximation framework implemented in the BAPC package. Future rates were projected by extrapolating the estimated temporal effects beyond the observed period. Uncertainty in the projections was quantified using 95% credible intervals (CrIs) derived from the posterior distributions.

Statistical analysis

Temporal trends in ASIR, prevalence, mortality, and DALY rates were summarized using the APC and AAPC derived from joinpoint regression analysis. A temporal trend was considered statistically significant when the 95% CI for the APC or AAPC did not include zero. Descriptive comparisons of the burden of RA were conducted across SDI quintiles and GBD regions. Associations between SDI and ASRs were assessed using Pearson correlation coefficients and interpreted as exploratory ecological analyses. Data management was performed using Microsoft Excel, and statistical analyses and visualizations were conducted in R (version 4.3.3) using appropriate packages.

RESULTS

Global burden and overall trends, 1990–2021

In 2021, the global ASIR of RA among MAA was 19.53 (95% UI: 12.60–27.98) per 100,000 population. The ASPR was 368.73 (95% UI: 298.90–446.08) per 100,000, the ASMR was 0.19 (95% UI: 0.16–0.22) per 100,000, and the ASDR was 56.74 (95% UI: 39.44–78.91) per 100,000 population.

Between 1990 and 2021, ASIR increased from 18.14 (95% UI: 11.61–26.26) per 100,000 in 1990 to 19.53 (95% UI: 12.60–27.98) per 100,000 in 2021 (AAPC = 0.24%, 95% CI: 0.23–0.25). The ASPR increased from 323.99 (95% UI: 260.33–395.49) to 368.73 (95% UI: 298.90–446.08) (AAPC = 0.43%, 95% CI: 0.42–0.44). In contrast, the ASMR decreased from 0.33 (95% UI: 0.29–0.37) to 0.19 (95% UI: 0.16–0.22) during the same period [AAPC = -1.70%, 95% CI: -1.75–(-1.65)]. Meanwhile, the ASDR changed from 55.85 (95% UI: 40.49–75.76) to 56.74 (95% UI: 39.44–78.91) (AAPC = 0.05%, 95% CI: 0.04–0.06).

Sex-specific burden and temporal trends, 1990–2021

In 2021, all ASRs of RA among MAA were higher in females than in males (Table 1). The global ASIR was 27.22 (95% UI: 17.63–38.72) per 100,000 in females and 11.83 (95% UI: 7.51–17.27) in males. The ASPR was 535.42 (95% UI: 437.92–640.43) in females compared with 201.41 (95% UI: 157.66–250.30) in males. The ASMR was 0.26 (95% UI: 0.23–0.30) in females and 0.13 (95% UI: 0.08–0.16) in males. Likewise, the ASDR was higher in females at 81.16 (95% UI: 56.41–113.43) than in males at 32.22 (95% UI: 22.21–45.17).

Between 1990 and 2021, ASIR increased in both sexes, with an AAPC of 0.28% (95% CI: 0.27–0.29) in males and 0.20% (95% CI: 0.19–0.20)

TABLE 1. Sex-Specific ASRs and Temporal Trends of RA Among Adults Aged 40–59 Years Globally, 1990–2021.

Measure	Male	Female
1990		
ASIR (per 100, 000 population, 95% UI)	10.86 (6.81 to 16.08)	25.64 (16.51 to 36.86)
ASPR (per 100, 000 population, 95% UI)	173.16 (133.73 to 217.74)	479.04 (388.27 to 578.1)
ASMR (per 100, 000 population, 95% UI)	0.18 (0.13 to 0.22)	0.47 (0.4 to 0.55)
ASDR (per 100, 000 population, 95% UI)	30.58 (22.01 to 41.98)	81.8 (59.13 to 110.5)
2021		
ASIR (per 100, 000 population, 95% UI)	11.83 (7.51 to 17.27)	27.22 (17.63 to 38.72)
ASPR (per 100, 000 population, 95% UI)	201.41 (157.66 to 250.3)	535.42 (437.92 to 640.43)
ASMR (per 100, 000 population, 95% UI)	0.13 (0.08 to 0.16)	0.26 (0.23 to 0.3)
ASDR (per 100, 000 population, 95% UI)	32.22 (22.21 to 45.17)	81.16 (56.41 to 113.43)
1990-2021		
AAPC of ASIR (95% CI)	0.28* (0.27 to 0.29)	0.20* (0.19 to 0.20)
AAPC of ASPR (95% CI)	0.50* (0.49 to 0.51)	0.37* (0.36 to 0.38)
AAPC of ASMR (95% CI)	-1.26* (-1.33 to -1.19)	-1.93* (-1.98 to -1.88)
AAPC of ASDR (95% CI)	0.17* (0.16 to 0.19)	-0.03* (-0.04 to -0.01)

ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate; ASPR, age-standardized prevalence rate; ASDR, age-standardized disability-adjusted life years rate; AAPC, average annual percentage change; UI, uncertainty interval; CI, confidence interval. *Significantly different from 0 at alpha = 0.05 ($p < 0.05$).

in females. ASPR also increased in both sexes, with an AAPC of 0.50% (95% CI: 0.49–0.51) in males and an AAPC of 0.37% (95% CI: 0.36–0.38) in females. In contrast, ASMR declined in both sexes, with a greater decrease observed in females (AAPC = -1.93%, 95% CI: -1.98 to -1.88) than in males (AAPC = -1.26%, 95% CI: -1.33 to -1.19). ASDR showed divergent trends, increasing slightly in males (AAPC = 0.17%, 95% CI: 0.16–0.19) but decreasing marginally in females [AAPC = -0.03%, 95% CI: -0.04–(-0.01)].

Regional variation by SDI quintiles and GBD regions, 1990–2021

In 2021, ASRs varied across SDI quintiles. The ASIR of RA among MAA was 30.93 (95% UI: 20.95–42.29) per 100,000 in high-SDI regions and 11.10 (95% UI: 7.06–16.11) per 100,000 in low-SDI regions. The ASPR ranged from 488.09 per 100,000 in high-SDI regions to 185.92 per 100,000 in low-SDI regions (Supplementary Table 1).

Between 1990 and 2021, ASIR remained stable in high-SDI regions [31.15–30.93; AAPC = -0.02%, 95% CI: -0.06–(-0.01)], whereas it increased in low-middle SDI regions (11.43–15.00; AAPC = 0.90%, 95% CI: 0.89–0.91). ASPR increased across SDI quintiles, including in low-middle SDI regions (AAPC = 0.89%, 95% CI: 0.88–0.91). In contrast, ASMR declined in all SDI categories, including high-SDI regions [0.37–0.15; AAPC = -2.71%, 95% CI: -2.96–(-2.52)]. ASDR increased in several lower SDI quintiles but decreased in high-SDI regions (AAPC = -0.18%, 95% CI: -0.20 to -0.15).

Across the 21 GBD regions, considerable variation was observed in both levels and trends. ASIR increased in Andean Latin America (AAPC = 2.11%, 95% CI: 2.06 to 2.16), Southern Latin America (AAPC = 1.80%, 95% CI: 1.78–1.81), Central Asia (AAPC = 1.35%, 95% CI: 1.32–1.37), and North Africa and the Middle East (AAPC = 1.38%, 95% CI: 1.36–1.39), but decreased in high-income Asia Pacific (AAPC = -0.65%, 95% CI: -0.71–(-0.61)).

ASMR declined in most regions, including high-income Asia Pacific (AAPC = -4.16%, 95% CI: -4.43 to -3.92), but increased in Central Asia (AAPC = 5.66%, 95% CI: 4.54 to 6.92). ASDR increased in Andean Latin America (AAPC = 1.32%, 95% CI: 1.26–1.38), while it decreased in Southern Sub-Saharan Africa [AAPC = -0.69%, 95% CI: -0.76–(-0.63)] and high-income Asia Pacific [AAPC = -0.62%, 95% CI: -0.66–(-0.59)].

Country-level variation in RA burden, 1990–2021

Marked variation was observed across countries in both levels and temporal trends of RA burden (Figure 1). In 2021, Ireland reported the highest ASIR (71.33 per 100,000; 95% UI: 44.90–100.62), whereas Kiribati recorded the lowest (3.15 per 100,000; 95% UI: 1.79–4.88). Similar disparities were observed in prevalence, mortality, and DALYs.

Between 1990 and 2021, substantial heterogeneity was identified in country-level trends. The largest increase in ASIR was observed in Guatemala (AAPC = 2.18%, 95% CI: 2.16–2.20), and Guatemala, which also showed the greatest increase in ASPR (AAPC = 2.01%, 95% CI: 2.00–2.03). For mortality, Guyana exhibited the largest increase in ASMR (AAPC = 8.16%, 95% CI: 7.42–8.82), whereas Norway experienced one of the most pronounced declines [AAPC = -4.99%, 95% CI: -5.40–(-4.43)]. Regarding DALYs, Mauritius showed the highest increase in ASDR (AAPC = 2.08%, 95% CI: 1.57–2.74). Detailed country-level estimates are provided in Supplementary Table 2.

Temporal trends identified by joinpoint regression

Joinpoint regression identified distinct phase-specific changes in the global RA burden among MAA from 1990 to 2021 (Figure 2). The ASIR remained relatively stable during 1990–1996 (APC = 0.06), increased during 1996–2000 (APC = 0.29%), rose more markedly

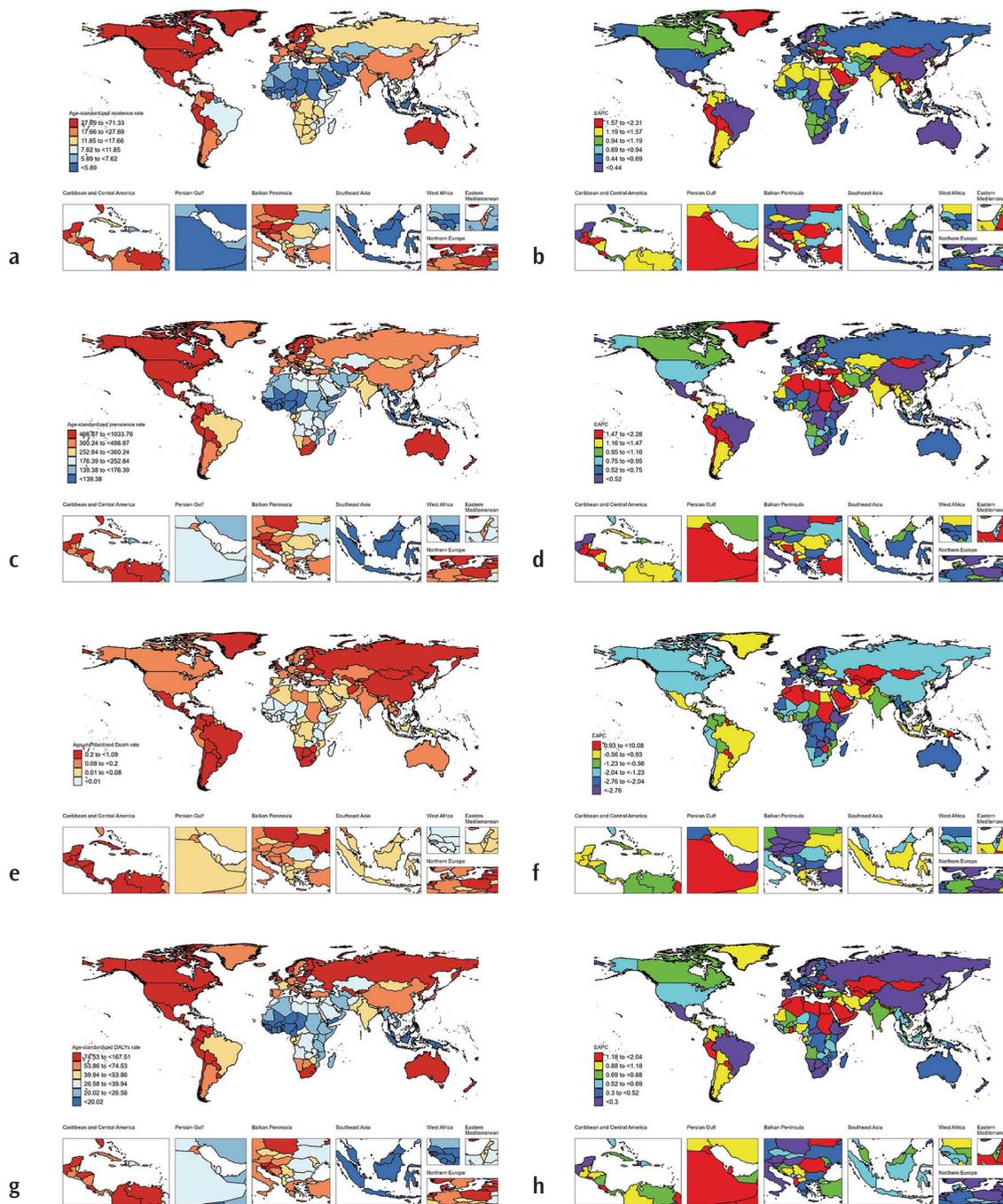


FIG. 1. Global distribution and temporal trends of age-standardized incidence (ASIR), prevalence (ASPR), death (ASMR), and disability-adjusted life years rates (ASDR) of rheumatoid arthritis among middle-aged adults in 2021 and their estimated annual percentage change (AAPC), 1990–2021. (a) ASIR; (b) AAPC of ASIR; (c) ASPR; (d) AAPC of ASPR; (e) ASMR; (f) AAPC of ASMR; (g) ASDR; (h) AAPC of ASDR.

during 2000–2009 (APC = 0.56%), and continued to increase at a slower rate during 2009–2021 (APC = 0.08%). The ASPR showed a similar pattern, with modest growth during 1990–1995 (APC = 0.11%), accelerated increases during 1995–2000 (APC = 0.49%) and 2000–2009 (APC = 0.80%), followed by continued but slower growth during 2009–2021 (APC = 0.25%). In contrast, ASMR declined during

1990–1998 (APC = -2.31%), increased briefly during 1998–2004 (APC = 0.83%), and then decreased substantially during 2004–2013 (APC = -2.82%) and 2013–2021 (APC = -1.70%). ASDR decreased during 1990–1992 (APC = -0.62%) and 1992–1998 (APC = -0.23%), increased during 1998–2005 (APC = 0.77%), and subsequently declined slightly during 2005–2021 (APC = -0.07%).

Association between disease burden and SDI

According to the GBD classification, countries and territories were grouped into five SDI quintiles (low, low-middle, middle, high-middle, and high). Across regions, ASIR and ASPR were positively correlated with SDI (ASIR: $R = 0.60$, $p < 0.001$; ASPR: $R = 0.62$, $p < 0.001$), with higher rates observed in high-SDI regions, such as Western Europe, high-income North America, and Australasia, and

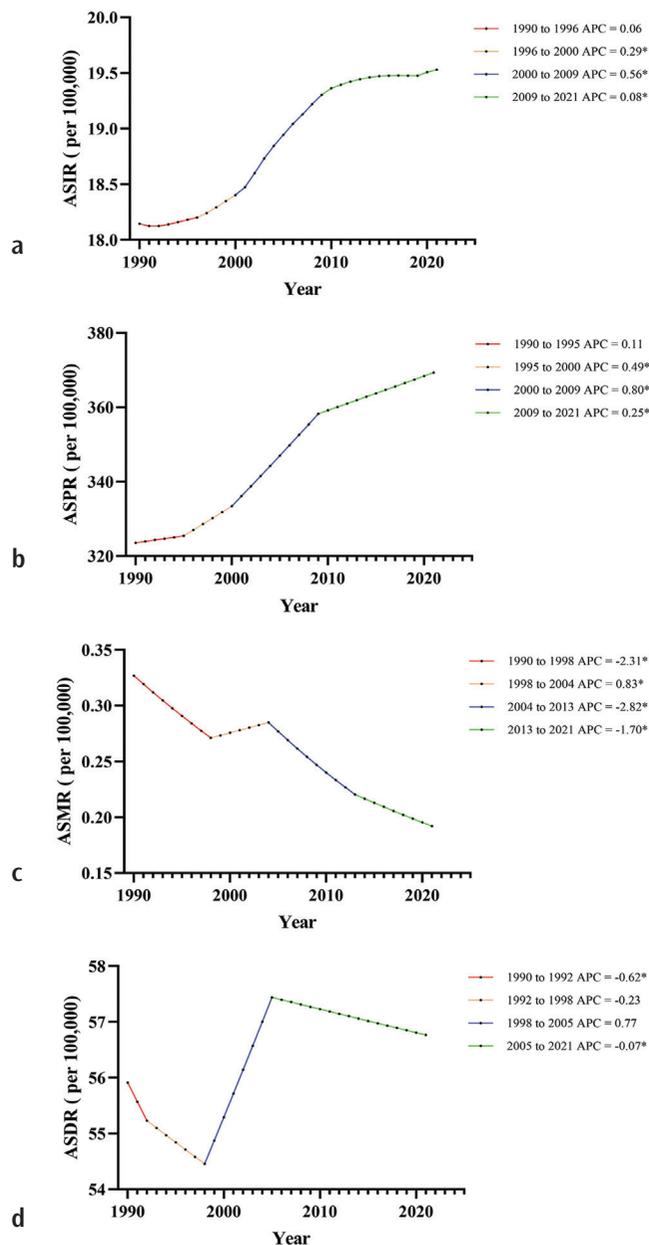


FIG. 2. Joinpoint regression analysis of global age-standardized incidence (ASIR), prevalence (ASPR), mortality (ASMR), and disability-adjusted life years rates (ASDR) of rheumatoid arthritis among middle-aged adults, 1990–2021. (a) ASIR; (b) ASPR; (c) ASMR; (d) ASDR. Solid lines indicate fitted trends, and segments are labeled with annual percentage change (APC, $p < 0.05$). APC, annual percentage change.

lower rates in Sub-Saharan Africa and South Asia. Andean Latin America and Central Latin America were located above the fitted regression line, whereas high-income Asia Pacific was below the fitted line. ASMR was negatively correlated with SDI ($R = 0.27$, $p < 0.001$), with Central Asia and Eastern Sub-Saharan Africa positioned above the fitted line. ASDR showed a positive correlation with SDI ($R = 0.56$, $p < 0.001$), with higher values observed in Andean, Southern, and Central Latin America, whereas high-income Asia Pacific remained below the fitted line (Figure 3).

Projected disease burden through 2050

Using the BAPC model, projected global ASRs of RA among MAA from 2022 to 2050 are presented in Figure 4. The projected ASIR was 19.53 (95% CrI: 19.47–19.59) per 100,000 in 2021 and is expected to reach 19.22 (95% CrI: 3.76–34.67) per 100,000 by 2050. The projected ASPR was 368.73 (95% CrI: 368.45–369.00) per 100,000 in 2021 and 367.47 (95% CrI: 88.31–646.63) per 100,000 in 2050. The projected ASMR was 0.193 (95% CrI: 0.187 to 0.198) per 100,000 in 2021 to 0.111 (95% CrI: 0.001–0.313) per 100,000 by 2050. Similarly, the projected ASDR was 56.74 (95% CrI: 56.63–56.85) per 100,000 in 2021 and is projected to decrease to 52.18 (95% CrI: 9.06–95.31) per 100,000 in 2050. The CrIs increased over the projection period (Figure 4).

DISCUSSION

This study quantified the burden of RA among MAA (40–59 years) using GBD 2021 estimates from 1990 to 2021. It examined ASIR, prevalence, mortality, and DALY rates across locations and over time, and provided projections to 2050. By focusing on the 40–59-year age range—a life stage associated with high work and family responsibilities—our findings provide age-specific evidence that complements prior GBD-based assessments of RA across all ages.

At the global level, the ASIR and ASPR increased between 1990 and 2021, whereas the ASMR decreased and the ASDR changed only slightly. Similar patterns have been reported in recent global analyses of RA using GBD data, which consistently describe rising ASIR and ASPR alongside declining ASMR.¹ These divergent trends should be interpreted descriptively within the context of GBD model-based estimates. Changes in observed incidence and prevalence may reflect multiple factors, including temporal variations in case ascertainment, diagnostic access, and classification practices, in addition to underlying disease occurrence. In this context, the periods of accelerated increases in incidence and prevalence beginning in the early 2000s and extending into subsequent years coincide with major changes in RA management and classification frameworks. During this time, treat-to-target strategies were formalized and widely disseminated, and the 2010 ACR/EULAR classification criteria were introduced to facilitate earlier classification of RA compared with the 1987 criteria.^{9,10} These contemporaneous developments may have contributed to changing epidemiological patterns; however, within the scope of the current analysis, they should be interpreted as potential contextual factors rather than established causal explanations.

Substantial geographic heterogeneity was observed across SDI quintiles and GBD regions. Incidence and prevalence were higher

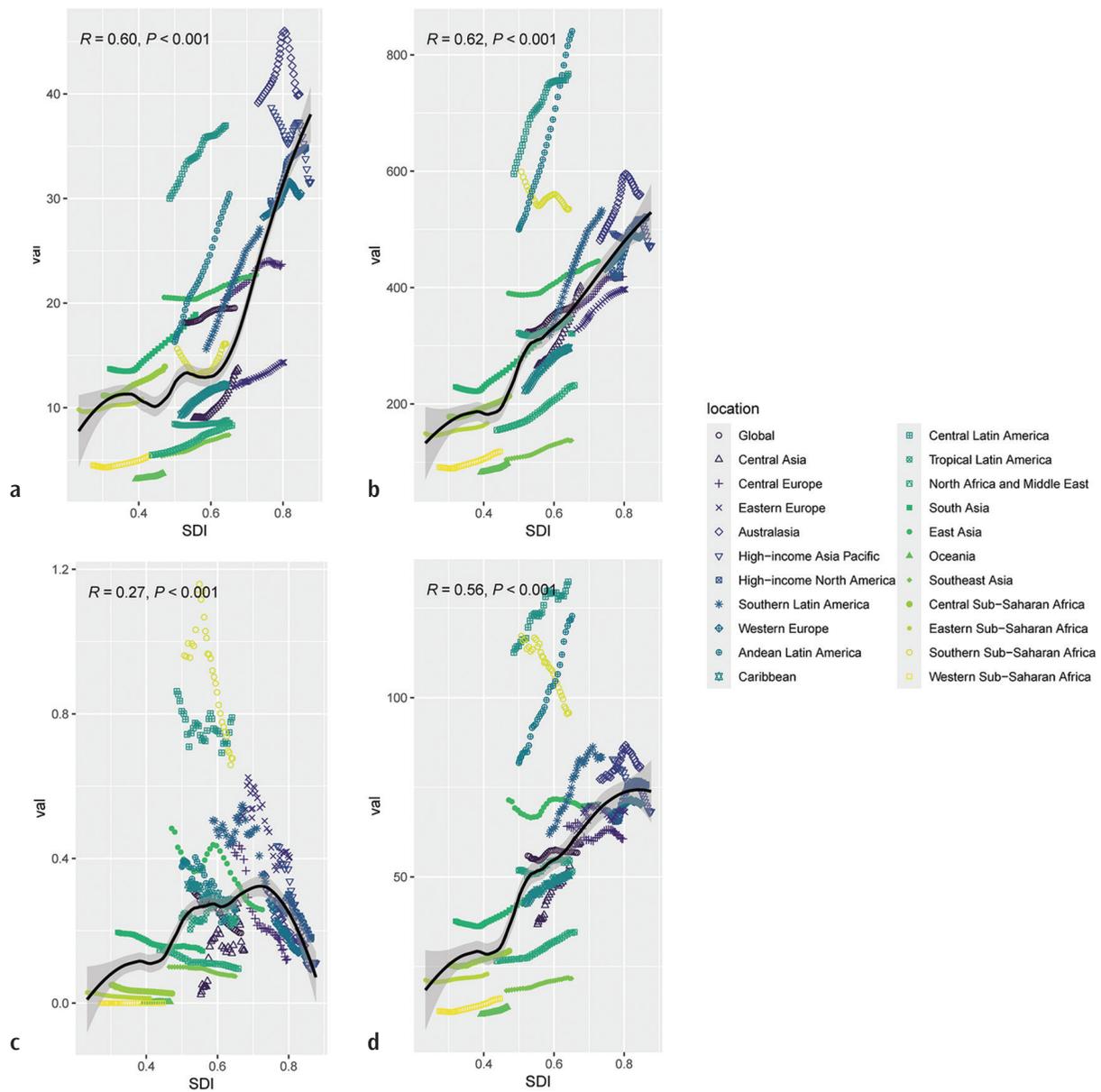


FIG. 3. Association between sociodemographic index and age-standardized incidence (ASIR), prevalence (ASPR), mortality (ASMR), and disability-adjusted life years rates (ASDR) of rheumatoid arthritis among middle-aged adults, 1990–2021. (a) ASIR across 21 Global Burden of Disease regions; (b) ASPR across 21 regions; (c) ASMR across 21 regions; (d) ASDR across 21 regions. Black lines represent fitted non-linear relationships; R indicates Pearson correlation coefficient.

in high-SDI settings, whereas mortality tended to be lower at higher SDI levels. This SDI pattern is consistent with the use of SDI in GBD studies as a composite indicator of development and with the broader observation that detection and reporting capacity, access to rheumatology services, and the availability of diagnostic tools often vary with health-system resources.¹¹ However, the SDI comparisons in this study are ecological and descriptive and therefore do not provide explanations for between-region differences. The country- and region-specific outliers shown in the SDI plots further highlight that substantial variation exists even among locations with

similar SDI, supporting the value of presenting results at multiple geographic levels.

Given the strong sex-dimorphism of RA, sex-stratified results are essential for interpretability. Prior epidemiological studies consistently report a higher RA burden in females, with female-to-male ratios commonly exceeding 2:1.¹ Consistent with this established pattern, our sex-stratified estimates demonstrate substantially higher incidence and prevalence among females than males in the 40–59-year group, along with differences in mortality and DALYs trends. These findings underscore that analyses restricted

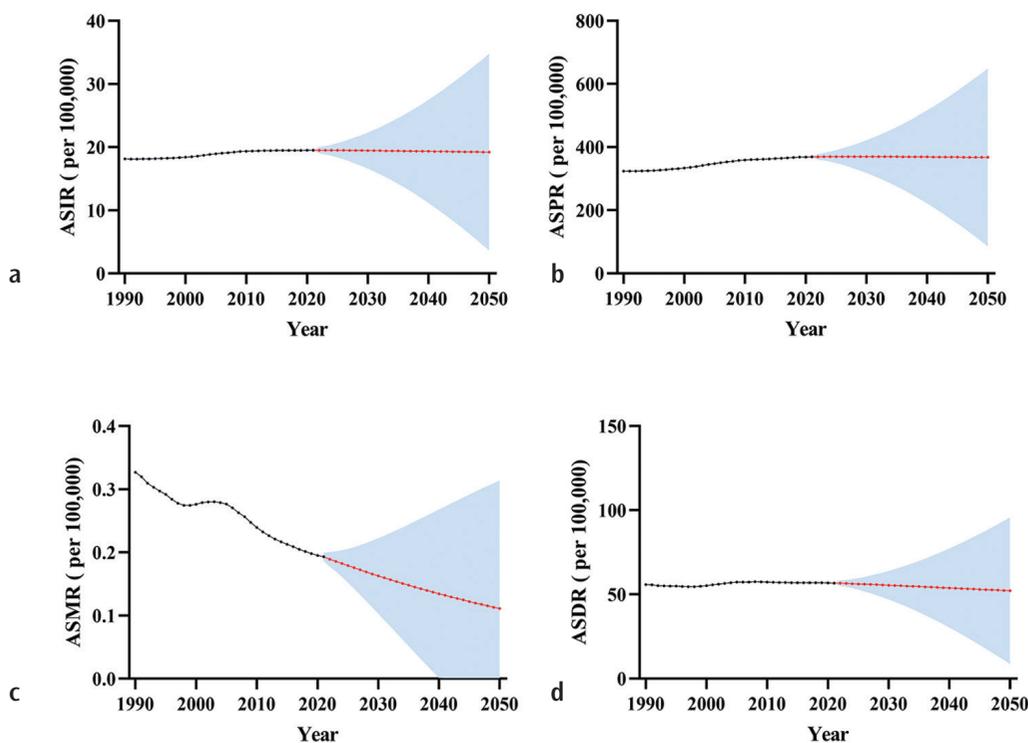


FIG. 4. Projected trends in age-standardized incidence (ASIR), prevalence (ASPR), mortality (ASMR), and disability-adjusted life years rates (ASDR) of rheumatoid arthritis among middle-aged adults through 2050. (a) ASIR; (b) ASPR; (c) ASMR; (d) ASDR. Red lines represent model-based projections from the Bayesian age–period–cohort model; shaded areas represent 95% uncertainty intervals.

to MAA remain clinically relevant only when sex-specific differences are explicitly presented.

Projections to 2050 suggested broadly stable incidence and prevalence, accompanied by declining mortality and DALYs among MAA. However, UIs widened over time. Such widening intervals are common in long-term projections and reflect the accumulation of uncertainty arising from both model structure and unobserved future conditions. The BAPC framework is widely used for epidemiological forecasting and can provide useful scenario-like estimates; nevertheless, projections should be interpreted with caution, particularly when UIs become very wide.^{12,13} In this study, the large uncertainty bounds projected for 2050 should therefore be interpreted as indicating limited precision rather than exact predictions of future levels.

Several limitations should be considered. First, GBD 2021 estimates are model-based syntheses that rely on the availability and quality of underlying data sources as well as the assumptions embedded within the GBD modeling framework. Second, the ecological SDI analyses do not capture within-country heterogeneity and do not incorporate treatment coverage or health-system variables. Therefore, interpretations related to differences in diagnosis or access to therapy should be considered hypotheses rather than definitive inferences. Third, RA is a heterogeneous condition (e.g., seropositive vs. seronegative phenotypes), but the GBD outputs do not stratify RA by serostatus; future studies integrating subtype-specific data could enable more refined comparisons across

settings. Finally, projections to 2050 inherently rely on modeling assumptions and should be interpreted alongside their UIs.

Overall, this GBD 2021–based analysis characterizes the long-term burden of RA among adults aged 40–59 years. The findings highlight a persistent burden, substantial geographic variation, clear sex differences, and substantial uncertainty in long-term projections. Together, these descriptive results complement existing global RA assessments by providing an age-specific perspective and may support comparative monitoring across regions and over time.

Using GBD 2021 estimates, this study quantified the global burden of RA among MAA (40–59 years) from 1990 to 2021 and examined projected trends through 2050. During the study period, the ASIR and ASPR increased, whereas the ASMR declined. The ASDR showed limited overall change. Substantial heterogeneity was observed across SDI quintiles, GBD regions, countries, and sexes. Projections to 2050 indicate that median ASIR and ASPR remain close to recent levels, whereas median ASMR and ASDR decline over time, with CrIs widening in later years. These age-specific findings complement existing all-age RA assessments and support comparative epidemiological monitoring across locations and over time.

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Informed Consent: Not applicable.

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Supplementary Table 1: <https://balkanmedicaljournal.org/img/files/y-SUPPLEMENTARY-TABLE-1.pdf>

Supplementary Table 2: <https://www.balkanmedicaljournal.org/img/files/balkan-12-228%281%29.pdf>

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